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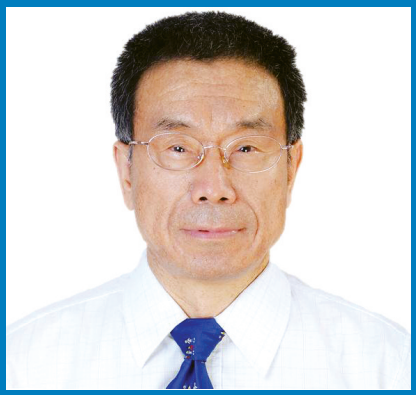
Editor-in-Chief
GEORGE CHAKHUNASHVILI
MD,PhD,DSc,
Professor, Academician
(Georgia)

GEORGIAN PEDIATRIC CARDIOLOGY ASSOCIATION

GPCA was founded on the base of TSMU pediatric clinics in 1992 and was registered in 1999. Association was founded by five persons according to Georgian Civil Codex Regulation in 1997. Association work is not limited, has independent balance in Georgian and foreign banks. Main goals of this association is early diagnostics of diseases like – Rheumatic and None-Rheumatic Cardiovascular diseases, heart ischemic diseases, myocardial infarction, different cardiomyopathy diseases, children hypertensions, Athlete's Heart and etc. Also, one of the main goals of GPCA is to help all young people who are interested in Pediatric Cardiology. Association works include bloodless instrumental research like – ECG in 15 inclinations, PCG– during load, electric velometry, capillaroscopy, rheography, echocardiography and others, research ofimmunological and genetic markers. Members of Association can be lawyers who share the goals and main principles of work. Members of GPCA have determined rights and duties: to participate in governing of Association and various projects, use the consultations and recommendations of Association, get financial support from Association funds and leave Association. The governing system of Association is represented by general meeting of the members which is held once in a year. Each member has one vote. These charters are in action after registration. So, this association has important duties and function, which is stimulated by doctor's sensitiveness and creative work in this field.

Address: LublianaN21 TBILISI(Georgia) E-mail: euscigeo@yahoo.comContact: Goerge Chakhunashvili



Editor-in-Chief
FUYONG JIAO
MD Prof and Head Children's Hospital of Shaanxi Provincial People's Hospital of Xi, an Jiaotong University, The Society of Promotion Children's Health of Shaanxi Province. Executive Councillor of ISPCAN (CHINA)

1. Shaanxi International Medical Exchange Promotion Association（SIMEA）

Date of establishment: June 1994

Registration number: 51610000520157511D

Address: No. 22, Huancheng East Road, Xincheng District, Xi'an City, Shaanxi Province

E-mail: 3105089948@qq.com

Contact: Fuyong Jiao

SIMEA was established in 1994 with the approval of the Shaanxi Provincial Department of Civil Affairs. It is a first-level social organization under the charge of the Shaanxi Provincial Health and Family Planning Commission. The concept of "seeking well-being" will give full play to the advantages and characteristics of the gathering of experts, a wide range of disciplines, and a sound network, aiming to build a platform for international medical exchanges and mutual learning.

2. Children's Hospital of Shaanxi Provincial People's Hospital

Date of establishment: 1950

Address: No. 256, Youyi West Road, Beilin District, Shaanxi Province

Contact: Fuyong Jiao

Since its establishment in 1950, the Children's Hospital of Shaanxi Provincial People's Hospital has experienced more than 70 years of development. It is now the Children's Hospital of the Third Affiliated Hospital of Xi'an Jiaotong University. It is a children's hospital integrating medical treatment, teaching, and scientific research. Shaanxi Province Kawasaki Disease Diagnosis and Treatment Center, Shaanxi Province Pediatrics Clinical Medicine Research Center, National Drug Research Institute (Children Neuromedicine Specialty), Shanghai Cooperation Organization Hospital Cooperative Alliance International Exchange Center, and China Kawasaki Disease Website (ww.chinakd.org) have been established.), European Center for Traditional Chinese Medicine (Prague). Insist on innovating the "send out and invite in" communication methods for academic exchanges and scientific research cooperation.

3.The Institution of Shaanxi Province Clinical Medicine Demonstration International Science and Technology Cooperation

Established time: 2020

Address: No. 256, Youyi West Road, Beilin District, Xi'an City, Shaanxi Province

Contact: Fuyong Jiao

E-mail: 3105089948@qq.com

The Shaanxi Provincial Clinical Medicine Demonstration International Science and Technology Cooperation Base was established in 2020. It is an organization approved by the Shaanxi Provincial Department of Science and Technology to promote international cooperation and exchanges in clinical medicine and guide the province to carry out international cooperation and exchanges in clinical medicine. The cooperation base is set up in Shaanxi Provincial People's Hospital. Actively expand foreign medical resources, and provide a lasting communication channel for domestic medical and health institutions and public health service units to learn international advanced management experience and strengthen the training of talent teams.

GEORGIAN PEDIATRIC CARDIOLOGY ASSOCIATION

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Children's Hospital of Shaanxi Provincial People's Hospital
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Science and Technology Cooperation

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PREFACE

Children is the hope of society, the future of world and mankind!

Strong children make the world strong! In order to strengthen international medical academic exchanges and improve the diagnostic and therapeutic skills of pediatricians, nurses and general practitioners around the world, the international Journal of Pediatrics was organized by the joint efforts of pediatricians and general practitioners from China, Georgia, Poland, The Czech Republic, Turkmenistan and India et al. This journal is of great clinical significance and academic value to promote international communication among pediatric medical staff and improve the diagnostic and treatment technology level of pediatric diseases. We hope that with our joint efforts and hard work, this journal will take root, sprout and grow in the world, bringing good news to the health of children around the world and benefiting children all over the world!

GEORGE CHAKHUNASHVILI (Georgia) and FUYONG JIAO (China)

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E-mail: 3105089948@qq.com (China)
euscigeo@yahoo.com (Georgia)
Tel.: office: 0086.029-85368194 (China)
Mob.: 15398082028 //18966928051 (China)
Mob.: (+995 593) 337154 (Georgia)

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ADVANCED ARTICLE

CLINICAL-INSTRUMENTAL CHARACTERIZATIONS OF CARDIOVASCULAR SYSTEM DURING SOME CONGENITAL, INFLAMMATORY AND ACQUIRED NONINFLAMMATORY DISEASES IN CHILDHOOD AND POSSIBILITIES OF THE INVOLVEMENT OF PREPARATION GA-40 IN THE TREATMENT

NINO JOBAVA,
MD, PH.D
GEORGE CHAKHUNASHVILI,
Doctor of Medical Sciences, Professor
Tbilisi State Medical University
(Tbilisi,Georgia)

ABSTRACT

Vegetative cardiovascular dystony, myocardial dystrophy, cardiopathy, nonrheumatoid carditis - these are diseases, which require a timely diagnostics, treatment and prophylaxis in childhood in order to avoid complications and difficulties in future.

It is well-known that at present such diseases as atherosclerosis, cardiosclerosis, cardiac ischemic disease, myocardial infarction, etc. are very rare. But probably it is necessary and timely to pay attention to children of that risk-groups (risk groups of atherosclerosis, cardiac ischemic disease, myocardial infarction), which require dispensary and corresponding prophylaxis. Proceeding from above-said and according to thorough analysis of data of some authors (G. Chakhunashvili, K. Chakhunashvili, N. Uberi, P. Kherkheulidze, N Jobava) it should be outlined 5 stages of prophylaxis of atherosclerosis and cardiac ischemic disease:

I stage - manifestation of risk-factors: anamnesis, anthropometry, measuring of arterial pressure, estimation of nutrition regime, investigation of emotional tone. It is important to note about children prematurity (if it is possible) and its character, suffered diseases in childhood (nonrheumatoid carditis, rheumatoid arthritis, myocardial dystrophy, cardiopathy, vegetative cardiovascular dystony, mitral valve prolapse, congenital heart disease (it should be mentioned if a patient was subjected to the surgery and when), tonsillogenous cardiopathy, etc. - is performed by a district pediatrician and school physician.

II stage - complex estimation of vegetative nervous system - reactivity, maintenance of vegetative action (methods, cardiointervalography, clinoorthostatic tests), determination of cholesterol and triglyceride levels in blood plasma by means of determination of different changes of ST segment and T wave (of course, taking into account age peculiarities) - is performed by a district pediatrician, cardiorheumatologist or cardiologist.

III stage - in the conditions of hospital a deep, complex clinical-instrumental investigation of cardiovascular system by means of cholesterol distribution in lipoprotein fractions, investigation of hemostasis and fibrinolysis system. Indications for the study of this stage appear to be a content of cholesterol level above 4,4 mmol/l, triglycerides - above 0,79 mmol/l, vegetative cardiovascular dystony and different versions of clinoorthostatic tests, taking into account form of ST segment, its J error and by determination of T wave height and depth (is performed by children cardiologists).

IV stage - a rational nutrition dietary regime, timely health-resort seasonal treatment together with rehabilitation measures (if the latter is necessary), immunorehabilitation of children in risk-groups, etc.

V stage - to outline and perform preventive measures together with governmental and NGO (centers, associations, etc.) - is carried on by leading clinics using the programs of disease diagnostics, planned by scientific-analytical group.

Thus, only rationally organised, individual prophylactic measures commenced at the earlier stage are able to move the development of cardiac ischemic disease to relatively distant age group.

Key words: *CARDIOVASCULAR SYSTEM, PREPARATION, THE TREATMENT, mitral valve prolapse (MVP), Atherosclerosis, ECG- ST segment and T wave, Vegetative-cardiovascular dystony (VCD), Cardiac ischemic disease.*

GENERAL CHARACTERIZATION OF THE WORK

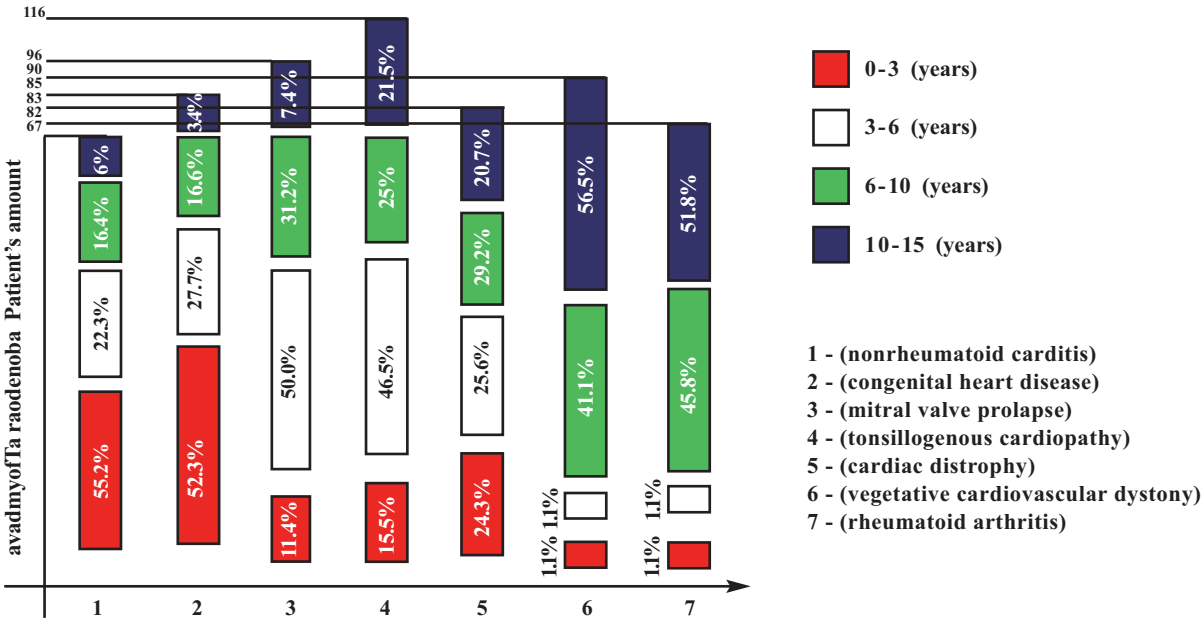
Topicality of the problem. At the modern stage pathology of cardiovascular system takes a significant importance in paediatrics. If about twenty years ago only diagnoses of rheumatism and congenital heart diseases had a priority, nowadays such terms as nonrheumatic carditis, cardiomyopathy, myocardial dystrophy, coronary insufficiency, mitral valve prolapse, myocardial infarction, risk factors of atherosclerosis, cardiac ischemic diseases, etc. are not alien to clinician pediatricians (G. Chakhunasvili, 1980, 1988, 1992, 2001, 2002;NNN. Uberi, 1997; P. Kherkheulidze, 1994; K Chakhunasvili, 2002; M. Ghudushauri, 2003; N.A. Belokon, M.B. Kuberger, 1987; I.P. Shabolov, 2002; N.N. Kipshidze et al., 1985; N.A. Belokon, V.P. Pozdniakov, 1991; S.S.Ostropolets et al., 1991; N. Bride et al., 1980; Zelikovie et al., 1981).

Nowadays it is known that cardiovascular system is involved in pathologic process during different forms of rheumatic arthritis. At the same time provision with coronary blood is disrurbed both during some congenital and acquired noninflammatory diseases. In this respect it is expedient to determine exactly changes in clinical-instrumental data during all these diseases and give a proper explanation to them by means of thorough analysis.

By this time there is no doubt that precondition of atherosclerosis and cardiac ischemic disease belongs to the age of childhood. Proceeding from this beginning of preventive measures must be introduced into the paediatrics (A.I. Kliorin, 1981;

N1 (Diagram No 1)

Distribution of clinical material according to studied nosologies and age structure of each nosology



N.A. Belokon, 1984; A.A. Aleksandrov, 1991; N.S. Porfieva, D.B. Shestov, 1995; Poledne et al., 1994) the more so, as if in childhood the patients were subjected to such diseases when cardiovascular system was damaged with expressed coronary insufficiency and disorder of the function of cardiac contractility.

Just because of it, in childhood it must be done a thorough analysis of the state of cardiovascular system during congenital and acquired diseases, the more so, as if it concerns inflammatory and noninflammatory diseases of blood circulation apparatus.

At the same time at the modern stage it is expedient to pose a question about the usage of immunocorrectors in paediatric cardiology. If this question regards the possibilities of new preparation used only at nonpediatric age, then the sphere of the topicality of the problems given in this work will be considerably extended (I. Malashkhia, 2000;GG. Chakhunashvili, N. Gumbaridze, 2002; NN. Jobava, G. Chakhunasvili, 2003; N. Jobava, G. Didava, 2003; M. Matiashvili, M. Zhvania, G. Chakhunashvili, 2003; V.I. Litvinov, I.V. Rubtsov, 1990; A. Fontana, 1994; P. Shikant, E.N. Benveniste, 1996).

Thus, together with the data of clinical-instrumental study of cardiovascular system during some congenital, inflammatory and acquired noninflammatory diseases in childhood, the analysis of complex investigation of vegetative nervous system and capillary net were not found out in the literature, as well as an analogous approach to the investigation of blood circulation apparatus in children of risk groups and possibilities of involvement of the preparation GA-40 in their treatment.

Only rational organisation of individual primary prophylactic measures at the earlier stage can transfer the development of atherosclerosis and cardiac ischemic disease to relatively distant age groups.

All above-said has determined goals and tasks of our investigation.

The aim of this work was to develop differential-diagnostic criteria during some congenital, inflammatory and acquired noninflammatory diseases in childhood and to carry on their thorough clinical analysis as well as to determine possibilities of involvement of the preparation GA-40 in the treatment.

The tasks of the work were:

1. To give a differential estimation of changes in blood circulation apparatus during nonrheumatic carditis, rheumatic arthritis, vegetal-cardiovascular dystonia, congenital heart disease, tonsillogenous cardiopathies, myocardiodystrophies and mitral valve prolapse.

2. To ascertain a character and frequency of cardiovascular system damages taking into account age and sex of the patients.

3. To give an estimation to the contingent of above-said diseases and ascertain if in future they appear to be risk-groups of atherosclerosis and cardiac ischemic disease.

4. To study an action of GA-40 on cardiovascular system in the experiment and analyse both instrumental indices and morphological data.

Scientific novelty of this work appears to be:

1. Age norms of changes in ST segment and T wave in healthy children have been established for the first time.

2. On the basis of complex investigation criteria of pre- and postcapillary system disturbances during some inflammatory and acquired noninflammatory diseases have been developed for the first time, taking into account age and sex of children.

3. Correlative accordance of the 12th recording of ECG and the 3rd recording of NeHB and possibilities of their introduction into the clinics have been studied for the first time on the background of different diseases.

4.The action of GA-40 preparation in the experiment (instrumental and morphological data of cardiovascular system) has been studied for the first time.

Theoretical significance of the work:

1. The essence of changes in pre- and postcapillary system during some con-

genital, inflammatory and acquired noninflammatory diseases are explained in childhood taking into account the form of the disease and age of the patients.

2. For the first time the question was posed to consider as risk-factors of adults atherosclerosis and cardiac ischemic diseases the inflammatory and acquired noninflammatory diseases suffered in childhood.

3. A conception about the involvement of the preparation GA-40 in the treatment of disturbances in blood circulation apparatus will be developed for the first time.

Practical significance. The data obtained based on the results of clinical-instrumental and experimental investigations may be introduced in children medical institutions in order to estimate inflammatory and noninflammatory changes in cardiovascular system, to prescribe an adequate therapy and to prognosticate the duration of these diseases. At the same time it is necessary to carry on 5-stage measures for the prevention of atherosclerosis and cardiac ischemic disease.

Main topics presented for defense of the dissertation:

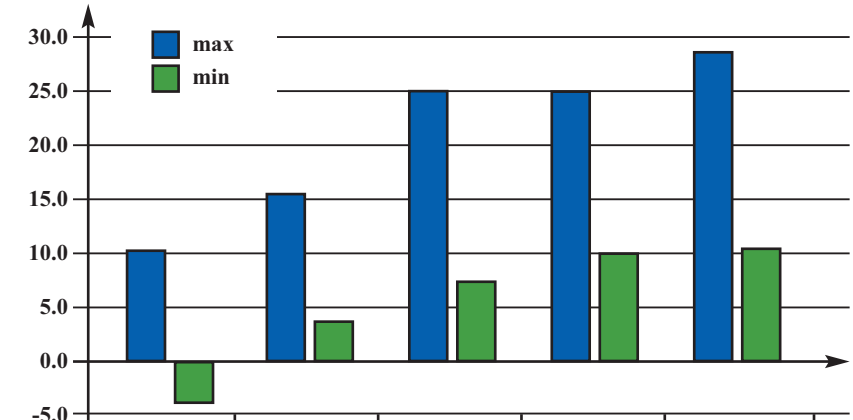
1. Function of contractility of the myocardium during inflammatory and acquired noninflammatory diseases, as well as central and peripheral hemodynamics together with capillaroscopic and cardiointervalographic data differs by its frequency and degree.

2. A complex of electrocardiographic data (in usual 12 and additional 3 NeHb recordings) is characterized by the peculiarities both in healthy and ill children, taking into account changes in ST segment and T wave.

3. Action of GA-40 preparation on cardiovascular system in the experiment (ECG, phonocardiography, rheography) and its morphological characterization in the rabbits, as the possibility of its future usage.

4. A complex of elaborated diagnostic criteria together with new therapeutic drugs may be used in treatment of nonrhematoid carditis, rheumatoid arthritis, vegetal-cardiovascular dystonia, congenital heart disease, tonsillogenous cardiopathies, myocardiodystrophies and mitral valve prolapse in patients in order to carry on a well-grounded rational therapy and prevention of cardiovascular system complications.

N2 (Diagram No 2)



	1 Tve	1 w.	2 w.	6 w.	12 w.
max	11.0	16.5	25.0	25.0	29.3
min	-3.7	3.7	7.5	10.0	10.7

Introduction into the practice. The data obtained are introduced into G. Zhvania Paediatric Clinics of Tbilisi State Medical University, Tbilisi Mother and Children Cardiology Center. Besides, these data may be involved in the cycle of lectures and practical works of the departments of Tbilisi State Medical University and other medical institutes.

Approbation of the work. The presented work has been approbated on the departments of pathological anatomy and forensic medicine, human normal anatomy, histology, embryology and cytology of Tbilisi State Medical Academy and on the united scientific session of collaborators of Paediatric Clinics of Tbilisi State Medical University (November 16, 2004, proceedings No 5/1).

The main topics of the dissertation were reported on: IV-V Joint Conferences of the Association of Physicians and Defense of Social Paediatrics (Tbilisi, 1999-2000); XXIII Congress of the European Society of Cardiology (Stockholm, Sweden, 2001); the Ist National Symposium of Georgian International Cardiomyopathy Society (Tbilisi, 2002); the IInd Conference of the Association of Children Cardiologists (Tbilisi, 2003); XI Joint (II International) Conference of the Associations of Physicians and Paediatrics of Georgia (Tbilisi, 2004).

Publications. 4 articles have been published concerning the theme of the given dissertation.

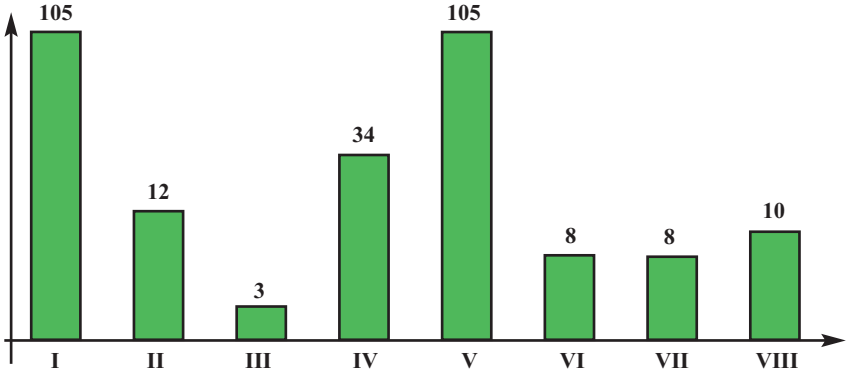
Structure and volume of the dissertation. The work is spread on 185 computer-printed pages and consists of: introduction, the review of literature, Material and methods of investigation, obtained results and their discussion, conclusions, practical recommendations and list of literature (222 sources). The work contains 4 diagrams, 6 tables.

MATERIAL, METHODS OF THE INVESTIGATION AND ANALYSIS

The material of this study appears to be the results of complex clinical-instrumental investigations carried out in

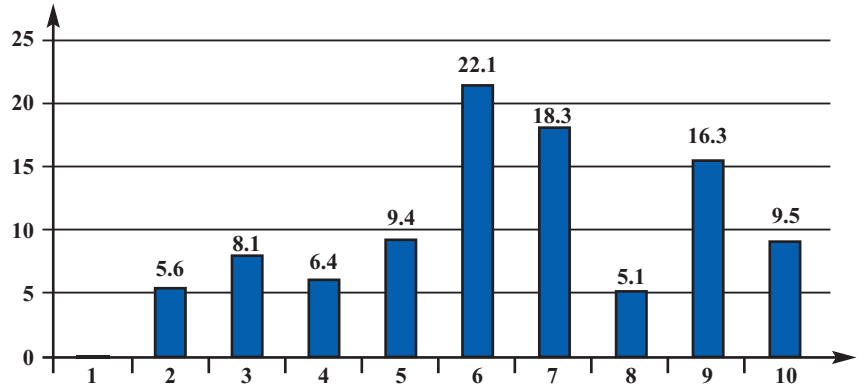
N3 (Diagram No 3)

Frequency of changes in ST segment and T wave



N4 (Diagram No 4)

An average arithmetical index of percentage distribution of combination versions of an initial tone of vegetative nervous system and types of vegetative reactivity



Tbilisi Children Hospitals (No 2 and Railway Hospital No 6), Paediatric Clinics of Tbilisi State Medical University, Tbilisi Prophylactic Centre for Mother and Child during the period of 1979-2003 years.

Total of 658 patients in the age of 0 to 15 were analysed, among them 308 were girls and 350 – boys. Total of 120 practically healthy children in the same age made up a control group (girls, boys). The criteria for their selection were: absence of somatic, non-infectious and acute infectious diseases before the examination during 3 weeks, absence of complaints, the correspondence of biological age to the data of patients' passports. According to the nosology, the following diseases were studied: 115 cases of rheumatoid arthritis (among them: 83 cases of articular form and 32 – of articular-visceral form), 71 cases of nonrheumatoid carditis, 125 cases of tonsillogenous cardiopathy and 60 cases of congenital heart disease (among them: 13 cases of interatrial septum defect, 15 cases of interventricular septum defect, 10 cases of Fallot's tetrad, 12 cases of coarctation of aorta and 10 cases of stenosis of aortic valve). Also were studied 96 cases of mitral valve prolapse, 85 cases of vegetative-cardiovascular dystony and 80 cases of myocardial dystrophy. The distribution of diseases according to the age and clinical forms is given in the Diagram No 1.

N1 (Table No 1)

Maximal and minimal height of T wave in 15 recordings of ECG (usual 12 and NeHb 3 recordings) in different age groups of healthy children

Recordings	Age									
	One month		0-2 years		3-5 years		6-10 years		10-15 years	
	min	max	min	max	min	max	min	max	min	max
I	-1	4,5	1	5	1,5	5	2	5,5	2	3
II	0	6,5	1,5	7	1,5	5,5	1,5	7	1,5	6,5
III	-1	4,5	-2	5	1,5	3	1,5	4,5	1,5	3
AVR	-1,5	-4,5	-3	-5	-3,5	-6	-3	-5	-3	-3
AVL	-2	3	-1	3,5	-2	4,5	-3	4,5	1,5	2,5
AVF	1	3	1	4,5	-1	3,5	-1,5	5	-1	3,5
V1	-6	1	-6	-1	-5,5	-1	-5	-1	-5,5	1
V2	-5,5	3	-5	3	-3,5	5	-5,5	6	-7	5,5
V3	-4	3	-3	4	-4	8	-5,5	7	-6	5
V4	-1	5,5	-2	12	-1	10	1	11	1	5
V5	1,5	6	1,5	8	2	9	2,5	10,5	2	5
V6	1	5	2	6	2,5	7,5	2	7,5	2	6
D	-1,5	3	-1	4,25	-2,5	5,75	-3,5	6	-3.5	4,25
A	-4	2	-3,5	1,25	-3,8	1,75	-4	1,75	-3,5	1,75
I	-1,5	3	-1	4,25	-2,5	5,75	-3,5	6	-3,5	4,25

In 120 practically healthy children the error of ST segment and T wave area were studied and analysed in usual 12 and 3 NeHb recordings (A.D.I.).

In the conditions of experiment the action of GA-40 preparation on cardiovascular system has been analysed (data of ECK, PhG, RhG) as well as morphological characterisation of blood circulation apparatus in rabbits. Experimental investigations were performed on the bases of Central Laboratory of Tbilisi State Medical University, Tbilisi Center for Adult and Children Pathology, Pathoanatomical scientific-practical Centre and the department of pathological anatomy and forensic medicine of Tbilisi State Medical Academy.

The preparation GA-40 (registration MP NO 003008, December 8, 1999_) appears to be a complex of polypeptides obtained from ecologically pure natural plant raw material using biochemical methods of purification. It contains a standartized combination of chromatographically cleaned polypeptides. In practical medicine it is used as colourless liquid as immunocorrector i.e. It belongs to the class of preparations of immunorehabilitation type.

Clinical-anamnestic investigation. During clinical investigations an attention was drawn to: study of anamnesis and complaints in detail, physical and supplementary methods of the investigation, character of damages of organs and description of the manifestation.

Laboratory investigation. All patients under the investigation were subjected to clinical and biochemical laboratory investigations, particularly: total blood count, analysis of the urine, analysis of feces; in blood serum: determination of common protein, hexoses, neuroaminic acid, investigation on rheumatoid factors, as well as circulating immune factors (using precipitation method), etc.

Analysis of laboratory data was carried on in the complex with other clinical and instrumental data.

Methods of instrumental investigation. Electrocardiogram was registered on 12 usual and 3 NeHb recordings (A, D, I). Besides the visual estimation of electrocardiogram, the calculation of their parameters was done.

In addition a qualitative characterisation of ST segment error and T wave

an area of ST segment error and T wave was determined.

Roentgenography of organs of the thorax. Polycardiography and rheographic investigations were carried out using well-known methods. Capillaroscopy was done on the fourth finger by means of the microscope using general method (35-70-fold magnification). The skin was preliminarily treated with glycerol and vaseline. During capillaroscopy a great attention was drawn to the colour of main background and its transparency, diameter of capillaries, their forms, arrangement, character of blood flow and general capillary picture. Capillary background of healthy children was rose-coloured and transparent.

Clinoorthostatic tests were offered by N.A. Belokon and M.A. Kuberger in 1987 for the manifestation of vegetative dysfunction and circulatory hyperreactivity.

Method of echocardiography investigation. The investigation was performed by means of the equipment "LOGIQ-400" (USA) when a patient was laying supine or on the left side, using 3,5 MHz and 5,0 MHz transducer and transthoracic echoscopy, as well as subcostal, apical, parasternal and suprasternal windows.

Statistic processing of the material. The digital data obtained were mainly treated by the method of variation statistics. An average arithmetical (M) index and an average square deviation were determined.

$$(C = \pm \sqrt{\frac{ed^2}{n-1}})$$

The difference of an average error of average arithmetical index, borders of reliability interval (M±G) were reliable when t>2,07. The reliability (P) of the error was determined; a correlation analysis was performed (using coefficients "r" and "R").

RESULTS AND THEIR DISCUSSION

Analysis of age structure of studied diseases has shown that more than a half of patients suffering from nonrheumatoid carditis and congenital heart disease were in the of 0 to 3 years, a majority of patients with mitral valve prolapse (MVP) and tonsillogenous cardiopathy consists age group of 3-6 years. Patients with vegetative-cardiovascular dystony

N2 (Table No 2)

Types of changes in ST segment and T wave during some inflammatory and noninflammatory diseases of the heart

Types	articular form of rheuma-toid arthritis	articular-visceral form of rheuma-toid arthritis	nonrheu-matoid carditis	tonsillo-genous car-dio-pathy	mitral valve prolapse	vegetative cardio-vascu-lar dystony	myocardial dys-trophy	in all
I	22	3	-	15	-	65	-	105
II	-	2	10	-	-	-	-	12
III	-	-	3	-	-	-	-	3
IV	2	17	8	-	-	-	7	34
V	-	22	30	10	1	2	40	105
VI	-	2	3	-	-	-	-	5
VII	-	3	5	-	-	-	-	8
VIII	-	4	6	-	-	-	-	10

N3 (Table No 3)

Correlation indices of ECG in 12 usual and 3 NeHb recordings (D.A.I.)

```
      Δ1←EK2[1;;12]
      Δ2←EK2[1;;13 14 15]
      0 CORO ΔMATR
>Δ1
>Δ2   Δ1[;I]    Δ2[;J]    N       R    [   R1    ;   R2    ]     T
>∇          1         1  225    .357 [  .279  ;  .429 ]   5.714
            1         2  222    .347 [  .268  ;  .420 ]   5.499
            1         3  223    .395 [  .319  ;  .465 ]   6.406
            2         1  207    .639 [  .582  ;  .688 ]  11.927
            2         2  203    .551 [  .483  ;  .610 ]   9.377
            2         3  203    .581 [  .517  ;  .637 ]  10.143
            3         1  220    .376 [  .298  ;  .447 ]   6.004
            3         2  217    .295 [  .212  ;  .372 ]   4.529
            3         3  217    .361 [  .282  ;  .434 ]   5.692
            4         1  203    .106 [  .016  ;  .195 ]   1.521
            4         2  200   -.079 [ -.012  ;  .169 ]   1.123
            4         3  201   -.050 [ -.140  ;  .041 ]   -.704
            5         1  225    .384 [  .307  ;  .454 ]   6.216
            5         2  222    .256 [  .173  ;  .335 ]   3.943
            5         3  223    .512 [  .444  ;  .572 ]   8.873
            6         1  230    .459 [  .388  ;  .522 ]   7.808
            6         2  227    .301 [  .221  ;  .375 ]   4.745
            6         3  227    .572 [  .511  ;  .626 ]  10.492
            7         1  209    .459 [  .385  ;  .525 ]   7.452
            7         2  206    .328 [  .245  ;  .405 ]   4.969
            7         3  207    .419 [  .341  ;  .489 ]   6.622
            8         1  213    .592 [  .531  ;  .646 ]  10.704
            8         2  210    .590 [  .527  ;  .644 ]  10.553
            8         3  211    .335 [  .253  ;  .410 ]   5.146
            9         1  215    .623 [  .566  ;  .673 ]  11.662
            9         2  212    .542 [  .475  ;  .600 ]   9.358
            9         3  212    .448 [  .374  ;  .515 ]   7.280
           10         1  213    .705 [  .656  ;  .746 ]  14.461
           10         2  210    .622 [  .564  ;  .673 ]  11.491
           10         3  211    .491 [  .420  ;  .555 ]   8.175
           11         1  215    .697 [  .648  ;  .739 ]  14.232
           11         2  213    .553 [  .488  ;  .611 ]   9.668
           11         3  214    .444 [  .370  ;  .511 ]   7.233
           12         1  220    .688 [  .639  ;  .731 ]  14.046
           12         2  217    .476 [  .405  ;  .540 ]   7.963
           12         3  218    .572 [  .510  ;  .627 ]  10.279
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N4 (Table No 4)

Main indices of left ventricle systole phases during some inflammatory and noninflammatory diseases in childhood

Indices	age	norm	Rheumatoid arthritis		Tonsillo-genous car-diopathy	Nonrheuma-toid carditis	P_1	P_2	P_3	P_4
			articular form	articular-visceral form						
R-R	6-10 11-15	0.69±0.4 0.84±0.6	0.63±0.07 0.72±0.05	0.59±0.07 0.69±0.08	0.64±0.07 0.75±0.07	0.62±0.03 0.70±0.04	<reliable tendency	<0.05 <0.05	tendency tendency	tendency <0.05
Ac	6-10 11-15	0.060±0.001 0.062±0.0012	0.068±0.0008 0.074±0.0008	0.072±0.0008 0.080±0.0009	0.064±0.0007 0.073±0.0001	0.06±0.0008 0.07±0.0007	<0.05 <0.02	<0.01 <0.01	<0.05 <0.02	<0.05 <0.05
Uc	6-10 11-15	0.24±0.0009 0.028±0.0009	0.017±0.00062 0.020±0.0006	0.029±0.0007 0.034±0.0008	0.016±0.0008 0.022±0.0001	0.031±0.0004 0.032±0.0007	<0.05 <0.05	<0.05 <0.02	<0.05 tendency	<0.05 <0.05
T	6-10 11-15	0.081±0.0013 0.090±0.0014	0.090±0.0009 0.094±0.0009	0.103±0.0010 0.109±0.0011	0.086±0.001 0.097±0.001	0.096±0.001 0.107±0.001	<0.05 <0.05	<0.05 <0.02	tendency tendency	<0.05 <0.05
E0	6-10 11-15	0.140±0.004 0.246±0.005	0.225±0.004 0.248±0.004	0.270±0.006 0.272±0.006	0.21±0.004 0.22±0.004	0.254±0.007 0.260±0.008	<0.05 <reliable	<0.05 <0.02	tendency tendency	tendency <0.05
Sm	6-10 11-15	0.265±0.004 0.274±0.005	0.250±0.005 0.274±0.005	0.283±0.007 0.293±0.008	0.248±0.004 0.263±0.005	0.269±0.008 0.283±0.007	tendency <reliable	<0.05 <0.05	tendency <reliable	<reliable tendency
BCG	6-10 11-15	90.7±0.9 89.8±0.8	90.0±0.8 90.5±0.7	94.3±0.7 95.2±0.8	84.6±0.9 83.6±1.0	90.9±1.4 90.2±1.0	<reliable <reliable	<0.05 <0.02	<0.05 <0.05	<reliable <reliable
HNM	6-10 11-15	24.7±0.32 25.1±0.44	29.3±0.4 30.4±0.7	29.3±0.42 37.9±0.38	30.5±0.4 36.8±0.7	27.3±0.96 29.9±0.94	<0.01 <0.01	<0.02 <0.05	<0.01 0.02	<0.05 <0.05
MK	6-10 11-15	3.01±0.09 2.78±0.08	3.58±0.11 3.74±0.12	2.37±0.07 2.42±0.06	3.46±0.10 3.68±0.11	2.83±0.06 2.33.±0.08	0.01 0.001	<0.05 <0.05	<0.15 <0.001	<0.05 <0.05

(VCD) and rheumatoid arthritis were in the age of 6-15 years (Diagram No 1).

While clinical investigation a great attention was drawn to the study of anamnesis and complaints in detail.

Clinical symptomatology was more minutely studied by means of ECG and PhCG.

Electrocardiograph data of the experimental contingent were analyzed according to the nosologies. ECG was registered in main 12 and NeHb 3 recordings. Their quantitative and qualitative processing was performed.

Analysis of ECG data in control group has shown that they are variable according to the age. Duration of waves and intervals are shorter than in adults. More often were noted: a negative T wave, initial deformation of QRS complex (W and M types), negative biphasic or corrected R wave (the III recording), pointed R wave was observed in earlier age, deep Q wave (II-III recordings), etc. T wave and ST segment are very important. The existence of negative T waves (III, V1-V4 recordings) is characteristic for ECG in childhood. Besides, ST segment appears to be the most labile element on ECG. Its changes are considered together with the changes of T wave. In the norm ST segment does not completely coincide with isoelectric line. Its exact horizontal direction except the II recordings, its lifting or lowering in standard recordings over 1 mm and in thoracic recordings over 1,5-2 mm, as well as changes in its forms should be supposed as its pathology. However, in case of high T wave lifting of ST segment by 2 mm and lowering of negative or biphasic T wave by 1,5 mm may be not supposed as pathology. So, the estimation of changes in ST segment and T wave is very important (Table No 1, Diagram No 2).

In the experimental contingent changes obtained in result of electrocardiographic investigation were classified as the following: normal, moderate, pronounced, strongly pronounced and unclear. Changes were within the limits of the norm only in a part of the patients, particularly, during articular form of rheumatoid arthritis (11%), tonsillogenous cardiopathy (15%), mitral valve prolapse (20%) and vegetative-cardiovascular dystony (40%). In other cases changes were deviated from the norm.

Moderately expressed changes were observed during articular form of rheumatoid arthritis in 33% of patients, articular-visceral form - in 41%, nonrheumatoid carditis - in 15%, tonsillogenous cardiopathy - in 18%, mitral valve prolapse - in 10%, vegetative-cardiovascular dystony - in 12%. The highest percentage was found in case of myocardial dystrophy (48%).

Pronounced changes were noted during articular form of rheumatoid arthritis in 3% of the patients, articular-visceral form - in 27%, nonrheumatoid carditis - in 65%, tonsillogenous cardiopathy and myocardial dystrophy - in 10% and 47%, correspondingly. During mitral valve prolapse and vegetative-cardiovascular dystony analogous changes have an episodic character.

Strongly pronounced changes were observed only during articular-visceral form of rheumatoid arthritis (14%) and nonrheumatoid carditis (15%). In other cases changes had a unclear character.

Our attention was paid to the changes in ST segment and T wave. During articular form of rheumatoid arthritis T wave amplitude change in the thorax were noted in 3 cases, during articular-visceral form - in 38 cases, during myocardial dystrophy - in 47 cases. Changes in T wave were more often noted during carditis (85 cases). Analogous changes were rarely observed during tonsillogenous cardiopathy and vegetative-cardiovascular dystony

Changes in ST segment were more often noted during nonrheumatoid carditis (65 cases), articular form of rheumatoid arthritis (50 cases) and myocardial dystrophy (47 cases), while during tonsillogenous cardiopathy changes were noted only in 10 cases.

In order to carry on an analysis, it is necessary to consider morphological changes in ST segment and T waver in

common context. These changes are of different types, particularly: the I type was more often observed during vegetative-cardiovascular dystony (65 cases), relatively less - during articular form of rheumatoid arthritis (22 cases) and tonsillogenous cardiopathy (15 cases). The II type was pronounced during nonrheumatoid carditis (10 cases) and articular-visceral form of rheumatoid arthritis. The III type was noted only at nonrheumatoid carditis. The IV type was more often found during articular-visceral form of rheumatoid arthritis (17 cases), relatively less it was found during nonrheumatoid carditis and myocardial dystrophy. (Table No 2, Diagram No 3).

In the experimental contingent changes of the V type were more often observed. These changes were found everywhere except articular form of rheumatoid arthritis, particularly during articular visceral form they were met in 22 cases, nonrheumatoid carditis - in 30 cases, the frequency of these changes was much lower (10 cases) during tonsillogenous cardiopathy, while during myocardial dystrophy it was the highest (40 cases).

In the experimental contingent the VI-VII and VIII types were less presented, mainly it concerned with articular-visceral form of rheumatoid arthritis and nonrheumatoid carditis.

During above-mentioned heart diseases, morphological parameters of ST segment and T wave are characterized by strongly pronounced changes and after the determination of their types it is necessary to find some more information about coronary blood circulation.

Correlation of St segment with ST in standard 12 and NeHb 3 recordings (D, A, I) was very important and varied (it varies within the limits of 9-14). Correlation indices (especially high they were in V5-V6) and correspondingly in dorsal (D) recording of NeHb (>14). In V4 this index was high in arterior of NeHb (11,491), while in inferior of NeHb the index of correlation was comparatively high in AVF recording (10,492) (Table No 3).

Thus, it should be noted that recordings of NeHb give an important information in childhood and they should play an important role in the cardiology of children.

As to results of phonocardiographic investigation, different data were obtained according to the nosologies.

Analysis of results of contractility function of the myocardium has shown (Table No 4) that phasic structure of ventricular systole undergoes dramatic changes, in particular: prolongation of tension period (at the expense of both asynchronous and isometric contractions) prolongation of expulsion period of mechanical systole. Mentioned changes were more strongly pronounced during articular-visceral form of rheumatoid arthritis. The prolongation of isometric tension points to decrease of inotropic function of heart contractile elements and the prolongation of electric systole, decrease of mechanical coefficient, energodynamic insufficiency of the myocardium. These data corroborate the existence of heart hyperfunction. Simultaneously the intensification of contractile process a synthesis of cycles increases, there takes place an expressed mobilization of the energy, what is followed by the exhaustion of power resources of the myocardium. Phasic shifts were more expressed in age group of 6-10 years, what points that functional state of the myocardium in the younger children group is unreliable and requires to carry on preventive measures in order to avoid changes of myocardial dystrophy.

Study of types of central hemodynamics has shown (Table No 5) that these changes have a compensatory-adaptive character and are directed to active blood supply of the CNS (recovery of neuron trophicity), on the one hand, and on the other hand, to the overcoming of cardiovascular resistance with the aim of provision of enough blood flow in the tissues. The type of hemodynamics in a definite way determines a clinical-anatomical form of process course.

Hemodynamics of eukinetic type was more often observed during vegetative-vascular dystony and myocardial dystrophy (>60,0) and more rarely - during articular form of rheumatoid arthritis. Hemodynamics of hyperkinetic type was more expressed during articular form of rheumatoid arthritis (80,0) and tonsillogenous cardiopathy and least expressed - in case of nonrheumatoid carditis. Hypokinetic type was more often noted during articular-visceral form of rheumatoid arthritis (91,7) and nonrheumatoid carditis (64,8).

As it appeared during both hypokinetic and hyperkinetic types of hemodynamics there takes place a reliable increase of common and specific resistance. In this period the heart functionates in the regime of hypercompensation. During articular form of rheumatoid arthritis, tonsillogenous cardiopathy and vegetative-cardiovascular dystony, this hypercompensation appeares to be enough for the provision of blood flow in tissues and organs, while during articular-visceral form of rheumatoid arthritis, myocardial dystrophy and nonrheumatoid carditis there takes place an insufficiency of contractile and pump functions of left ventricle.

At present the existing data of capillaroscopy and cardiointervalography cannot give a complete idea during what diseases takes place an involvement of this or that link of microcirculation net in pathological process, what is a diagnostic value of these changes and what influence has dysfunction of vegetative nervous system on them. Vegetative-vascular dysfunction appears to be a risk-factor for cardiac ischemic disease and hypertonic disease. But it should not be important only for adult age. Dysfunction of vegetative nervous system associates with the metabolism of lipids and disorders of transport. There are data that vegetative nervous system plays an important role in the regulation of processes of hemocoagulation and fibrinolysis. So, discussion of

N5 (Table No 5)

Distribution of the types of central hemodynamics during some inflammatory and noninflammatory diseases

Types	Rheumatoid arthritis		Tonsillogenous cardiopathy	Nonrheumatoid arthritis	vegetative cardio-vascular dystony	Myocardial dystrophy
	articular form	articular-visceral form				
Eukinetic	5.0	8.3	10.0	23.5	63.6	60.6
Hyperkinetic	80.0	--	74.0	11.7	27.2	30.4
Hypokinetic	15.0	91.7	16	64.8	9.2	9

N6 (Table No 6)

Percentage indices of initial tone of vegetative nervous system and versions of reactivity combinations during studied diseases

Versions of initial tone of vegetative nervous system and reactivity, %		Rheumatoid arthritis		Vegetative-cardiovas-cular dystony	Non-rheumatoid cardiris	Myo-car-dial dys-tro-phy	Mitral valve prolapse	Tonsillo-genous carditis	Conge-nital heart di-sease	An average arithmetical of percentage indices, M
		articular form	articular-visceral form							
		N =83	N =32	N =85	N =71	N =80	N =96	N=125	N =60	
1	E+N	-	-	7	-	2	25.5	10	-	5.6
2	E+H	5	6	10	6.5	7	6	9.5	9.5	8.1
3	E+A	4	-	8	1.5	1	20.5	12.5	4	6.4
4	S+N	7.5	9	11	8	11	8	10	11	9.4
5	S+H	30.5	35	22	33.5	27.5	1	3	24.5	22.1
6	S+A	25	28	15	26.5	24.5	1	3	23.0	18.3
7	V+N	-	-	5	-	3	13	20	-	5.1
8	V+H	18	22	12	22	19	6	10	21	16.3
9	V+A	10	-	11	2	5	19	22	7	9.5

capillaroscopy data together with cardiointervalography may give more complete picture of pre- and postcapillary system.

According to the nosologies, capillaroscopy changes were heterogeneous. During rheumatoid arthritis, especially at articular-visceral form the changes had an important character. Because of the aggregation of erythrocytes blood circulation was very slow, interrupted, a main background was dim and turbid, capillary had changed forms (curve, roller-like). The amount was 2-3 in visual area, arteriole-venular links changed, manifested in the spasm of arterioles (1,0-1,5 mkm) and dilatation (6,7-7,0 mkm) of venules. The tendency to the disappeasrance of functional capillaries (1-2 in visual area). The changes were more pronounced in 1-6 years old patients (slow blood flow, a sharp reduction of functional capillaries, spastic-atonic state) as compared to 6-16 years old children.

Also, during nonrheumatoid carditis the amount of capillaries decreased (3-4 in the visual area). A main background had cyanotic tint, transparency decreased, in arterial part of capillaries a spasm was noted, while in venous part – a dilatation. Capillaries were arranged unsystematically and had a curved form.

During congenital heart disease, besides the reduction of capillaries'amount, an attention was drawn to decrease of transparency, cyanotic background, a great amount of capillary loops and anastomosis.

During myocardial dystrophy, tonsillogenous cardiopathy and vegetative cardiovascular dystony a capillaroscopy background is rose-colored, the amount of capillaries increases, the arrangement is regulated, blood flow is homogeneous. In case of vegetative cardiovascular dystony, heterogeneity of capillaries' diameter, winding, abundance of loops and anastomosis have drawn an attention. During myocardial dystrophy a negligible slowing of blood flow was observed.

During mitral valve prolapse a diameter of capillaries in venous part was widened several times, in other cases capillaroscopy picture corresponded to the norm.

On the basis of cardiointervalography significant differences were revealed in experimental and control groups. In control group vagotonia was observed in 25%, eutonia - in 68,5%, while sympathicotonia - only in 6,5%. In experimental group vagotonia was less expressed during nonrheumatoid carditis (22,5%), while it was more expressed in case of mitral valve prolapse (26,5%). Indices of other nosologies varied between them.

The index of eutonia was comparatively lower during articular-visceral form of rheumatoid arthritis (30%) and very high - in case of mitral valve prolapse. During other nosologies the index varied within this interval.

Sympathicotonia (S) was least expressed during mitral valve prolapse (7%) and the highest - during articular-visceral form of rheumatoid arthritis (46%).

In the experimental contingent the most important and reliable indices ($P<0,001$) of the association of vegetative nervous system and an initial tone were observed in all children under the examination (initial sympathicotonia) except the cases of mitral valve prolapse and tonsillogenous cardiopathy.

A significant difference was also observed during clinoorthostatic tests. Normal vegetative reactivity was revealed in 72,5% of children in control group. In experimental group according to the nosologies, it has been shown that the index is comparatively close to the norm only in cases of mitral valve prolapse and tonsillogenous cardiopathy (70,8% and 66%, correspondingly). In case of other diseases the index of normal vegetative reactivity was below the control.

In control group hypersympathicotonic reactivity was revealed in 10,5% of the patients, articular-visceral form of rheumatoid arthritis - in 55%. The lowest index was noted in cases of mitral valve prolapse (12%) and tonsillogenous cardiopathy (17%).

The index of asymathicotonic (A) reactivity was 17% in control group. During nonrheumatoid carditis it was 20%. The lowest indices were in cases of tonsillogenous cardiopathy and congenital heart disease (17% and 16,5%, correspondingly).

During clinoorthostatic tests results of study of vegetative reactivity using cardiointervalography have shown that during investigated diseases normal vegetative reactivity significantly decreased ($P<0,001$), while hypersympathicotonic (H) reactivity - significantly increased. It was more expressed during rheumatoid arthritis, nonrheumatoid

carditis and congenital heart disease, relatively less - in cases of vegetative-cardiovascular dystony and myocardial dystrophy.

The analysis of intercombinations of types of vegetative reactivity and initial tone of vegetative nervous system has shown that during rheumatoid arthritis, nonrheumtoid carditis and myocardial dystrophy the frequency of sympathicotonia+hypersympathicotonia and sympathicotonia+asympathicotonia versions (22,1% and 18,3%) is comparatively higher, while during mitral valve prolapse and tonsillogenous cardiopathy - much low (Table No 6, Diagram No 4).

In cases of above-mentioned diseases high indices of given versions probably appear to be a risk-factor of cardiac ischemic disease, what in dynamics needs a special examination.

It is known that during diseases of cardiovascular system an immune system is actively involved in the process. On the one hand, during these diseases autoantigenes are produced and, on the other hand, anti-inflammatory preparations used in the treatment have an influence on the immune system. Because of it at present the usage of immunocorrectors in the treatment and prevention of diseases of cardiovascular system appears to be very urgent. But in case of the usage of immunotropic substance in the clinics it is necessary to study its activity, pharmacological action, optimal dose, etc. With this aim, GA-40 preparation was studied in the experiments in rabbits. Results of ECG and PhCG investigations have shown that after the injection of 50-fold dose of GA-40 during 14 days, the dynamics of phasic structure of heart contractility do not change and all indices vary within the limits of initial level. This allows to conclude that in result of GA-40 preparation action, the functioning of cardiovascular system of these animals is stable.

Besides above-mentioned, injection of different doses of GA-40 (1 ml/kg and 5 ml/kg) on cardiomyocytes of experimental animals has shown that this preparation in dose of 1 ml/kg has an immunomodulator effect. In cardiomyocytes of animals an activation of metabolic processes takes place both in cellular nucleus and the cytoplasm. In addition, a positive effect on the endothelium of capillaries was also noted in the aspect of structural organization. So, experiments in rabbits have corroborated a positive immunomodulating effect of GA-40 on cardiomyocytes as well as on the endothelium of capillaries.

Effect of GA-40 on cardiovascular system in the experiment allows us to suppose that this preparation may be used in the treatment and prevention of cardiovascular diseases.

It should be noted that a professional estimation of pre- and postcapillary system plays an important role in the diagnostics of acquired noninflammatory diseases of blood circulation organs (vegetative cardiovascular dystony, myocardial dystony, etc.) in children and adults.

Vegetative cardiovascular dystony, myocardial dystrophy, cardiopathy, nonrheumatoid carditis - these are diseases, which require a timely diagnostics, treatment and prophylaxis in childhood in order to avoid complications and difficulties in future.

It is well-known that at present such diseases as atherosclerosis, cardiosclerosis, cardiac ischemic disease, myocardial infarction, etc. are very rare. But probably it is necessary and timely to pay attention to children of that risk-groups (risk groups of atherosclerosis, cardiac ischemic disease, myocardial infarction), which require dispensary and corresponding prophylaxis. **Proceeding from above-said and according to thorough analysis of data of some authors (G. Chakhunashvili, K. Chakhunashvili, N. Uberi, P. Kherkheulidze, N Jobava) it should be outlined 5 stages of prophylaxis of atherosclerosis and cardiac ischemic disease:**

I stage - manifestation of risk-factors: anamnesis, anthropometry, measuring of arterial pressure, estimation of nutrition regime, investigation of emotional tone. It is important to note about children prematurity (if it is possible) and its character, suffered diseases in childhood (nonrheumatoid carditis, rheumatoid arthritis, myocardial dystrophy, cardiopathy, vegetative cardiovascular dystony, mitral valve prolapse, congenital heart disease (it should be mentioned if a patient was subjected to the surgery and when), tonsillogenous cardiopathy, etc. - is performed by a district pediatrician and school physician.

II stage - complex estimation of vegetative nervous system - reactivity, maintenance of vegetative action (methods, cardiointervalography, clinoorthostatic tests), determination of cholesterol and triglyceride levels in blood plasma by means of determination of different changes of ST segment and T wave (of course, taking into account age peculiarities) - is performed by a district pediatrician, cardiorheumatologist or cardiologist.

III stage - in the conditions of hospital a deep, complex clinical-instrumental investigation of cardiovascular system by means of cholesterol distribution in lipoprotein fractions, investigation of hemostasis and fibrinolysis system. Indications for the study of this stage appear to be a content of cholesterol level above 4,4 mmol/l, triglycerides - above 0,79 mmol/l, vegetative cardiovascular dystony and different versions of clinoorthostatic tests, taking into account form of ST segment, its J error and by determination of T wave height and depth (is performed by children cardiologists).

IV stage - a rational nutrition dietary regime, timely health-resort seasonal treatment together with rehabilitation measures (if the latter is necessary), immunorehabilitation of children in risk-groups, etc.

V stage - to outline and perform preventive measures together with governmental and NGO (centers, associations, etc.) - is carried on by leading clinics using the programs of disease diagnostics, planned by scientific-analytical group.

Thus, only rationally organised, individual prophylactic measures commenced at the earlier stage are able to move the development of cardiac ischemic disease to relatively distant age group.

CONCLUSIONS

1. In childhood a function of contractility of the myocardium during nonrhematoid carditis, tonsillogenous cardiopathy, articular and articular-visceral forms of rhematoid arthritis, mitral valve prolapse, vegetative-cardiovascular dystonia, congenital heart diseases and myocardial dystrophy, as well as central and peripheral hemodynamics together with the data of capillaroscopy and cardiointervalography differs by the frequency and degree of disturbance.

2. Data of ST segment and T wave in healthy children are characterized by age peculiarities.

3. In childhood it is possible to determine depression of T wave:

- in the I standard recording (except one month age);
- in the II standard recording (in all age groups);
- in AVF recording (age - 0-3 years);
- in V4 recording (in 6-16 years age group);
- in V5-V6 recordingas (in all age groups). The latter appears to be leading diagnostic criteria in the cardiology of premature and new-borns. They are important both for the treatment of diseases and estimation and prognosis of the dynamics and what is especially significant, in the period of rehabilitation in order to prevent diseases of cardiovascular system.

4. Error of ST segment above isoelectric line in healthy children is observed in all age groups, but it does not exceed 1 mm, while below isoelectric line, except V5-V6 recordings, a maximal depth is about 1 mm.

5. Morphological changes in ST segment and T wave should be considered by determination of one of the 8 types worked out in common context both in healthy and ill children.

6. Changes in ST segment and T wave in different age groups in childhood require an individual approach that should remain as bearing a profound clinical information from childhood up to old age.

7. Recordings of NeHb give an important information both for healthy and ill children and they will play a significant role in the development of children cardiology both at therapeutic and rehabilitation and preventive stages of these diseases in spite of their age.

8. During vegetative-cardiovascular dystony, tonsillogenous cardiopathy and articular form of rheumatoid arthritis there takes place heart activities in the conditions of hypercompensation which is enough for provision of blood flow in tissues and organs, while during articular-visceral form of rheumatoid arthritis, myocardial dystrophy and nonrheumatoid carditis there takes place insufficiency of contractile and pump functions of the left ventricle.

9. Investigation of heart contractile function in different age groups has shown that in 0-3 years old children the reason of disorder of this function may be coronary insufficiency, while in 6 years old children and above just coronary insufficiency may condition negative phasic shifts of functional state of the myocardium.

10. During investigated nosologies normal vegetative reactivity considerably decreases, while hypersympathicotonic reactivity sharply increases. It is more expressed in cases of rheumatoid arthritis, nonrheumatoid carditis and congenital heart disease, while in cases of vegetative-cardiovascular dystonia and myocardial dystrophy it is less pronounced.

11. Sympathicotonia of initial tone of vegetative nervous system and hypersympathicotonia of vegetative reactivity and their existence in intercombination by ≈22% during vegetative-cardiovascular dystonia, suffered nonrheumatoid carditis and different forms of rheumatoid arthritis may be risk-factors of cardiac ischemic disease. As to myocardial dystrophy and mitral valve prolapse in future they require multiple observation and analysis.

12. Usage of 50-fold doses of GA-40 preparation in the experiment has no negative action on the state and functioning of cardiovascular system.

13. Injection of GA-40 preparation in the dose of 1 ml/kg per animal weight gives an immunomodulating effect. Changes are mainly observed in nuclear structures of cardiomyocytes. Changes in cardiomyocytes are also noted in the endothelium of capillaries of this group. The intensity is the same as in case of cardiomyocytes.

14. Action of GA-40 preparation on cardiovascular system in the experiment (ECG, phonocardiography, rheology) and its morphological characterization in the rabbits allows us to use the preperation in the clinics in future.

PRACTICAL RECOMMENDATIONS

1. A complex of elaborated clinical and instrumental diagnostic criteria together with new therapeutic drugs may be used in treatment of nonrheumatoid carditis, rheumatoid arthritis, vegetative-cardiovascular dystonia, congenital heart disease, tonsillogenous cardiopathies, myocardial dystrophies and mitral valve prolapse in patients in order to carry on a well-grounded rational therapy and prevention of cardiovascular system complications

2. On the basis of experimental data it is expedient to continue the further study of GA-40 preparation in the clinics as it is a presumable possibility of its usage in the complex treatment of cardiovascular system.

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ORIGINAL ARTICLES AND SCIENTIFIC ACTIVITIES IN PEDIATRICS

UPDATE RESEARCH OF KAWASAKI DISEASE

FUYONG JIAO,
The Center for Kawasaki Disease of Shaanxi province
Shaanxi provincial people's hospital

YAO JING XIAN,
Medical College Master of Clinical Medicine

WEI YU XI'AN,
Medical College Clinical Medicine (Pediatrics) Class 1401

Corresponding Author : **FUYONG JIAO**
E-mail: 3105089948@qq.com

ABSTRACT:

Kawasaki disease is an acute, self-limited vasculitis of unknown etiology, which mainly occurs in infants and children. The target organs of Kawasaki disease are coronary arteries and other cardiovascular structures. The initial manifestations of Kawasaki disease are high fever, inflammation of skin and mucosa, and enlargement of cervical lymph nodes. About 25% of children who are not treated with intravenous immunoglobulin during the acute phase of the disease will develop coronary artery aneurysms. Nowadays, Kawasaki disease has replaced rheumatic fever as the main cause of acquired heart disease in children in developed countries. However, there is still no specific diagnostic test, echocardiography is still the main diagnostic method of coronary artery involvement in children with Kawasaki disease, and risk stratification assessment is carried out according to Z value to assist in the short-term and long-term diagnosis and treatment of Kawasaki disease. In the aspect of treatment, there are reports on the application of corticosteroids, infliximab, cyclosporine, methotrexate, interleukin receptor blockers and so on.

1. EPIDEMIOLOGY

Kawasaki disease was first reported and named after Fuzuo Kawasaki in 1967. Kawasaki disease is more common in children, 80% of the age is less than five years old, and there are also teenagers. The young age of onset indicates that the susceptibility may be related to the maturity of the immune system [1]. Now we have some knowledge and understanding of Kawasaki disease, and its incidence varies greatly in different populations. Japan has the highest incidence rate, and the number of cases continues to rise. According to the survey, the incidence rate has reached 264.8 per 100000 children (< 5 years old) [2]. South Korea is also increasing year by year, according to a retrospective epidemiological survey, the incidence rate has reached 217.2 per 100000 children (< 5 years old) [3]. In China, the incidence rate of a 10-year survey in Beijing has reached 55.1 per 100000 children (< 5 years old); the result of a five-year survey in Shanghai is 46.3; in a recent survey in Taiwan, the incidence rate is 82.8 per 100000 children (< 5 years old), ranking third in the world [4] [5] [6]. The United States passive Monitoring and Analysis Management Database shows that the incidence rate is 19 per 100000 children (< 5 years old) and 24.7 per 100000 children (< 5 years old) in California [7]. Among American children in Hawaii and California, the high incidence of children of Asian and Pacific island descent suggests that there may be an important gene contributing to their susceptibility (incidence rates are 210,50.4 per 100000 children (< 5 years old) respectively) [8] [9]. A genome-related study in Japan also shows that susceptibility to Kawasaki disease may be related to genes [10]. In France, it is 7 per 100000 children (< 5 years old), while in Japan it is 30 times that of France. And Kawasaki disease has obvious seasonality in the northern hemisphere [11].

When people with genetic susceptibility to Kawasaki disease are exposed to an environment where Kawasaki disease triggers may be widely distributed, they cause an immune response if they enter the upper respiratory tract [12]. Some genetically susceptible children will have irreversible coronary artery wall damage. Available records can indicate the accumulation of cases in time and space, but there is still no evidence of human-to-human transmission [13]. It is assumed that potential cases can occur under the following two triggers: 1) replication of infectious pathogens in mucosal epithelial cells of the upper respiratory tract; and 2) widespread distribution of antigens in the environment. Recently, some data support the interesting hypothesis that the triggers of Kawasaki disease are carried by large-scale convective air. Moreover, the seasonal clusters and annual epidemics of Kawasaki disease cases in Japan, Hawaii and southern California are in the north-eastern provinces of China [1].

2. PATHOLOGY

Among the pathological changes caused by Kawasaki disease, the most

common is to affect the coronary artery, followed by other substantive muscular arteries. A comprehensive review of 32 cases of Kawasaki autopsy and 8 cases of heart transplantation described three points related to the progression of vascular lesions in the arterial wall: necrotizing arteritis, subacute / chronic vasculitis and myofibroblast hyperplasia [14].

1) Acute arteritis is characterized by neutrophil infiltration from the vascular lumen and is associated with extensive necrosis of the vascular walls of coronary arteries and other medium-sized arteries [15]. Neutrophil elastase may also cause some damage to the internal and external elastic membrane of the vascular wall, leading to the formation of aneurysms. Neutrophil elastase inhibitors have been used to block this pathway in Japan [16].

2) subacute vasculitis begins a few weeks after fever, or months and years later, and is closely related to the proliferation of myofibroblasts in the third process [13]. Inflammatory cells mainly infiltrate the lymphatic system and adventitia, and the involvement of CD8+ cytotoxic T lymphocytes has been confirmed, suggesting that anti-T cell therapy may be effective, such as calcineurin inhibitors cyclosporine and tacrolimus [17] [18] [19].

3) the proliferation of myofibroblasts may be the pathological process of myofibroblasts derived from smooth muscle cells mediated by transforming growth factor-β [20] [21]. The polymorphism of transforming growth factor pathway is associated with increased susceptibility to aneurysm inflammation in patients with Kawasaki disease [22]. Myofibroblast proliferation can lead to lumen stenosis and myocardial ischemia. A prominent histological feature of late aneurysms is that layered thrombus is commonly found in calcification-related aneurysms, which can be detected by computed tomography ((CT)) [23]. It should be noted that because the histological description of Kawasaki disease is mainly based on autopsy of individuals with vasculitis complications, it is characterized by severe cardiovascular pathological changes. These data can be used to judge the condition of patients with potential risk of cardiovascular complications.

3. DIAGNOSIS

At present, there is no specific diagnosis of Kawasaki disease. The diagnosis is now based on clinical standards developed by the Japanese Ministry of Health and adopted by the American Heart Association, alongside non-specific laboratory tests that support the diagnosis. Timely diagnosis and treatment is very important, which largely depends on careful medical history collection and thorough physical examination.

3.1 CLINICAL MANIFESTATIONS

The common clinical features of Kawasaki disease are as follows: fever for five days or more, conjunctival congestion in both eyes, red lips, red bayberry tongue, diffuse hyperemia in oral and pharyngeal mucosa, pleomorphic erythema and rash, hard edema of hands and feet, erythema of metatarsus and toes, and membranous peeling at the skin migration of nail bed at fingertip (convalescent stage). Non-suppurative cervical lymph node enlargement was found in the acute stage, often unilateral and > 1.5cm in diameter. [24]

3.1.1 TYPICAL KAWASAKI DISEASE

The diagnosis of classical Kawasaki disease is based on fever for more than 5 days and the presence of 4 or more clinical features [24]. Experienced clinicians may make a diagnosis in rare cases where the hands and feet are red and swollen, and the diagnosis takes only 4 days of fever. Fever usually dissipates within 36 hours after the completion of IVIG infusion. If not, the patient is considered to be resistant to IVIG and needs further treatment. In addition, fever that dissipates spontaneously after 7 days cannot be considered evidence that the diagnosis of Kawasaki disease has been excluded. Kawasaki disease should be considered in infants with long-term fever with unexplained aseptic meningitis or culture-negative shock and ineffective antibiotic treatment of cervical lymphadenitis.[25]

These typical clinical features do not necessarily appear at the same time, and often can not be found early in the process of diagnosis, and some clinical features may be weakened with the delay of time, so it is necessary for clinicians to carefully examine the symptoms and signs of children in order to make an early diagnosis and prevent delays in the disease.

3.1.2 INCOMPLETE KAWASAKI DISEASE

For incomplete (atypical) Kawasaki disease, infants or children with long-term fever of unknown causes and children with less than 4 main clinical features need to consider its possibility, if there are relevant laboratory tests and echocardiography, it can be diagnosed as incomplete Kawasaki disease [25]. Although the Z score of left anterior descending branch or right coronary artery branch is not sensitive, it has high specificity for diagnosis [26] [27].

3.2 LABORATORY INSPECTION

(1) the laboratory indicators in the acute and subacute stages of Kawasaki disease have been summarized in the process of continuous accumulation, including the following:

1) the acute phase of Kawasaki disease is characterized by an increase in immature and mature granulocytes, positive cell euchromic anemia, and high protein in the acute phase. 2) Thrombocytopenia may occur in the process of intravascular thrombosis and degradation, which is characterized by a significant increase in the level of D-dimer. 3) Thrombocytopenia may occur in the subacute stage of Kawasaki disease. 4) about 35% of the patients had mild to moderate increase in serum transaminase or γ-glutamyl transpeptidase activity. 5) about 10% of patients have mild hyperbilirubinemia. 6) hypoproteinemia may occur in patients, which is also a serious acute manifestation of correlation. 7) up to 80% of children's urine tests showed the presence of sterile pyuria [28]. 8) some patients may have elevated N-terminal B-type brain natriuretic peptide (NT-BNP), but this only indicates cardiac involvement and does not fully diagnose Kawasaki disease, and its meaningful numerical increment has not been determined [24].

3.3 ECHOCARDIOGRAPHY:

Echocardiography is the main cardiac imaging in acute phase. In North America, echocardiographic measurements of the internal diameter of the proximal coronary artery segment corrected based on body surface area have been standardized [29]. The American Heart Association classifies as: small aneurysms $2.5 \leq Z < 5$; moderate aneurysms $5 \leq Z < 10$; giant aneurysms $Z \geq$ or inner di-

ameter > 8 mm [30]. The Japanese standard is to define the size of an aneurysm according to the size of the lumen: small aneurysms ≤ 4 mm, medium aneurysms > 4 mm and ≤ 8 mm, and giant aneurysms > 8 mm. In children ≥ 5 years old, the size of aneurysms can also be classified by the ratio of their internal diameter to adjacent segments: 1.5 times for small aneurysms, 1.5 times to 4 times for moderate aneurysms, and more than 4 times for giant aneurysms [31] [32].

3.4 DIFFERENTIAL DIAGNOSIS:

Because there are no specific diagnostic criteria, it needs to be distinguished from other diseases with similar clinical manifestations, including EB virus, adenovirus, echo virus, measles, toxic shock syndrome, scarlet fever, idiopathic juvenile arthritis, nodular polyarteritis, Rocky Mountain spotted fever leptospirosis, adolescent mercury poisoning and adverse drug reactions, Stephens-Johnson syndrome, etc. [33] [34] [35].

4. STAGES OF CLINICAL COURSE OF DISEASE

The clinical process of Kawasaki disease is divided into four stages:

(1) Acute phase: this stage will last for 1-2 weeks without treatment. Children usually present with relaxation fever, which can reach as high as 40 ℃ at the peak of the disease, and show some major symptoms such as cardiac changes, including valvulitis, pericarditis and myocarditis. (2) subacute stage: this stage is about 2 weeks. As the fever recedes, the child is at high risk of sudden death from myocardial infarction.

(3)in the recovery stage, the clinical symptoms basically disappeared and the level of serum reactants returned to normal in the acute stage.

(4) chronic phase: mainly patients with coronary artery involvement who need follow-up treatment. Therefore, we should make diagnosis and timely treatment in the acute phase as soon as possible to reduce inflammation and reduce the risk of coronary artery involvement in the later stage of the disease.

5. EVALUATION OF ACUTE KAWASAKI DISEASE

Clinical laboratory examination can support clinicians' suspicion of Kawasaki disease, but it needs to be combined with symptoms and auxiliary examinations to assist in differential diagnosis and assess the intensity of inflammation. There are no systematic and accurate diagnostic methods for both clinical standards and laboratory characteristics, and clinical standards depend on nonspecific symptoms that may not occur, but can be present in many other vasculitis toxin-mediated diseases [33], as mentioned above. It is not possible to rely solely on clinical criteria, because the characteristics of Kawasaki disease do not necessarily occur at the same time. The main clinical manifestations may be accompanied by a variety of symptoms of febrile vasculitis, including arthritis, gastrointestinal discomfort, fatigue and other systematic clinical manifestations, all of which may lead to misdiagnosis and delay treatment [24] [36]. Especially in infants under 6 months of age, clinical symptoms may only find high fever of unknown causes, and most of them are irritable or sleepy [1]. Easily misdiagnosed as upper respiratory tract infection, acute conjunctivitis, skin allergy, lymphadenitis. Other occasional features such as abnormally increased cells in pyuria and cerebrospinal fluid may indicate the presence of other infections that may delay diagnosis [37]. The diversity of symptoms makes it difficult for clinicians to make a diagnosis. It is necessary to consider the delay of Kawasaki disease in any case and other fever of unknown causes. This also hinders the diagnosis of incomplete Kawasaki disease, which is an important part of patients with Kawasaki disease.

Children less than 1 year old and children over 5 years old are more likely to develop incomplete Kawasaki disease [38] [39]. These patients account for about 25% [40] of Kawasaki disease, and may delay treatment due to a high misdiagnosis rate, resulting in an increased risk of coronary artery complications. A case-control study in Australia has shown that for children with potentially high cardiovascular risk, changes in aortic intima-media thickness are likely to be a sensitive indicator of cardiovascular risk after Kawasaki disease. however, it is not clear whether this change in mid-childhood indicates atherosclerotic burden or cardiovascular risk in adulthood [41].

5.1 CHANGES IN LABORATORY TESTS DURING THE ACUTE PHASE

Including neutropenia, euchromic anemia, and acute high protein, there are also changes in platelets, slightly higher activity of serum transaminase or γ-glutamyl transpeptidase, hypoproteinemia, aseptic pyuria, and so on.

5.2 ECHOCARDIOGRAPHY IS THE MAIN MANIFESTATION OF CARDIAC IMAGING IN ACUTE PHASE.

1) the Japanese standard defines the size of the aneurysm according to the size of the lumen, and it can also be classified by the ratio of the internal diameter to the adjacent segments. The American Heart Association's assessment of coronary artery abnormalities has been described earlier.

2) Echocardiography is an important auxiliary method in abnormal diagnosis. But normal echocardiography does not rule out Kawasaki disease. In addition, normal baseline echocardiography does not rule out the possibility of later development of coronary artery aneurysms in the first week of onset; therefore, echocardiography should be reexamined at 1-2 weeks and 4-6 weeks after treatment. Coronary artery z values > 2 at baseline or with high-risk clinical features (e.g. persistent fever, intravenous gamma globulin resistance) should be examined more frequently [1].

3) two-dimensional and M-mode echocardiography only showed temporary left ventricular dilatation, systolic dysfunction, pericardial effusion and valvular regurgitation (especially mitral regurgitation). Systolic dysfunction on the echocardiographic baseline is a risk factor for coronary artery aneurysms [42]. Kawasaki disease shock syndrome is rare in patients, and warm shock usually occurs with decreased peripheral vascular resistance [43], which can be confused with toxic shock syndrome or sepsis.

6. ACUTE PHASE MANAGEMENT

6.1 INITIAL TREATMENT

The purpose of acute treatment is to minimize systemic and cardiovascular inflammation in order to prevent cardiovascular sequelae. The main method is high-dose IVIG combined with aspirin,

fever within 10 days (early) C ball should reduce the incidence of coronary artery disease from 25% to 5% [44] [45].

Although the mechanism of Kawasaki disease is not fully understood, the efficacy of intravenous immunoglobulin (IVIG) as first-line treatment for acute Kawasaki disease has been verified in many prospective multicenter trials. Administration of IVIG within ten days after fever helps to reduce inflammation, but has little effect on preventing coronary artery damage. Aspirin is widely recognized as a therapeutic drug, but there is little evidence of its therapeutic benefits. A retrospective study in Canada showed that low-dose aspirin was no less effective in reducing the risk of coronary artery abnormalities than high-dose aspirin in the case of combined immunoglobulin injection [36]. However, the risk of high-dose aspirin administration, including aspirin toxicity, Wright's syndrome and conductive hearing loss, has led to adjustments in administration practices in some countries, including Japan, where the recommended acute dose has been reduced to 30-50mg/kg/d [46]. Timely treatment is the key to prevent the adverse outcome of coronary artery.

6.2 TREATMENT OF PATIENTS WITH IVIG RESISTANCE

(AHA) of the American Heart Association defines drug-resistant Kawasaki disease as "relapse or persistent fever at least 36 hours after the first injection of IVIG." [25] it is reported that if patients are treated in the first five days of fever, the rate of IVIG resistance is higher, although it is not clear whether early treatment will lead to a worse prognosis, or whether patients with Kawasaki disease have more severe symptoms on the fifth day [47]. Two kinds of IVIG action mechanisms have been established in patients' peripheral blood mononuclear cell related studies in vitro: the first is to stimulate myeloid dendritic cells to secrete IL-10, and make T cells differentiate into regulatory phenotypes through the constant region of immunoglobulin molecule Fc. The second mechanism is to present the treated Fc peptide to a subset of regulatory T cells to amplify and produce IL-10 [49]. Peptide mapping studies have identified the specific Fc region that mediates this amplification [50]. As the effect of gamma globulin on fever and the improvement of skin and mucosal symptoms is very rapid, other mechanisms such as anti-cytokines and anti-idiotypic antibodies, although lack of specific data, may also be important. Most patients with rapid improvement in clinical experience and infusion of gamma globulin will stop fever, but about 10% to 20% of patients will develop recurrent fever and require additional anti-inflammatory treatment [51]. The prognosis of IVIG resistance is poor because intractable fever indicates progressive arteritis, and these patients tend to have a higher risk of developing coronary artery aneurysms.

6.2.1 SECOND DOSE OF IMMUNOGLOBULIN

Many authorities recommend the use of a second dose of IVIG2g/kg for treatment. Repetitive IVIG has been shown to be safe and effective, but it has not been proved by sufficient randomized trials. There may be a theoretical advantage when using different IVIG products for initial treatment, as preparations from different donor pools may have different antibody sequences or different quantities and components, as well as other anti-inflammatory factors [52].

6.2.2 CORTICOSTEROIDS

The use of steroids in the treatment of Kawasaki disease has gone through a tortuous process, which is more reasonable and acceptable because of its wide availability and relatively low price. There is evidence that the use of steroids can improve inflammatory markers, disappear rapidly, and may reduce the incidence of CALS [52]. AHA suggests that a short course of high-dose steroids can be used as a reasonable change in the second intravenous gamma globulin, or as a reasonable treatment after two doses of IVIG are ineffective. AHA's alternative recommendation for drug-resistant KD is to start taking steroids in addition to a second dose of IVIG and aspirin [25]. However, there is no clear evidence of the optimal dose, formulation, duration and duration of corticosteroids. A recent randomized controlled trial in Japan found that prednisolone added to the standard IVIG regimen significantly reduced the incidence of undesirable coronary arteries, but these have not been found outside the Japanese population [53].

6.2.3 INFLIXIMAB

Infliximab in patients with IVIG resistance can solve fever and inflammatory markers more quickly, reduce hospitalization days, reduce medical costs, and have better tolerance. In the largest randomized trial of infliximab as an adjuvant primary therapy for IVIG, there was no evidence that infliximab reduced resistance to Kawasaki disease [54]. On the basis of retrospective data, AHA believes that infliximab can replace the second dose IVIG [25].

6.2.4 CYCLOSPORINE

The efficacy of cyclosporine has been shown in some cases, and studies have shown that targeting the calcium signaling pathway may prevent T cells from destroying the coronary artery wall [18] [19]. Small sample studies have shown that cyclosporine has few serious adverse events and is a good choice for patients with drug-resistant Kawasaki disease, but further research is needed [52].

6.2.5 METHOTREXATE

A retrospective study and evaluation of 10 years' data in South Korea showed that low-dose methotrexate was effective in the treatment of patients with IVIG resistance. The results showed that the clinical symptoms of the patients were improved, the fever disappeared rapidly, the reactants decreased in the acute phase, and no adverse reactions of methotrexate were observed [37]. Therefore, methotrexate may be a candidate treatment for patients with anti-IVIG resistance.

6.2.6 INTERLEUKIN RECEPTOR BLOCKERS

Data indicate that Atto vastatin inhibits the transformation of endothelial cells to mesenchymal cells in children with Kawasaki disease and coronary artery abnormalities in children) and promotes T cell regulation in an interleukin receptor blocker, anabhitin (an acute disease with abnormal coronary artery in infants and children), phase I/Ila trials investigate whether it is effective (pharmacokinetics / safety study in children with Kawasaki disease and coronary artery abnormalities). However, further clinical trials are needed to improve its therapeutic effects and methods.

6.2.7 CYCLOPHOSPHAMIDE

Cyclophosphamide, a cytotoxic drug, is often used in combination

with corticosteroids to treat other rare cases of refractory severe progressive aneurysms [56].

There are many reports on the use of other drugs, including other biological agents, cytotoxic agents, ulinastatin and plasma exchangers in drug-resistant Kawasaki disease [57]. In the case of severe inflammation, patients with giant aneurysms have a higher risk of coronary artery thrombosis. These drugs are used in refractory patients who fail to treat. However, further research and clinical practice are needed for the treatment of Kawasaki disease.

6.2.8 PERCUTANEOUS CORONARY INTERVENTION IN THE TREATMENT OF ANEURYSM

The treatment of aneurysms in the acute phase of Kawasaki disease is an uncertain area. If echocardiography shows coronary artery dilatation or aneurysm diagnosis, pediatric cardiologists should participate in patient care and develop individualized treatment plans. The existence of coronary artery dilatation requires the early participation of pediatric cardiologists, multiple echocardiographic monitoring of the coronary artery, and long-term routine stress and perfusion tests on the heart [58] [59].

In patients with high risk of ischemia, percutaneous coronary intervention is feasible. This includes intracoronary thrombolysis, balloon angioplasty, stent implantation and rotational grinding, and should be performed in patients with symptomatic ischemia, laboratory examinations showing ischemia, or patients with severe stenosis, and in patients with progressive coronary artery ischemia. If angiography detects severe occlusion or endangers collateral blood supply, coronary artery bypass surgery should be performed [57] [59].

7. LONG-TERM ASSESSMENT

AHA stratifies the risk of coronary artery disease according to the risk of coronary artery thrombosis or stenosis / occlusion associated with myocardial ischemia [25], which facilitates long-term prediction and individualized management of patients, including follow-up, diagnostic trials, assessment and management of cardiovascular risk factors, drug therapy, thrombosis prevention, physical activity and reproductive counseling. (1) Coronary artery lumen diameter measured by echocardiography, risk stratification was performed using Z value converted to body surface area correction (class II a, class B); (2) based on the most severe degree of coronary artery involvement and current coronary artery involvement (type II a, grade C). (3) in addition to coronary artery diameter, other clinical features that may increase the risk of long-term myocardial infarction (such as distal terminal aneurysm, number of aneurysms, number of affected coronary artery branches, irregular coronary artery lumen, irregular inner layer of coronary artery wall (calcification, wall fibrosis), coronary artery dysfunction (vasodilation damage, hemodynamic changes), lack of collateral circulation, insufficient blood supply. Premature angiogenesis, premature thrombus regeneration, premature myocardial infarction, ventricular dysfunction) were considered for risk stratification (class II a, class C). In general, the coronary artery lumen Z score is stable, the lumen is no longer enlarged. If the Z value of the patient is still increasing after the end of the recovery period, coronary artery changes should be evaluated and followed up.

8. CHRONIC PHASE MANAGEMENT

The purpose of chronic phase management is to prevent coronary artery occlusion and myocardial infarction by reducing platelet aggregation and inhibiting thrombosis.

Long-term treatment included antiplatelet aspirin dose of 3-5 mg / kg / day until normal echocardiography was displayed at 6-8 weeks [25]. If the abnormality of the coronary artery cannot be reversed during this period, long-term drug treatment and diagnostic follow-up are involved. Patients with coronary artery involvement need to take aspirin for a long time to fight platelets. In addition, systemic anticoagulation therapy with warfarin or low molecular weight heparin is used in patients with large or multiple large aneurysms. Low molecular weight heparin may be statistically beneficial to reduce coronary artery score and is unlikely to cause severe bleeding, which makes it a feasible choice for children with severe coronary artery involvement [60]. Children with Kawasaki disease and children with acute coronary artery disease should reduce exposure to atherosclerotic risk factors, including obesity, hyperlipidemia and smoking [61]. There is a delay in immunization in children treated with IVIG, as this treatment blocks the acquisition of active immunization by preventing the replication of live viral vaccines [62], so immunization should be postponed appropriately.

8. CLINICAL RESULTS

Possible results of Kawasaki disease include [62]:

(1) no cardiac sequelae;

(2) coronary artery abnormalities, of which about 60% are reversed within one year;

(3) cardiac involvement, including myocarditis, aneurysm thrombosis, cardiac rhythm disorders or myocardial infarction.

(4) recurrence of Kawasaki disease:

Before IVIG was found as a safe and effective treatment in 3% of patients, 20 to 30% of patients progressed to coronary artery dilatation, with a mortality rate of 2% [63] [64]. If IVIG was treated within 10 days of fever, only 3% of children had transient coronary artery relaxation and 1% developed giant aneurysms [65]. The risk factors of cardiovascular sequelae in patients with Kawasaki disease include longer duration of fever before treatment, low serum albumin at admission (< 3g/L), age less than 1 year or more than 5 years old, and IVIG resistance or incomplete Kawasaki disease [62]. During the 5-year period, Shanxai Provincial people's Hospital classified and analyzed 170 children with Kawasaki disease, and regularly followed up and found that nearly 1/4 were incomplete Kawasaki disease, and about 1/5 had abnormal coronary arteries. Most of the children with giant aneurysms recovered after treatment but often showed persistent abnormalities [66]. For healthy survivors of Kawasaki disease, the long-term effect is to accelerate the development of atherosclerosis. Only a few cadavers have been studied in patients with coronary artery involvement, and there appears to be endothelial dysfunction and coronary artery scarring. Although the contractile force of patients with transient myocarditis is normal during Kawasaki disease, there are histopathological abnormalities during myocardial

biopsies [24]. However, the increase in secondary atherosclerosis with intramural fibrotic degeneration indicates an increased risk of atherosclerosis development, which may become apparent as asymptomatic Kawasaki disease patients approach middle age [67] [68].

9. CONCLUSION

Kawasaki disease is a disease with high risk and there is no specific diagnosis. The main features of Kawasaki disease and the rational use of echocardiography are helpful to timely treatment and improve the prognosis of patients, but the diagnosis of incomplete Kawasaki disease is more complicated and accompanied by severe coronary artery disease. If patients with Kawasaki disease have not been diagnosed and treated, coronary artery disease may become an important factor in the morbidity and mortality of heart disease. More and more people in developing countries such as China and India realize that Kawasaki disease may replace rheumatic fever as the most common cause of childhood acquired heart disease, which is of great significance to doctors and cardiologists. it may also affect the health care system in developing countries, so Kawasaki disease is by no means a childhood disease, it has significant public health importance. Especially for developing countries like China and India [69] [70]. In view of the serious consequences of late diagnosis and the rising global incidence of Kawasaki disease, newborns and pediatric clinicians should be prepared to diagnose Kawasaki disease for children with long-term fever.

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THE NEW RELATIONSHIP BETWEEN KAWASAKI DISEASE AND MIS-C

FUYONG JIAO,
Children hospital of Shaanxi Provincial People's Hospital, Xi'an,China

XIAOJIN DING,
Children hospital of Shaanxi Provincial People's Hospital, Xi'an, China

HAOTIAN XU,
Dept of pediatrics, Heyang County Hospital, Shaanxi Province, China

JIALE WANG,
Class 4 of Master, Xi'an Medical University

KARIM ELAKABAWI,
Dept of Cardiology, Benha university, Egypt

HO-CHANG KUO,
Ho-Chang Kuo, Kaohsiung Chang Gung Memorial Hospital, Taiwan

Corresponding author:
E-mail: dr.hckuo@gmail.com
E-mail:3105089948@qq.com
Kaohsiung Chang Gung Memorial Hospital, Taiwan
JIAO FUYONG, Children hospital of Shaanxi Provincial People's Hospital, Xi'an, China

ABSTRACT

Kawasaki disease (KD) is a childhood disease associated with serious coronary artery complications. It is the most common cause of pediatric acquired heart disease in developed countries and is increasingly reported from many developing countries. The etiology of KD is still uncertain; interaction between a genetic predisposition and several environmental and immunological factors has been hypothesized. The Centers for Disease Control and Prevention reported that many children with MIS-C were infected with the new coronavirus or had close contact with people with the new coronavirus. Children with MIS-C show symptoms similar to severe cases of Kawasaki disease. An early discussion of similarities and differences between the novel coronavirus and Kawasaki disease was initiated towards the end of March 2020 between Dr. Karim Elakabawi, Benha university, Egypt; Prof. Manuel Katz, the chairman of the global CIP, Israel; and Prof. Jiao Fuyong, the head of the Center of Kawasaki disease diagnosis and treatment, shaanxi province, China. The three doctors discussed their strong observations about the epidemiologic distribution of KD cases and global affection of the Corona viruses family: SARS, MERS, and the most recently COVID-19. This article mainly summarizes the similarities and differences between KD and MIS-C.

Key words: *Kawasaki disease (KD) COVID-19 Children's Multiple System Inflammatory Syndrome(MIS-C) similarities differences*

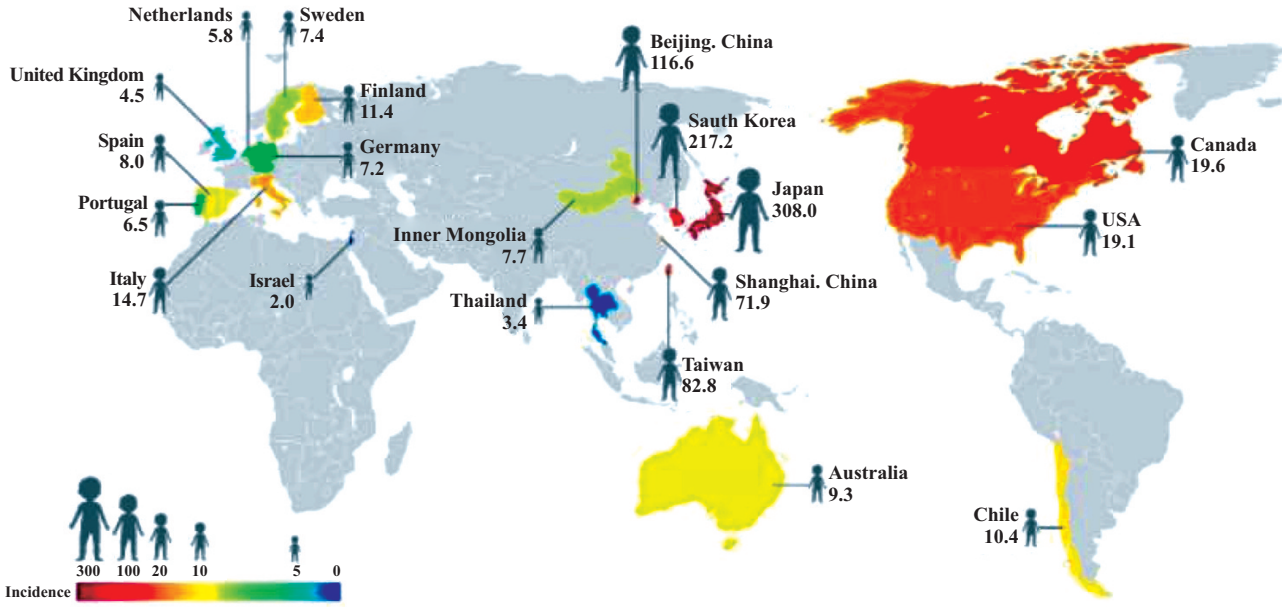


Figure 1

INTRODUCTION

Kawasaki disease is also known as mucocutaneous lymph node syndrome. Typical clinical manifestations include persistent fever (more than 5 days), pleomorphic rash, non-purulent conjunctival hyperemia, oropharyngeal mucosal hyperemia, swelling of the limbs, desquamation near the fingers or toes, and Suppurative cervical lymphadenopathy and coronary artery disease. KD is generally self-limiting. It is estimated that about 20%-30% of untreated patients will eventually develop severe vascular complications such as coronary artery dilation, coronary artery stenosis, or coronary artery fistula[1].So far, the exact cause of KD is still unclear. According to the seasonality of its onset and the usual history of infection 30 days before diagnosis, it is speculated that it may be related to viral infection[2]. However, more and more evidence supports that genetic factors play a key role in its occurrence and development. A large number of evidences show that the incidence of KD is increasing in certain groups of people. Many genes are involved in the development of Kawasaki disease and the development of complicated coronary artery lesions: for example, ITPKC, CASP3, TGF-s, BLK, CD40, FCGR2A, KCNN2, PECAMP-1, NMNA, etc[3].

Children's Multiple System Inflammatory Syndrome (MIS-C) refers to the swelling of organs including the heart, lungs and kidneys. The Centers for Disease Control and Prevention reported that many children with MIS-C were infected with the new coronavirus or had close contact with people with the new coronavirus.The patient developed MIS-C symptoms after being infected with COVID-19, including fever, abdominal pain, and inflammation. The inflammation manifested as diffuse rash, conjunctivitis, and swelling. In more severe cases, multiple organ dysfunctions may occur, including respiratory distress, hypotension, liver and kidney damage, and changes in mental status.Because the symptoms are very similar to the "children's heart killer" Kawasaki disease, some doctors call the children's strange disease quasi-Kawasaki disease. There are articles reporting that perineal desquamation is an early clue to the KD phenotype of MIS-C[4]. Findings of the present systematic review show that the incidence of KD-like syndrome in the COVID-19 pandemic increased significantly[5].The emergence of patterns that seem quite similar in several cities certainly points to a causal association between COVID-19 infection and KD.

THE TWO EPIDEMIOLOGIC SIMILARITIES BETWEEN THE TWO DISEASES:

Regional distribution

The global epidemiologic distribution of KD mimics the pattern of which Corona viruses spread to the world. Both diseases first recognized in East Eastern countries then increasing numbers and severe affection are mainly reported from developed countries in western Europe and USA. The theory behind KD distribution is thought that the disease is affected by genetic susceptibility and environmental factors like air pollution and increased industrialization that favor its prevalence in the more developed countries. The highest rates of KD affected children are reported from East Eastern Asian countries followed by Western Europe and North America, with increasing numbers started to be reported from rapidly developing countries as India, South America, and some middle Eastern countries like Turkey and Iran. KD is rare in sub-Saharan Africa, middle Asia, and the remaining middle Eastern countries (Figure 1).

On the other hand, The Corona Viruses SARS and COVID-19 the initial focus was in China, then spread mainly to Western Europe and north America. However, in last weeks the number of Covid- 19 cases start to rise in less developed and developing countries. This distinctive pattern of disease propagation was hypothesized to be because of people's mobility and traveling along commercial airline routes[6].

Of note, the severity of cases and mortality rates of COVID-19 up till now is much lower in middle Eastern and sub-Saharan African countries compared to European countries, for example for the date 6th of May 2020, the total reported cases in Saudi Arabia and Qatar are 30,251 and 17,142 patients, respectively with reported mortality rates of 0.7% and 0.07% respectively. When these numbers are compared with

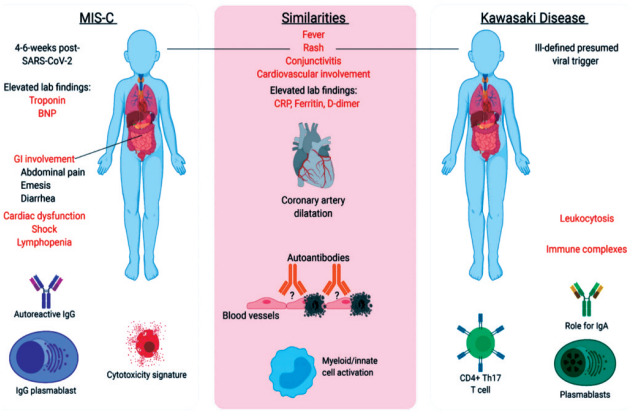


Figure 2[10]. A comparison of MIS-C and KD. The common and different clinical and immunological features of MIS-C and KD are shown. The major characteristic similarities or differences between the two conditions are highlighted in red. Th17, T helper type 17 cell.

European countries with similar reported total number of cases like Switzerland (30,009 patients) and Ireland (21,983 patients), they report mortality rates of about 6%. In 2003, also the outbreak of SARS infection had almost no effect on the middle eastern and African countries.

seasonal pattern

KD has a defined seasonal patterns in the extra-tropical latitudes of the Northern Hemisphere characterized by a peak of reported cases occurring in winter season starting in January through March[7]. The corona viruses also appear to be linked to the winter and cold seasons. The SARS-CoV appeared in November 2002 in the Guangdong province of southern China, and declined suddenly by July 2003. The new COVID-19 virus was first reported in December 2019 in Hubei Province, China and massively spread globally since late February 2020.

THE OTHER SIMILARITIES BETWEEN THE TWO DISEASES:

Pathogenesis

The specific cause of MD is not clear, but it is currently found to be related to viral infection and genetic susceptibility, which causes excessive immune response and platelet activation, which in turn leads to changes in systemic small blood vessel inflammation, which manifests as multiple organ damage, including coronary artery damage. Studies have pointed out along with platelet number, platelet activation may be a major determinant of various complications associated with KD, which confirms the rationale of antiplatelet therapy in KD[8]. some findings suggest that most enriched innate immune response pathways were shared between transcriptomes of KD and COVID-19 with moderate severity. Geneticpolymorphisms associated with innate immune dysregulation and KD susceptibility, together with variants in STING and STAT3, might predict COVID-19 severity and potentially susceptibility to COVID-19 related MIS-C[9]. some studies further suggest that rare inborn errors of immunity (IEIs) altering the immune response to SARS-CoV-2 may underlie the pathogenesis of MIS-C in some children. The discovery of monogenic IEIs underlying MIS-C would shed light on its pathogenesis, paving the way for a new genetic approach to classic KD, revisited as a heterogeneous collection of IEIs to viruses[10].

Clinical manifestations

MIS-C and KD both involve hyperinflammatory responses,presenting clinically with persistent high fever, often accompanied by a visible rash and conjunctivitis. These two conditionsremain elusive. They appear to be related but different conditions, with a clinical and immunological overlap (Figure 2)[10]. The specific manifestations of MIS-C are: fever, rash, vomiting, neck lymphatic enlargement, chapped lips and diarrhea, etc., similar to the clinical features of KD.

The differences between the two diseases:

The multisystemic inflammatory syndrome in children (MIS-C) related to the SARS-CoV-2 pandemic (also termed Kawasaki-like disease, or Kawa-COVID-19) appears to share clinical, pathogenetic and laboratory features with KD. But at present, there are also many differences between the two diseases. An article pointed out[11] that the most important difference between MIS-C and KD is the older age of onset, more frequent gastrointestinal involvement, myocarditis and/or cardiogenic shock and heart failure requiring positive muscle support, circulatory assistance, and PICU admission. In addition, MIS-C may be resistant to IVIG infusion therapy. MIS-C is a cytokine storm driven mainly by IL-6 and IL-8, and in KD patients, IL-1 seems to be the main mediator of coronary artery inflammation. An article reported[12] three cases of KD-like cases that occurred in severely affected areas in northern Italy during the SARS-CoV-2 pandemic, manifesting as persistent fever, diarrhea, elevated inflammatory markers, and myocardial damage. An article pointed out [13]that about two-thirds of COVID-19-related KD children have been admitted to PICU. In addition, about a quarter of people need mechanical ventilation/intubation, and even some of them need to be readmitted to the hospital. In general, MIS-C is in a serious condition.

There is a more pronounced difference between the two extreme manifestations of Kawasaki disease shock and MISC shock. Both patient populations who experienced shock showed elevated levels of CRP and ferritin, but the laboratory abnormalities shown in MIS-C shock cases were more pronounced. In MIS-C, the ethnicity of the patient population is mainly African-American/Hispanic, while the KD patients who experience shock are more Asian[14]. There are some other differences see chart (Figure 3)[14].

A key distinguishing feature between the classic KD and the current virus-related hyperinflammatory syndrome is their platelet count. MIS thrombocytopenia, KD thrombocytopenia. One possible explanation for this is that their underlying

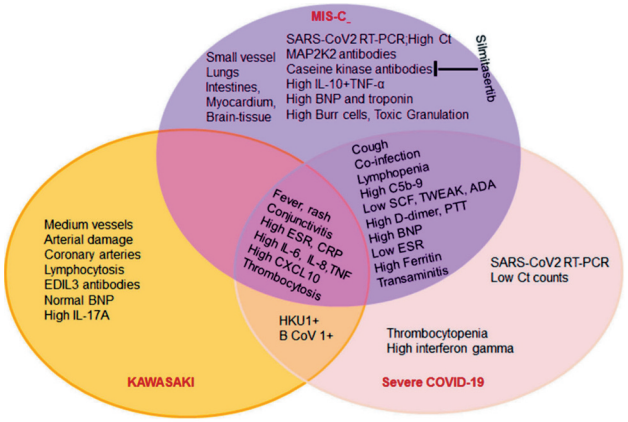
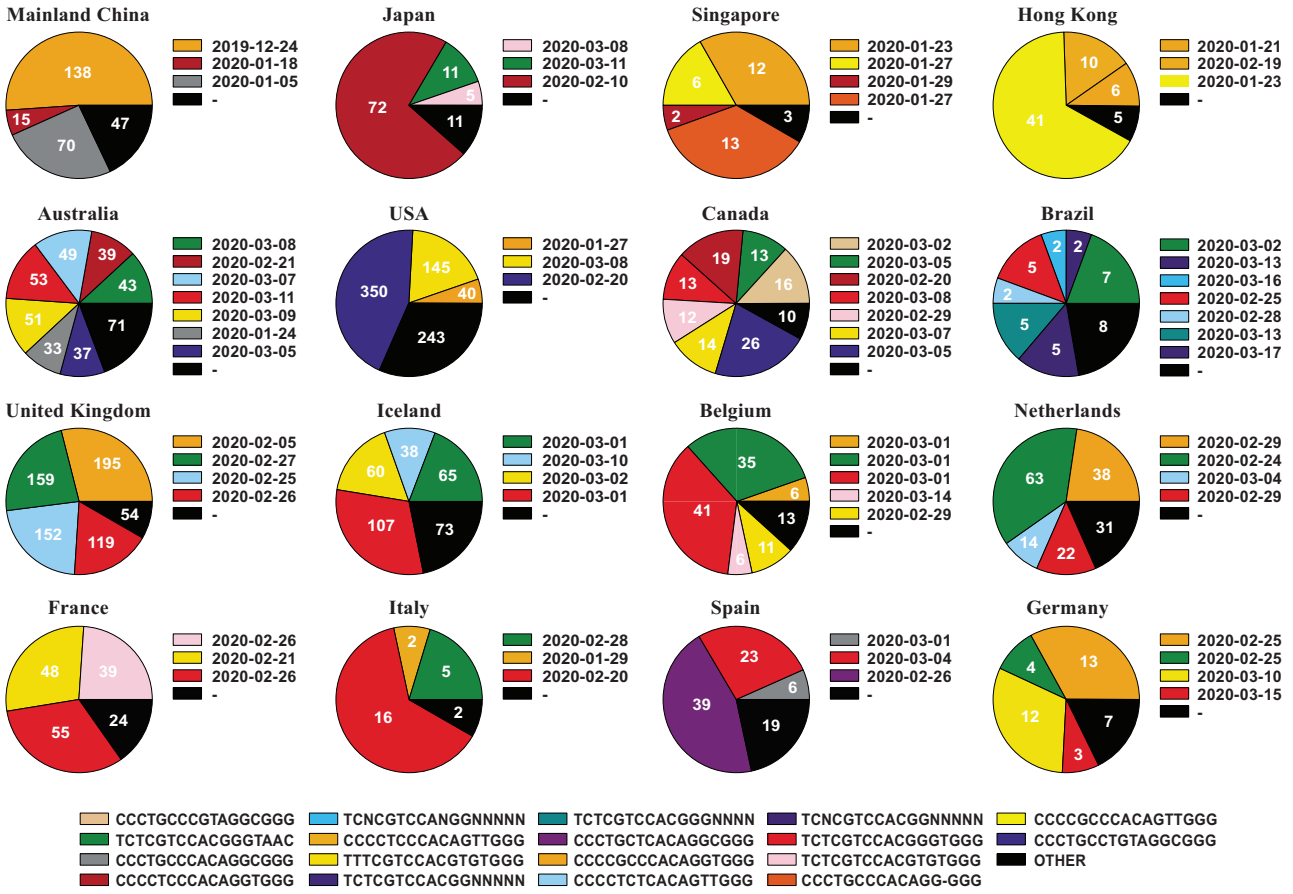


Figure 3



(Figure 4)[18]Major SARS-CoV-2 genetic subtypes in countries/regions with the most sequences (indicating date subtype was first sequenced in that country/region). Subtypes with less than 5% abundance are plotted as "OTHER."

immune pathogenesis is different[15]. Notable features of Kawasaki disease-like disease associated with SARS-CoV-2 include older age, more frequent sub-Saharan African descent, gastrointestinal involvement, shock, myocarditis, lymphopenia, and higher levels of inflammatory markers. This is the difference from KD[16]. This COVID-19-related syndrome seems to have a greater impact on older children, with a higher rate of heart involvement, and more severe conditions that require ICU management[17]. Unlike KD, the guidance statement does not recommend immunomodulatory treatment for most pediatric patients who usually develop mild or moderate COVID-19. For children with severe or critical illness, the use of immunomodulators may be beneficial[17,19].

DISCUSSION

The similarities of both diseases are raising several questions that would help better understanding and managing both. The aetiology of KD is still unknown, it is believed to be a result of adverse immune response to an environmental trigger believed to unknown viral infection occurring in genetically susceptible patients. Interestingly in the last two weeks a growing number of hospitals in the U.S., U.K. and other European countries have reported several cases of children with Kawasaki-like symptoms that is believed to be related to the recent COVID-19 infection. KD mainly affects children under 5 years old and is thought to be due to hyperimmune response to unnoticed infection. Corona viruses showed sparing to children or cause few symptoms and signs, but the recent reports of children with documented COVID-19 and Kawasaki- like characteristics may raise concerns about the true effects on pediatrics populations. Treatment of KD patients with intravenous immunoglobulin (IVIG) within 10 days after disease onset can lower the incidence of serious coronary complications from 25% to <5%. Similarly, if this theory is true, the complications of COVID-19 resulting from hyperimmune response in some patients may be better managed if IVIG is considered early in the course of treatment. Lastly, thinking about what causes Atypical Kawasaki syndrome in Australia, UK, and middle east, and not in China where KD is endemic? The reason probably is related to the genetic code of the virus that changes during replication and spread around the planet. Similar to the detected different COVID-19 virus subtypes that cause different clinical features and severity in different regions(Figure 4)[18]. There are many similarities between the two diseases, but the current findings are also different. In the future, more research is needed to better guide clinical treatment to achieve better treatment effects and prognosis.

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FEVER CLINIC: THE FIRST LINE OF PREVENTION AND CONTROL COVID-19 IN CHINA

XIANGLONG DUAN, LIANG SHAN, LIU PENG, JIAO FUYONG*,
Department of Clinical Medicine, Shaanxi Provincial People's Hospital

OMAR MOHAMUD HASSAN, RUI LI,
Department of Pediatrics and Child Health, Xiangya second hospital, Central South University, Changsha, Hunan Province, People's Republic of China.

YUXIAN ZHANG,
Children's Hospital, Shaanxi Provincial People's Hospital of Xi'an Jiaotong University, Xi'an, People's Republic of China

YINGYING YANG,
Xi'an Medical University, Xi'an, People's Republic of China

Correspondence author: JIAO FUYONG; e-mail: 3105089948@qq.com

ABSTRACT

Objective: To establish a fever clinic for the effective control and interruption of COVID-19 transmission in hospitals.

Methods: By referring to literature and various materials, specific and feasible methods were summarized from the aspects of setting up, site selection, layout, ventilation, disinfection and isolation system, staff configuration, and workflow of fever clinic. Results: During the COVID-19 outbreak, the fever clinic played an essential role in effectively controlling and reducing the hospital's transmission and infection. Conclusion: The existence of a fever clinic is popular and necessary, and it should be continuously improved to make it play a more significant role in the critical moment.

Keywords: *Fever clinic, COVID-19, China*

1. BACKGROUND

To implement the work requirements of "Preventing imported COVID-19 from the Outside and preventing rebound from inside" in the regular epidemic prevention and control work, the Comprehensive Group of COVID-19 Joint Prevention and Control Mechanism of the State Council issued the Notice on The Implementation of the Requirements of Regular Epidemic Prevention and Control to Further Strengthen the Infection Prevention and Control Work in Medical Institutions".[1][2] Clear to compaction fever outpatient medical institutions" outpost "responsibility, fever outpatient medical staff should master and implement the COVID - 19 scheme of prevention and control and diagnosis and treatment, the patients with suspected and confirmed, should promptly report and isolation, on time to the fixed-point hospital, not to allow patients to transfer or departure from the hospital, this is the first step to reduce COVID - 19 strong infectious measures.

A fever clinic is a special clinic set up by the outpatient department of a regular hospital during the prevention and control of acute infectious diseases according to the superior's instructions, which is specially used for screening suspected infectious patients and treating fever patients. The medical staff working in the clinic should strictly abide by the "law on prevention and control of infectious diseases" and the government's relevant laws and regulations during the prevention and control of infectious diseases. We should not fail to report a patient, report a patient well, and not infect a medical staff.

On June 11, 2020, the National Health Commission issued the "notice on giving full play to the sentinel role of medical institutions to do a good job in normalized epidemic prevention and control," it is stipulated that the "sentinel" role of fever clinic, primary medical institutions and emergency center should be brought into full play. Suppose the "sentinel" fails to implement the measures such as detection, registration, reporting, guidance, etc., leading to "failure to be inspected." It is necessary to carry out the responsibility reverse check and investigate the relevant institutions and responsible persons per laws and regulations.[3]

2. METHOD

Through consulting literature and various documents, we summarized the experience of predecessors, elaborated the significance of the establishment and existence of fever clinic, and wrote this article.

3. STRUCTURE

3.1 Hardware

In terms of setting, the fever clinic setting should be included in the overall construction plan of the hospital, and the layout should be reasonably arranged according to the functional needs. The interior of the fever clinic should also be strictly set up protection zones, strictly distinguish the cleaning and pollution routes of people flow and logistics, take safety isolation measures, and strictly prevent cross-contamination and infection. All kinds of functional rooms should have good flexibility and scalability, to achieve the goal. When the hardware facilities cannot meet the needs, we should take measures to improve the system, process, disinfection, and isolation to make up for the defects and deficiencies of hardware facilities and prevent cross-contamination and infection in the hospital.

In terms of site selection, to prevent cross-contamination, the fever clinic should keep a proper distance from other buildings and public places. It should also be set up in an independent area of the medical institution. It is separated from the general outpatient service and has eye-catching signs.

In terms of layout, the fever clinic should be completely separated from other special outpatient services, so that airflow is not connected. The fever patients and medical staff should be equipped with special entrances and special passage, and the entrance and exit of cleaning and polluting articles should be set up with eye-catching signs. Pollution, semi-pollution, and clean areas should also be set up. The three areas should be divided without crossing each other and have eye-catching signs. To prevent fever patients from crossing with other personnel, the fever clinic should be equipped with a consulting room, treatment room, check-up observation room, medical staff changing room, and each room must be independent.

In terms of ventilation and exhaust, natural ventilation should be used as far as possible in the respiratory fever clinic. In case of poor natural ventilation, adequate mechanical ventilation facilities should be installed for forced ventilation. All external windows should be opened, and indoor air should be kept in circulation. To avoid cross-infection of air, the air conditioning system of the fever clinic should be set up independently, and the following air conditioning systems are prohibited: air conditioning system with circulating return air. Water-air air-conditioning system without fresh air and window ventilation. Air conditioning system without windows, fresh air and exhaust system, and air conditioning system with adiabatic humidification device. If the central air conditioning system is set, the airflow direction should be adjusted to make the airflow from the clean area to the semi polluted area and then to the polluted area, and the negative pressure should be maintained in the polluted area. Clean and disinfect the air conditioning system 1～2 times a week. Collect the cooling water of the air conditioner and discharge it after disinfection. All fresh air conditioning systems shall be set up, and natural ventilation shall be ensured if there is no air conditioning system.

In terms of sanitation and disinfection, the wastewater, sewage, and other wastes in fever clinic should be strictly disinfected, which should strictly meet the requirements of health regulations, norms, and standards such as "Regulations on the management of medical waste", "Measures for the management of medical waste in medical and health institutions", "Sewage discharge requirements of medical institutions" and "Technical specifications for hospital disinfection". Also, set up a special disinfection room. Ensure strict disinfection. All business rooms must be equipped with an ultraviolet lamp, non-hand washing device, disinfection box, screen window and screen door, insect and rodent prevention, and other disinfection and isolation and sanitation facilities.

3.2 Medical Staff and Basic Equipment

In terms of medical personnel allocation, 1～2 doctors who have been trained and more than 3 nurses who have obtained the qualification of practicing doctors shall be allocated. Among them, one doctor shall have the professional and tech-

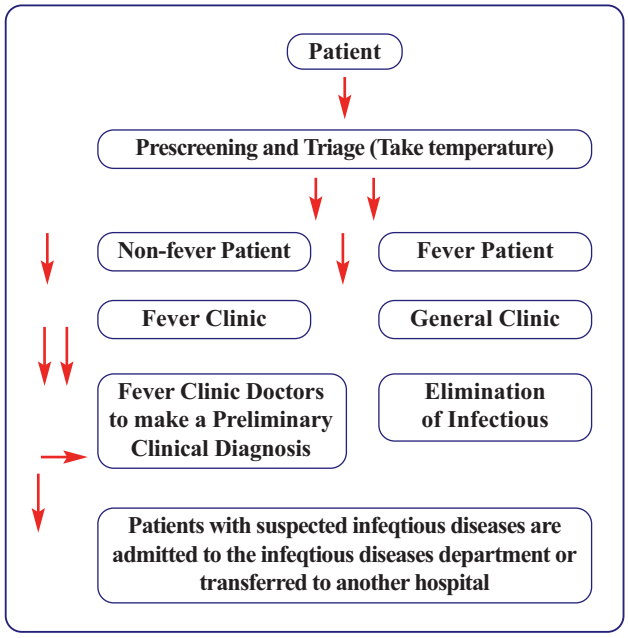
nical post-qualification of infectious diseases department or respiratory department, to ensure the effective development of 24-hour duty.

In terms of equipment, it is necessary to set up a proper amount of consulting bed, diagnosis table, diagnosis stool, observation bed, stethoscope, sphygmomanometer, thermometer, dirt bucket, disposable tongue depressor, disposal table, disposable syringe, disposable infusion set, gauze jar, square plate, medicine cabinet, ultraviolet lamp, sterilization equipment, formalin fumigation and disinfection cabinet, hand disinfection facilities, ECG machine, etc.

In terms of communication facilities, the working room should have telephone contact with the outside, and the working telephone should be announced to the public.

4. PROCESS

The Outpatient Treatment Process of Fever



In terms of optimizing the service process of fever outpatient service, we should strengthen personnel screening, strengthen epidemiological history inquiry, strictly screen travel history and contact history. For patients with clinical symptoms, we should isolate them for observation at the first time, achieve "four early" (early detection, early diagnosis, early isolation, and early treatment) and "four arrivals", and detect the gene sequence of virus in early isolation. Only in this way can we effectively implement the "four early". The scope of nucleic acid detection should be expanded, and the fever clinic should carry out nucleic acid detection for all patients to ensure that they should be fully examined. For the unclear cases, the fever clinic should carry out isolation, observation, treatment, and detection at the same time, to ensure the timely and effective diagnosis and treatment of patients.[4][5]

In terms of the implementation of the normalization of nosocomial infection prevention and control, according to the requirements of the State Council's notice, we should strengthen the awareness and ability of nosocomial infection prevention and control, strictly implement the standard prevention, require all kinds of personnel to wear masks correctly, do a good job in cleaning, ventilation, and disinfection, and timely dispose of the left garbage and domestic garbage.

During the epidemic period, given the new type of COVID-19 can cause damage to all systems of the body, the whole hospital can be deployed to carry out online diagnosis and treatment, appointment diagnosis and treatment, and establish a multidisciplinary expert team to fully cooperate with the hospital epidemic prevention and control work, and improve the cure rate.

5. RESULT

The fever clinic is a special product of the SARS period, which plays an important role in this critical moment. It not only effectively controls the spread of SARS, but also reduces the cross-infection rate in the hospital. It has an irreplaceable position in other outpatient and wards. With the understanding and treatment of febrile patients, fever clinic has become the first clinic of infectious diseases, which can effectively control the spread of infectious diseases. Fever clinic played a great role in the fight against COVID-19, effective and timely control of the new crown pneumonia continued to spread and spread. Its existence is necessary for the state and society.

6. DISCUSSION

Since SARS in 2003, fever clinics have been widely set up in public hospitals in China, and practice has proved that the establishment of fever clinics plays a very obvious role in the epidemic and transmission of infectious diseases and has its value of existence.

Countries in the aspect of fever clinics also attach great importance to, in the rapid spread of the new champions, issued the related National Health Commission of the People's Republic of China hospital of fever clinics set up the management requirements, such as: "two or more integrated hospital in principle shall be set up independent fever clinics, local health administrative departments to strengthen the management of the local medical institution's fever clinics, local fever outpatient Settings to the public." "Fever clinics should be located in relatively independent areas within medical institutions, in relative isolation from the general (emergency) clinic. Fever clinics shall be marked with eye-catching signs. There shall be special channels for patients and special channels for medical personnel, and each channel shall be marked. The prominent position of the general door (emergency) should also be provided with a guide sign so that patients with fever can reach the fever clinic according to the sign guidelines." "Fever clinics shall at least have functional rooms and areas such as consulting rooms, treatment rooms, isolation wards (rooms), dressing rooms for medical staff, temporary storage points for medical waste," "Medical institutions shall strengthen pre-examination and triage. In principle, the first place of diagnosis for patients with acute fever should be the fever clinic. If a fever clinic patient considers that he/she has a fever due to infectious diseases, he/she should adopt a completely closed medical treatment process. In principle, diagnosis and treatment activities such as registration, medical treatment, payment of fees, and medicine collection can all be completed in this area." "Patients with fever must first go through the fever clinic for pre-examination, and then enter the corresponding clinic for treatment after pre-examination triage." This series of initiatives can be the most rapid screening and identify common fever and

COVID - 19, the implementation of early detection, early diagnosis, early quarantine and early treatment and control nosocomial cross-infection, it was under these measures, China can quickly and efficiently in a short period to stop its spread and spread, of almost one hundred thousand people from the beginning to now more than one thousand people, compared the foreign outbreak, China has this proud achievement in this aspect, the fever clinics.[6][7][8][9][10][11]

To sum up, the existence of a fever clinic is inevitable and necessary. What we should do is constantly improve and upgrade. If there is a big public health event in the future, we can take our time to deal with it.

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FIGHTING TO MEDICAL DISASTERS: METHOD OF INVESTIGATION OF VIBRATIONAL PROPERTIES OF VIRUSES AND OTHER PATHOGENIC NANOBIOPARTICLES

P.J. KERVALISHVILI,
President of the Georgian Academy of Natural Sciences, Tbilisi, Georgia

"And Wuhan-400 has other, equally important advantages over most biological agents. For one thing, you can become an infectious carrier only four hours after coming into contact with the virus" - The eyes of darkness by Dean Koontz, Berkley edition /July 1996

INTRODUCTION

Medical disasters prediction, management and control are one of the main parts medical planning and preparation. The term "disaster medicine" first appeared in the medical lexicon in the post World War II era. Although coined by former and current military physicians who had served in World War II, the term grow out of a concern for the need to care for military casualties, or nuclear holocaust victim, but out of the need to provide care to the survivors of natural disasters and the not yet distant memory of the 1917-1918 Influenza Pandemic [1]. The term "disaster medicine" would continue to appear sporadically in both the medical and popular press until the 1980s when the first concerted efforts to organize a medical response corps for disasters grew into the National Disaster Medical System. Simultaneous with this was the formation of a disaster and Emergency Medicine discussion and study group under the American Medical Association (AMA) in the United States as well as groups in Great Britain, Israel and other countries. Throughout this period, incomplete and faltering medical responses to disaster events and control of different epidemics made it increasingly apparent in the United States of America that federal, state and local emergency management organizations were in need of a mechanism to identify qualified physicians in the face of a global upturn in the rate of medical disasters [2].

2004 Stokholm

2017 Tbilisi

Development of new treatments is greatly facilitated by an improved understanding of the pathophysiology of epidemic diseases. There is therefore a need to address the current knowledge gaps in disease aetiology in order to support innovation in the development of evidence-based treatments. In this context, a better understanding of the mechanisms that are common to several diseases, in particular of those leading to co-morbidities, constitutes an important challenge. The special attention must be focused on the integration of pre-clinical and clinical studies for the identification of mechanisms common to several diseases. Performing activities should assess and validate the relevance of these common mechanisms and of their biomarkers (where relevant) on the development of disease-specific pathophysiology, as well as their role in the development of co-morbidities in both males and females. The expected impact should provide:

- A better understanding of disease pathways and / or mechanisms common to a number of diseases
- New directions for clinical research for better disease prevention, health promotion, therapy development, and the management of co-morbidities.

In this direction the multidisciplinary development of ability to detect rapidly, directly and selectively individual virus particles has the potential to significantly impact healthcare, since it could enable diagnosis at the earliest stages of replication within a host's system. Simultaneous acquisition of the vibrational and electronic fingerprints of molecular systems of biological interest, at the interface between liquid media, or at the air/solid, air/liquid interfaces is difficult to achieve with conventional linear optical spectroscopy due to their rather poor sensitivity to the low number of molecules or their maladjustment to water environment (infrared absorption). It relies on inelastic scattering of monochromatic light, usually from a laser in the visible, near infrared, or near ultraviolet range. The laser light interacts with molecular vibrations, phonons or other excitations in the system, resulting in the energy of the laser photons being shifted up or down. The shift in energy gives information about the vibrational modes in the system. Infrared spectroscopy yields similar, but complementary, information. Spontaneous scattering is typically very weak, and as a result the main difficulty of this kind of spectroscopy is separating the weak nonelastically scattered light from the intense Rayleigh scattered laser light.

Viruses are assembled in the infected host cells of human, animals, or plants. Because of viral breeding the, host cell dies. There are especially viruses which are breeding in the cell of the bacteria. Viruses spread in many different ways. Just as many viruses are very specific as to which host species or tissue they attack, each species of virus relies on a particular propagation way.

SFG spectroscopy and ultrashort pulsed lasers based optical measurement methods are unique for investigation of vibrational modes of different viruses and other pathogenic microorganisms as well as study of nature of their oscillation processes and parameters of oscillation. Non linear optics and its resonance technologies is possible direction of organization of pathogenic microorganisms treatment in their different living media.

Viruses themselves have no fossil record, but it is quite possible that they have left traces in the history of life. Because viruses can transfer genetic material between different species of host, they are extensively used in genetic engineering. Viruses also carry out natural "genetic engineering": a virus may incorporate some genetic material from its host as it is replicating, and transfer this genetic information to a new host, even to a host unrelated to the previous host. This is known as transduction, and in some cases it may serve as a means of evolutionary change - although it is not clear how important an evolutionary mechanism transduction actually is [3,4].

Viruses are so called nanoparticles because of their geometry and size – tens of nanometers [5]. Beyond this basic architecture, viruses can have further elaborations such as protein collars, tails, connectors, lipid coats, surface receptors, enzymes, and molecular motors. To the materials engineer or nanotechnologist, viruses are perfectly defined organic nanoparticles which are commonly used as scaffolds or nano-vectors [6]. Following to definition of nanoscale at this level it is possible to have deliberate and controlled manipulation, precision placement, measurement, modeling and production of nanosize matter in order to create materials devices and systems with fundamentally new properties and functions (Fig.1)[7,8].

The one of the most important part of nanoscience and nanotechnology is nanobioscience and nanobiotechnology which are the children of the same father. The main objective of nanobiotechnology is cellular uptake of nanosize molecules functioning within the cell. If the size of molecules is bigger than 10nm are taken by the cell trough a clathhrin-assisted mode of endocytosis called pinocytosis, while particles of size

greater than 200 nm in diameter are usually phagocytosed by the macrophages. Phagocytosis occurs in specialized cells called phagocytes, which includes macrophages, neutrophils, and other white blood cells, which destroys the molecular association. Invagination produces so called phagosome which usually fuses with one or more lysosomes containing hydrolytic enzymes.

In comparison with cellular molecules (nanoensembles) the size of viruses varies from 20 to 300 nanometers. Practically all viruses by the sizes are smaller, than bacteria. However the largest viruses, for example a virus of cow smallpox, have the same sizes, as well as the smallest bacteria (hlamidiya and rikketsiya) who too are obligate parasites and breed only in living cells.

Therefore as distinctive features of viruses in comparison with other microscopic causative agents of infections the sizes or obligatory parasitism, and features of a structure and unique mechanisms of replication (reproduction themselves) serve not. Viruses are masterpieces of nanoengineering with a basic common architecture that consists of the capsid – a protein shell made up of repeating protein subunits- which packs within it the viral genome.

Nano-sized biological agents and pathogens such as viruses are known to be responsible for a wide variety diseases such as flu, AIDS and herpes, and have been used as bioreagents [9,10].

For today there are experimentally certified data that Viral nanoparticles are emptied virus cells that can carry drugs directly to cancer cells to kill them [11]. Scientists have engineered viral nanoparticles from plant viruses, insect viruses, and animal viruses [12]. Viral nanoparticles could revolutionize cancer treatment, acting not only as a safer, more specific form of cancer treatment, but also as a newimaging tool. The nanoparticles could create a type of drug delivery that is extremely tumor specific with greatly reduced side effects. The viral nanoparticles would be more soluble and have higher drug efficacy than current treatments [13,14].

Viruses and other biological species can be characterized according to size, shape, and optical/spectroscopic properties. These properties allow them to be distinguished from other biological species and from other particulates such as dust particles.

In response to new tasks which face medicine the XXI century development of a rapid and efficient diagnostic test is considered a high priority. In this direction the decisive word belongs to development of nanotechnologies which have a great potential for use in methods of detection, diagnosis and treatment. The gold nanorods (AuNR) are of particular interest, especially considering their optical properties and chemistry of the surface, which allows easy connection to organic molecules adapted to specific needs to For research of mechanisms of action of viruses and pathogenic microorganisms the study of their properties is very important including oscillations pervade biological systems at all scales. In bacteria, oscillations control fundamental processes, including gene expression, cell cycle progression, cell division, DNA segregation and cell polarity. Oscillations are generated by biochemical oscillators that incorporate the periodic variation in a parameter over time to generate an oscillatory output. Spatial oscillators incorporate the periodic variation in the localization of a protein to define subcellular positions such as the site of cell division and the localization of DNA. There are some data which are focuses on the mechanisms of oscillators and the design principles of temporal and spatial oscillatory systems [15].

Current optical detection methods which are well developed for single micrometer size particles, cannot be applied to nanoparticles due to a strong signal dependence on particle size. Typically, such sensors consist of a light source which illuminates a sample volume of an aerosol or a liquid flow containing the particles of interest. An off-axis detector measures power of scattered light.

The latter is a function of particle properties such as size, concentration, and optical density. In the tens of nanometers size regime particles act as dipoles, therefore the power of scattered light is proportional to the sixth power of particles size. Lowering the detection size limits for the existing detectors places an impossible requirement on noise optimization. Therefore, a signal which has weaker particle size dependence can allow access to smaller particles [16].

In the field of virology, for example, it is critical to accurately quantify virus particles to study the effects of drug therapy in patients; and also to study viral fitness, replication, and inhibition. There are several virus quantification techniques available to virologists, such as the quantitative PCR (polymerase chain reaction) method [17], the plaque titer method [18] and the image enhanced microscopy (IEM) technique [19]. However, a problem common to most of these techniques is that the analysis of a sample involves several tedious steps, which can take several hours to multi plays to complete.

The fast detection and characterization of nanoparticles, such as viruses or environmental pollutants, are important in fields ranging from biosensing to quality control. However, most existing techniques have practical throughput limitations, which significantly limit their applicability to low concentration analysis. There are some experimental dates that an integrated nanofluidic scheme for preconcentration and subsequent detection of nanoparticle samples within a continuous flow-through system. In these experiments using a Brownian ratchet mechanism increase the nanoparticle concentration 27-fold. Single nanoparticles are subsequently detected and characterized by optical heterodyne interferometry. A wide range of potential applications can be foreseen, including real-time analysis of clinically relevant virus samples and contamination control of processing fluids used in the semiconductor industry [20].

EXPERIMENTAL TECHNICS AND DISCUSSION

For nanoparticle structures identification very interesting method is Vibrational Spectroscopy (VS), which provides the most definitive means of identifying the surface species generated upon molecular adsorption and the species generated by surface

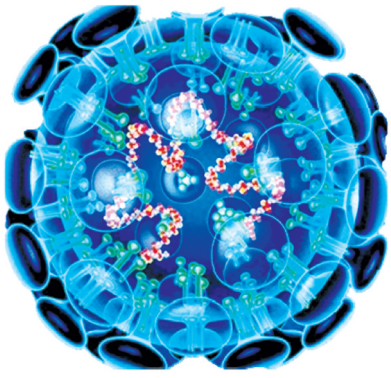

Figure 1. Corona virus ((Roger Harris/Science Photo Library/Getty Images)

In principle, any technique that can be used to obtain vibrational data from solid state or gas phase samples (IR, Raman etc.) can be applied to the study of surfaces - in addition there are a number of techniques which have been specifically developed to study the vibrations of molecules at interfaces (EELS, SFG etc.) [21, 22].

There are, however, only two techniques that are routinely used for vibrational studies of molecules on surfaces - these are : IR Spectroscopy (of various forms, e.g. RAIRS, MIR) and Electron Energy Loss Spectroscopy (EELS). There are both advantages and disadvantages in utilizing EELS, as opposed to IR techniques, for the study of surface species It offers the advantages of high sensitivity, variable selection rules, spectral acquisition to below 400 cm-1 but suffers from the limitations of use of low energy electrons. Raman spectroscopy is used to study low-wavenumber (≤20cm−1) acoustic vibrations of the M13 phage. A well-defined Raman line is observed at around 8.5cm−1. The experimental results are compared with theoretical calculations based on an elastic continuum model and appropriate Raman selection rules derived from a bond Polaris ability model. The observed Raman mode is shown to belong to one of the Raman-active axial modes of the M13 phage protein coat. It is expected that the detection and characterization of this low-frequency vibrational mode can be used for applications in biomedical nanotechnology such as for monitoring the process of virus functionalization and self-assembly.

Recently, a technique which departs radically from conventional approaches has been proposed. This novel technique utilizes biological objects such as viruses as nano-templates for the fabrication of nanostructure elements. For example, rod-shaped viruses such as the M13 phage and tobacco mosaic virus have been successfully used as biological templates for the synthesis of semiconductor and metallic nanowires. Low wave number (<or= 20 cm-1) acoustic vibrations of the M13 phage have been studied using Raman spectroscopy [23]. The experimental results are compared with theoretical calculations based on an elastic continuum model and appropriate Raman selection rules derived from a bond polarizability model.

It was also reported the use of a visible femtosecond laser system to excite a coherent acoustic Raman-active vibrational mode (which is associated with vibrations of viral capsids) in M13 phages through ISRS to such a high-energy state as to lead to their inactivation. This work demonstrates a new method of manipulating, controlling, and inactivating unwanted microorganisms [24]. It suggests that the basic principles of impulsive coherent excitation using a laser optical system can represent a general way to selectively alter the function of or even inactivate viruses and

2015 University of Paris

potentially other microorganisms through the property of their mechanical acoustic excitations. In addition, since structural change due to the mutation of microorganisms leads to very minimal variation of the vibrational frequency of their capsids, damage caused to viruses and/or other microorganisms through vibration of their mechanical structures likely would not be immune to simple mutation of cell surface receptors, and the same treatment procedure remains valid; our approach would thus not evoke problems of drug resistance and as a result would be applicable to drug-resistant strains of microorganisms.

ISRS has been successfully demonstrated to produce large-amplitude coherent vibrations in the molecules in liquids as well as in solid-state systems. It had been predicted that ISRS should occur with no laser intensity threshold even when only one ultra short laser pulse is passed through many types of media. In this case, ISRS is a forward-scattering process which is stimulated because the Stokes frequency is contained within the spectral width of the excitation pulse. Furthermore it was demonstrated that ISRS is a process through which excitation of a coherent lattice or molecular vibrations would take place whenever a sufficiently short laser pulse passed through a Raman-active solid or molecular liquid or gas.

Viruses and their genomes are mostly enclosed and protected by capsids - symmetric coats or shells composed primarily of multiple copies of protein subunits, and virus capsid assembles (Fig.2a,2b) [25-27].

Aside from serving as a protective layer, capsids are involved with various other aspects of their respective virus life cycles including timely viral genome encapsulation (self assembly and genome packaging), cell-to-cell virus transport, entry into host-cell (e.g., via cell receptor binding), genome release into host cell, etc. Despite their central importance to the life cycle, the various evolutionary pressures acting on spherical capsids are not well known. Half a century of empirical data has uncovered a large array of capsids sizes that range from tens to many thousands in subunit composition. Spherical capsids of all observed sizes may be obtained from a grouping of twelve pentamers (symmetric clusters of five subunits) separated by a variable number of hexamers (clusters of six subunits). This is the case for the T~7d papilloma viruses where all capsomers are made up of five subunits but they are in both hexavalent and pentavalent configuration, and larger viruses whose “hexamers” are actually trimers of “fused” or covalently bonded dimers.

Capsid size may be characterized by two integers, h and k, which describe the number of hexamers (hzk{1) one would have to “walk over” to get from one pentamer to an adjacent pentamer within a completed capsid. The utility of the class system is not entirely lost, however; specificed angle patterns within the capsid ensures the existence of distinct hexamer shapes (each shape is colored distinctly in. Evidence indicates that capsid formation is nucleated, often starting

with a single capsomer species (e.g., pentamers; for the purposes of this paper, a capsomer is a generally symmetric cluster of either five or six subunits), which then proceeds to completion by the addition of small subunit clusters (or single subunits). In T~1 capsids, where subunits are in identical/equivalent environments, nucleated assembly will be possible with no additional machinery. However, the formation of two or more capsomers from a single interaction site will require the employment of additional machinery to ensure high yields of the native state. For example, quasi-equivalent switches are required for the proper assembly of capsids containing two distinct capsomers: a pentamer and one type of hexamer. The addition of a second hexamershape necessitates the requirement of a second mechanism such as auxiliary proteins for proper assembly. For spherical virus capsids requiring more distinct hexamer shapes.

Additional mechanisms to stabilize those new shapes at exactly the right positions within the forming capsid are likely to be also needed dominantly form. Because capsids from different classes display markedly different geometries, they are bound to display different physical properties. The periodic nature of capsid hexamer contents also useful in understanding "T-switching": a process that permits canonical capsid subunits to more easily sample capsids containing similar hexamer shapes. This allows for a segue to understanding currently intractable and deadly pleomorphic viruses like ebola and arenaviruses. For example, from the above T-switching rule, the available diversity of an arena virus may only be explained if we assume that the biologically relevant form of the arenavirus is the T~12 capsid. Non-icosahedral capsids. Although the framework presented doesn't appear to readily explain non-icosahedral capsids (some are just "slightly" non-icosahedral, such as the natively prolate phi29 capsids, while others are wildly different in form, such as ebola with its natively filamentous shape), those capsids, like their icosahedral counterparts, also display capsomer sub-structures. In light of this, the geometric constraints analogous to endo angles that affect capsomer shape may be useful in obtaining insights into non-icosahedral capsid morphology, behavior, and classification. It will be exciting to see whether incorporating the non-icosahedral capsids into an expanded capsid periodic table will be possible.

All canonical capsids (made up of trapezoidal subunits) may be built from a single type of pentamer anda repertoire of distinct hexamer shapes (colored distinctly only once in each capsid. The hexamer shape is described by the number of endo angles it displays. It is necessary to underline that effect of destroy of human immunodeficiency virus (HIV) and other enveloped viruses is is based on the highly symmetric structure (e.g. icosahedral and others) of many viruses, which leads to a well-defined resonant frequency of ultrasound in the GHz range and which may be specifically absorbed by these structures and may subsequently lead to their irreversible damage.

The development of methods that allow microscale studies of complex biomaterials based on their molecular composition is of great interest to a wide range of research fields. Some experiments show that stimulated Raman scattering (SRS) microscopy is an excellent analytical tool to study distributions of different biomolecules in multiphasic systems [28]. SRS combines the label-free molecular specificity of vibrational spectroscopy with an enhanced sensitivity due to coherent excitation of molecular vibrations. Compared to previous imaging studies using coherent anti-Stokes Raman scattering microscopy, the main advantage of SRS microscopy is the absence of the unwanted non resonant background, which translates into a superior sensitivity and undistorted vibrational spectra. Raman spectroscopy also allows studying an individual print of investigated substance. It is the most exact method of measurement at present as each such print is unique Viruses has recently attracted attention as biological templates for assembly of nanostructures.

Raman and IR-Fourier spectroscopy are in fact complementary, mutually supplementing methods. Fluctuations which are strongly shown in IR a range (strong dipoles) are usually poorly shown in Raman a range.

In order to clarify the possible role of nanoparticles in diseases recently associated with them (such as Crohn's disease, neurodegenerative diseases, autoimmune diseases, and cancer), nanoscale characterization techniques should be used to a larger extent to identify nanoparticles at disease sites in affected organs or tissues, and to establish pertinent interaction mechanisms. Rapid, selective, and sensitive detection of viruses is central to implement an effective response to viral infection, such as through medication or quarantine. Established methods for viral analysis include plaque assays, immunological assays and transmission electron microscopy. These methods have not achieved rapid detection at a single virus level and often require a relatively high level of sample manipulation that is inconvenient for infectious materials. Yet, the ability to detect rapidly, directly, and selectively individual virus particles has the potential to significantly impact healthcare, since it could enable diagnosis at the earliest stages of replication within a host's system. One promising approach for the direct electrical detection of biological macromolecules uses semi-conducting nano-wires or carbon nano-tubes configured as field-effect transistors, which change conductance upon binding of charged macro-molecules to receptors linked to the device surfaces. One of the simplest medical nanomaterials is a surface perforated with holes, or nanopores. These pores are large enough to allow small molecules to pass but are small enough to impede the passage of much larger virus particles. The next step was cylindrical gold nano-tubules with inside diameters as small as 1.6 nm. When tubules were positively charged, positive ions were excluded and only negative ions were transported through the membrane. With a negative voltage, only positive ions could pass. The combining voltage gating with pore size, shape, and charge constraints allows achieving precise control of ion transportwith significant molecular specificity. Lieber's group has reported direct, real-time electrical detection of single

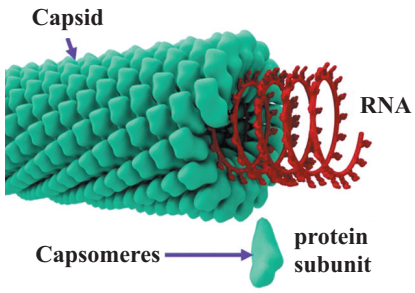

Fig. 2 a. Viral capsid. (By Thomas Splettstoesser, www.scistyle.com)

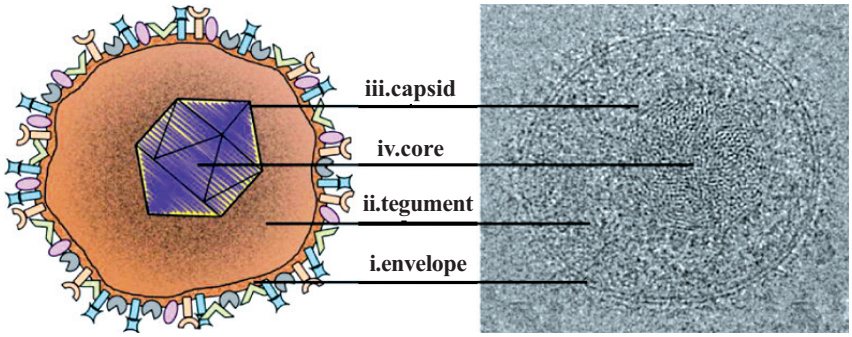

Figure 2b. Structure of the HSV-1 virion. The diagram at left depicts the four major structural components of the HSV-1 virion: (i) the outer envelope studded with various glycoproteins, (ii) the proteinaceous tegument layer, and (iii) the icosahedral capsid that houses (iv) the dsDNA core. Corresponding features in a cryo-electron micrograph of a virion are indicated at right. Bar = 500 Å.

virus particles with high selectivity using nano-wire field- effect transistors to measure discrete conductance changes characteristic of binding and unbinding on nano-wire arrays modified with viral anti-bodies. [29].

The integrity of such devices allows increasing the number of the detection viruses. The analysis of the manifold literature shows, that task of the detection pathogenic micro-organisms is timely. Therefore our available method would be one brick in the solution of the problems like that. Simultaneous acquisition of the vibrational and electronic fingerprints of molecular systems of biological interest, at the interface between liquid media, or at the air/solid, air/liquid interfaces in conditions similar to those encountered in nature or in model environments, requires the use of sensitive and specific spectroscopic probes. Such a characterization is difficult to achieve with conventional linear optical spectroscopies due to their rather poor sensitivity to the low number of molecules (Raman) or their maladjustment to water environment (infrared absorption), at the exception of PM-IRRAS in specific work conditions. In addition, these techniques are for most of them only partially surface specific. One of the promising solution of this problem is the use of the nonlinear Two-Color Sum-Frequency Generation Spectroscopy (2C-SFG) that meets the desired spectroscopic requirements. The goal of this approach is to probe membrane models of various forms and in various environments: (i) lipid monolayers and bilayers; (ii) deposited on substrates, floating on water as Langmuir layers and at a liquid-liquid interface; (iii) alone and in interaction with molecules, including peptides and proteins; (iv) submitted to controlled stress(chemical, pH, electrochemical potential).

The increasing amount of available data of protein three-dimensional atomic structures, determined mostly by X-ray crystallography (related to the fast expansion of that field around third generation synchrotron storage rings) and NMR, has given much information about role of many proteins in biological processes. However, it has been pointed out that knowing the structure does not directly lead to the knowledge of the function, and that the protein alone, without its environment or its partners of interaction, is not totally informative. Additionally, some proteins cannot be satisfactorily crystallized and thus cannot be accessed by X-ray crystallographic methods. Among them, membrane proteins need their membrane partners to fully play their role and are often not able to crystallize. In situ studies, and their according investigation techniques, are therefore favoured for such objects. In the following, in situ should not be understood as in vivo, but imply rather that the objects are designed and studied in an environment mimicking what they experience in vivo. On the other hand, due to their essential role as the barrier between the cell cytoplasm and the extracellular medium, membranes themselves also get a lot of attention regarding their shape, stability, structure, composition, modifications under stresses (pH, temperature, electric potential) and interaction with proteins, water and chemicals in solution. The electrical behaviour of bilayers makes them good candidates as membrane biosensors when attached to a conducting surface (semiconductor or metal). There are lots of possibilities to get average information on a given parameter of a membrane and its evolution under a given stress (e.g. diffusion of light, electrochemical methods, microbalance measurements). Specific in situ techniques allow direct investigation of key functional behaviours of synthetic membrane models (lipid mono and bilayers in an aqueous environment interacting either with selected proteins, ions or organic molecules) [30-31].

The strong absorption of the water vapor and the poor detection properties of conventional FTIR spectroscopy led to the discarding of this technique for the study of such interfacial systems. This evidence for the limited range of infrared spectroscopic tools dedicated to the study of such fragile objects in their specific environment was written only about ten years ago. From that time, there has been a lot of progress from the spectroscopic point of view. In addition to IR absorption spectroscopy (conventional or attenuated total reflection (ATR) configuration), three other IR-based spectroscopies have been able to address the issue of a molecular layer on water with a signal-to-noise ratio sufficient to extract scientific information from experimental data. PM-IRRAS, an IR absorption technique initially developed to study the nanosurface of metals, has been applied to that of liquids. Being less sensitive to IR radiation absorption and easier to detect, Raman spectroscopy is often used on biological environment, although the low count rate on monolayers requires long acquisition times.

Finally, the promising tool is SFG. Contrary to the previous ones, this second order nonlinear process is intrinsically specific to an interface, and involves no contribution from molecules in a centrosymmetric bulk, i.e., in solution or in gas phase. It has been extensively applied to solid interfaces in vacuum, controlled atmosphere and electrochemical conditions. For a few years, technological development of picosecond and femtosecond tunable laser sources have led both to an increase of the number of SFG experimental setups around the world and to a progressive application to fragile or buried interfaces. In addition to unique SFG setup is research based on usage of the CLIO Free Electron laser[32]. This latter allows probing specific vibrations located in the near and far infrared, which is again unique to date.

INSTEAD OF CONCLUSION

The ability of viruses to cause devastating epidemics in human societies has led to the concern that viruses could be weaponized for biological warfare. Further concern was raised by the successful recreation of the infamous 1918 influenza virus in a laboratory. The new approach of study and detection of viruses using their oscillation optical spectrum is the very promising step for development of novel methods of different diseases prevention and treatment in the modern health care. Optical spectroscopy's advantage of providing detailed and vast amounts of information on the viruses and other microorganisms under investigation can also be its disadvantage. For future developments in viruses and microorganisms identification, new instrumental designs need to utilize recent advancements while exclusively focusing on specific clinical needs. Furthermore, by building up extensive and reliable databases with probabilistic identification algorithms, optical spectroscopy has real potential as a noninvasive, easy-to-use, fast and reliable viruses characterization technique, ultimately giving identification at the single-cell level.

Unique characteristics of separate types the microorganisms, received by means of methods IR Fourier and Raman of spectroscopy, found the application in case of pathogenic biological agents identification. Advantages of spectroscopy methods before traditional methods of laboratory diagnostics are connected to the minimum expenditure of a researched material, speed of output of the response, absence the long stages of sample preparation, need uses of labelled reagents and chromogenic substrates, possibility of detection hardly cultivated and not cultivated forms of viruses. All this specifies perspective of use of new nonlinear optical methods of spectroscopy for indication of pathogenic biological agents, such are viruses and other pathogenic microorganisms provoking illnesses. For investigation of most suitable optical (vibrational) parameters of pathogenic microorganisms, including viruses, spread by an air flux by means of droplet of moisture and air-dust is necessary along with creation of advanced optical spectroscopy methods elaboration of optical nanoinstruments (sensors) which is the basis and challenge for development of novel measuring systems of XXI century health care.

Nowadays, due to issues of proliferation of dangerous viruses such as Ebola, different flu viruses (H1N1, H1N2, H2N1, H3N1, H3N2, H2N3), and others it is the very necessary to elaborate the novel procedures of biological security which will be based on advanced science and technology methods such as nonlinear optical spectroscopy which should be the tool not only for detection of viruses and other pathogenic microorganisms but very effective method of their treatment as well [33-39].

New and much stricter requirements for elaboration of effective actions for biological agents prevention are determined by the huge problems related to virus infections and epidemic diseases of over the world during recent years.

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The collection of knowledge and exchange of information about new achievements in development of methods and tools for study and treat the different viruses and other pathogenic microorganisms is the very important multidisciplinary task for researchers and practitioners.

The issue of developing of novel sensors compliant with the new requirements poses interesting technical challenges for researchers and engineers. The new optical sensors need to rely on one or more sensing mechanisms and produce a signal that indicates the oscillation properties of viruses.

Further activities should be addressed to utilization of scientific and technological potential of different research groups for development of physics and engineering methods and tools for detection of viruses and other pathogens as well as elaboration of equipment for their treatment, which will be novel and different way in modern biomedicine.

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KALEIDOSCOPE OF INTERESTING WORKS

THE CURRENT SITUATION OF CONVENTION ON THE RIGHTS OF THE CHILD IN CHINA IN RECENT 30 YEARS

FUYONG JIAO,
Children's Hospital, Shaanxi Provincial People's Hospital, xi'an China

JIALE WANG,
Xi'an medical university

HAOTIAN XU,
The Hospital of Heyan county, shaanxi province, China

WEN HUI,
Department of Pediatrics, Chang 'an Hospital, Xi'an China

ABSTRACT

It has been 30 years since the United Nations promulgated the Convention on the Rights of the Child on November 20,1989. That is a global convention. In the past 30 years, it has become a widely accepted legal regulation for the protection of children's survival and development. On November 20, 2012, the 20th anniversary of the China's accession to the UN Convention on the Rights of the Child was ceremoniously held in the Great Hall of the People's Republic of China [1]. In the 20years since joining the UN Convention on the Rights of the Child, China has made a historic achievements in the development of its Children cause. From 1992 to 2012, China's under-five mortality rate dropped from nearly 60 per thousand to 13.1 per thousand. At present, the net enrollment rate of primary School-age has reached 99.7% [2]. It plays an important role in promoting the health and development of children in China.

Keywords: *Children's Right, Promoting Development, Convention, Protection.*

INTRODUCTION

The Convention on the Rights of the Child applies to children who all over the world. The United Nations adopted the resolution 25 of the 44th Session of the General Assembly on November 20,1989, which was the first legally binding international agreement on the protection of Children's Rights, and entered into force worldwide on September 2, 1990. On December 29, 1991, the 23rd meeting of the Standing Committee of the Seventh National People's Congress ratified the Convention on the Rights of the Child and has become an International Convention widely recognized by China [3]. The Convention aims to create a good environment for the growth,survival and development of children [4]. The Convention is the "Charter" of the International Community for the Protection of Children's Rights. China always attaches great importance to the legislation on the protection of children's rights. China, as a state party, needs to further strengthen and improve legislation on the protection of the rights of the child.

1. LEGAL PROTECTION OF CHILDREN'S RIGHTS IN CHINA

Children are the future of the Chinese nation. China always attaches the great importance to the legal protection of Children's Rights. In order to protect children's rights in China, there are rules to follow. The passagment and implementation of the Law of the on the People's Republic of China on the Protection of minors make the work of protecting children's rights more legalized and institutionalized. Therefore, more extensive and in-depth publicity and implementation of the Convention on the Rights of the Child and the provisions on the protection of the rights of children in our laws have an urgent significance for promoting the overall development of children in our country.

1.1. Concept of Legal Protection of the Rights of the Child.

About the definition of child, China's law dose not make strict provision to this at present. Article 1 of the United Nations Convention on the Rights of the Child states: "A child is any person under the age of 18 years, unless the law applicable to him requires that the age of majority be below 18 years." [5]. According to the provisions of the Constitution and other relevant laws of our country, those who have reached the age of 18 are adults and those who have not reached the age of 18 are minors. Therefore, the legal boundary between adult and minor citizens has become the age of 18 and under. Article 2 of the Law of the People's Republic of China on the Protection of Minors stipulates, "Minors as mentioned in this Law refer to citizens under the age of 18." [6]. Since we have ratified the Convention on the Rights of the Child, adopted by the General Assembly of the United Nations on 20 November 1989, we shall in connection with the provisions of our national laws concerning adult and minor citizens [7].

1.2. The purposes and principles of China's legal protection of children's rights

The fundamental purpose of China's legal protection of children's rights is to fully protect their human rights and en-

able them to achieve all-round development and become successors to the cause of socialism. The constitution prescribed in paragraph 2 of article 46: "Fostering youth, children in Delhi, intellectual, physical all-round development from aspects such as" minors protection law "stipulated in article 1 for the purpose of the law" [8].“In order to protect the physical and mental health of minors, safeguard the legitimate rights and interests of minors, to promote minors totally developed in morality, intelligence, physique, training them as an ideal, morality, culture and discipline socialism after class, in accordance with the constitution, this law is enacted." [9]. The purpose of the Law on the Protection of Minors is actually the purpose of the legal protection of children's rights in China.

In accordance with the above purposes, China's legal protection of children's rights implements the following basic principles:

(1) The principle of priority for children.

(2) The principle of caring for the characteristics of children's physical and mental development.

(3) The principle of fairness and equality.

(4) Principle of adult obligation.

(5) The principle of comprehensive protection.

(6) The principle of combining general protection with special protection.

(7) Determine the principles of legal protection based on the actual national conditions and the actual needs of children.

(8) The principle of linking domestic law with international law.

2. CHINA'S ACHIEVEMENTS IN CHILDREN'S HEALTH AND DEVELOPMENT

2.1 The formation and development of child health care system

From the late Qing dynasty to the period of time before the founding of new China, our country has experienced many social conflict transformation. Child care institutions and professional staff team are not a system in our country, including woman's and children's health. Population health level and the western countries the gap are becoming bigger and bigger. Since 1950, the district medical personnel on duty of children in our country, to start from the neonatal period supervision, establish health card, for children's growth and development, health inspection and disease prevention and health care and is responsible for the guidance at any time [10]. At the same time, extensive community publicity and education on child health care has been carried out, with medical staff guiding newborn and premature infant care in the family and carrying out various preventive health care work in nurseries and kindergartens.

2.2 Establish a health care network

The penetration and intersection of disciplines promote the broadening and deepening of the medical field of child health care. In 2010 formally established the development of behavior that emerges from the child care the pediatric group, work closely with the child care group formation of academic communication mode, held every year at the same time behavior of child care and development of pediatrics academic conference, will promote the development of muti-disciplinary professional, promoting the comprehensive clinical ability of the child care physicians.2.3 improve nutritional status [11].

3. CONCLUSION

The legal protection of children's rights in China is extensive and comprehensive. The legal protection of children's rights is part of the protection of human rights. The basic characteristics of the legal protection of children's rights lie in its cohesiveness, restraint, authority and seriousness. The status of legal protection of children's rights indicates the level of legal civilization of a country. It is the task of the whole society to use legal weapons to protect the rights of children and promote their all-round development. With the implementation of the Law of the People's Republic of China on the Protection of Minors and other relevant laws, and the publicity and implementation of the UN Convention on the Rights of the Child. The legal protection of children's rights in Our country is bound to present a new situation.

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RESEARCH PROGRESS ON THE EFFECT OF VITAMIN D ON THE PATHOGENESIS OF KAWASAKI DISEASE AND THE PREDICTION OF CORONARY ARTERY LESION

FUYONG JIAO,
Children's hospital of Shaanxi Provincial People's Hospital Xi'an, Shaanxi 710001

GUOQIAN CHEN,
Xi'an Medical College Xi'an, Shaanxi 710068

XIAOHAN MEI,
Dept of pediatrics, the First people's Hospital of Xianyang, shaanxi, China

ZHONGDONG DU,
Beijing Children's hospital, Affiliated to Capital Medical University, Beijing, China

LIPING LI,
Xi'an Institute of Innovation, Yan'an University, Xi'an, Shaanxi 710001

Key Word: *Kawasaki disease vitamin D immune modulation of coronary artery disease*

Corresponding author: FUYONG JIAO, E-mail: 3105089948@qq.com

INTRODUCTION:

Kawasaki disease (KD), also known as mucocutaneous lymph node syndrome, is a kind of fever rash pediatric disease with systemic vasculitis as the main lesion. Its pathogenesis is not yet completely clear, the main pathological changes is systemic vasculitis, involving the small and medium-sized blood vessels of the body, especially coronary artery lesions are more obvious, can lead to coronary artery aneurysm, even serious sudden death. Because the disease can appear serious cardiovascular complications, has gradually attracted attention, in recent years, its incidence has gradually increased trend, has become one of the common pediatric acquired heart disease etiology.

Vitamin D acts on the VDR in various tissues and cells of the human body. Many studies have shown that vitamin D not only participates in the traditional calcium and phosphorus metabolism, but also participates in immune regulation through a variety of mechanisms. [1] Their roles in many human diseases such as cancer, diabetes, hypertension, cardiovascular disease, autoimmune and skin diseases have also been widely studied. [2] At present, the pathogenesis of KD is not completely clear, but most of the international scholars believe that it is an autoimmune disease, and the pathogenesis by many aspects of immune inflammatory factors. In view of the role of vitamin D in the regulation of immune response, and some studies have pointed out that there is a certain correlation between the levels of vitamin d and KD, especially in children with Kawasaki disease and coronary artery damage at low levels. [3] [4] Serum 25- (OH) D3 level in acute stage of Kawasaki disease has important predictive significance for the formation of CAL [5] The correlation between vitamin D and KD has attracted more and more attention in the world. In this paper, the study of vitamin D in recent years and KD in the role of the possible mechanism and vitamin D. Kawasaki disease with coronary artery disease to do a prediction.

1. METABOLISM AND PHYSIOLOGICAL ROLE OF VITAMIN D

Vitamin D is a fat-soluble vitamin, and is also an important steroid hormone. There are more than ten known types of vitamin D. But the most important ones are vitamin D2 and vitamin D3. Vitamin D3 is transformed from 7-dehydroxy cholesterol in the epidermis and dermis of most higher animals by ultraviolet radiation. VD3 is then converted by skin warming, then combined with vitamin D binding protein in plasma and transported to the liver, which is hydroxylated by 25-hydroxylase in mitochondria of liver cells. 25- (OH) D3 is transported to the kidney in blood and hydroxylated by cytochrome P450 in mitochondria of proximal tubular epithelial cells, resulting in the formation of 1,25 - (OH) 2D3,1,25-(OH) 2D3 As the most active form of vitamin D in the blood, it exerts its biological effects by specifically binding to the VDR. VDR in addition to the kidney cells, intestinal epithelial cells, thyroid cells, bone cells and other traditional cells, but also exists in macrophages, NK cells, T cells, B-cells, and other immune cells. [6][7][8] Vitamin D not only participates in the metabolism of calcium, phosphorus and parathyroid hormone, but also regulates the innate immune response and adaptive immunity by various mechanisms. [1][9][10][11]。

2. CORRELATION BETWEEN VITAMIN D AND KAWASAKI DISEASE

According to related literature, 25- (OH) D3 levels in children with KD were significantly lower than those in healthy children. It is considered that the decrease of 25- (OH) D3 level is involved in the pathological process of

KD, and the children who have the obvious decrease of the level of 25 (OHD) D 3 are more likely to have coronary artery injury. [12] In addition, according to a meta-analysis [13] Concentrations of 25- (OH) D3 were inversely associated with risk of cardiovascular disease morbidity and mortality, Reduced levels of vitamin D are associated with an increased relative risk of cardiovascular disease, so the extent of the decline is likely to be related to the presence of coronary artery damage in children with KD. According to recent epidemiological data on KD in Japan [14] The incidence of KD presents a certain seasonal: higher in winter (peak in January), Summer and autumn are lower (June to July lowest), which may also be related to shorter sunshine duration and lower vitamin D levels in winter.

3. MECHANISM OF VITAMIN D IN KAWASAKI DISEASE

At present, the pathogenesis of Kawasaki disease is not completely clear. The possible mechanisms include genetic susceptibility, infection, autoimmune and perinatal exposure [15] [16]. Vitamin D may be involved in the regulation of the pathogenesis of Kawasaki disease in the following aspects, of which immune disorders and inflammatory reactions are the most important mechanisms.

According to research, [11][17][18], the biological function of most 1,25 (OH) 2D3 is strong and related to the presence of vitamin D receptors (V DR) in almost all immune nuclei (including T cells, dendritic cells, mononuclear cells and macrophages, activated B cells). The specific combination is mediated. CD4+T cells are one of the targets of vitamin D action, which can be divided into Th1 cells, which secrete interleukin (IL)-2, tumor cell necrosis factor (TNF) beta, interferon (IFN) gamma, thus mediating cell immunity, and Th2 cells mainly secrete I L-6, IL-4, IL-5, IL-10, mediated humoral immunity, both of which are inhibitory T cells. Studies have shown that when VD3 is lacking, Th1 cell activity increases, Th2 cell and regulatory T cell activity weakens, inducing Th1 dominant immune response. VD3 can also bind to the VD reaction element (VDRE) in the IFN-γ promoter area through the VDR complex to directly inhibit the expression of IFN-γ. In addition, vitamin D can inhibit mononuclear.

Platelet activation occurred in the acute stage of Kawasaki disease, showing an increase in platelet-derived particle levels and platelet CD41 levels, resulting in the formation of coronary artery thrombosis [22][23]. Vitamin D receptors exist on platelets, so platelet function is affected by vitamin D. When the VD level is within a certain range, with the increase of vitamin D levels, the averages of MPV, P-LCR and PWD gradually decrease [24]. This shows that VD has the effect of inhibiting platelet activation, lipid factor release and inflammation. Vitamin D can reduce the expression of plasminogen activator I, tissue factors and thromboregulatory proteins. Its lack of adverse effects on hemostasis and thrombosis have been confirmed in vitro and animal experiments [25]. In addition, research shows that platelet activating factor in children with Kawasaki disease(PAF) content is significantly higher than that in healthy children, and the PAF content in the acute coronary artery injury group is higher than that in the non-injury group [26]. At the same time, the haploid type of platelet endothelial cell adhesion molecule 1 Leu-Ser-Arg may also be related to increased platelet count and the subsequent risk of chronic coronary artery lesions.. In the process of type I hypersensitivity reaction, IgE level is related to related inflammatory cytokines. The release of these inflammatory factors will also cause platelet activation, accelerate platelet release, and allow many immature large-volume tissues to enter local hematoma, which leads to an increase in MPV levels and thus expressing more Membrane protein molecules accelerate platelet activation, activate platelets or release a large number of bioactive substances, and participate in inflammatory reactions [24]. Therefore, vitamin D deficiency can increase platelet activation and promote inflammatory response through the above-mentioned mechanisms.

Endothelial dysfunction is also an important pathogenesis of Kawasaki disease. In mouse experiments using the Kawasaki disease model, it shows [27] [28]: the number of bone marrow endothelial progenitor cells in the Kawasaki disease mouse model has decreased significantly, and various functions and biological activities are seriously damaged. In the determination of an independent factor in the determination of elevated serum plasminogen activator inhibitor 1 (PAI-1EPC) in children with Kawasaki disease, active vitamin D can improve the activity of endothelin convertase-1 and its mRNA and related proteins by specifically binding vitamin D receptors expressed by endothelial cells. Da, promote endothelin-1 (ET-1) [31], suggesting that vitamin D can promote EPC synthesis. Therefore, vitamin D can improve endothelial cell disorders through the above mechanisms and thus reduce a series of effects caused by endothelial cell disorders in Kawasaki disease.

Some of the children with Kawasaki disease are significantly related to infection, and the pathogens of Kawasaki disease are not only related to bacteria and viruses, but may also be related to the increased activity of certain related enzymes of microorganisms such as chlamydia, ricketrus, mycoplasma and mites [32]. Recent studies have shown that bacterial superantigens are related to the etiology of KD. Among them, exogenous antigens are the antigens that cause Kawasaki disease, mainly toxic shock syndrome toxins, Streptococcus A-induced thermal exotoxin A-C, Staphylococcus aureus enterotoxin A-C, suggesting that Kawasaki disease is genetically susceptible. [33] caused by physical infection with pathogens. According to the results of Liu Zhiyuan and others [34], when the body lacks 25-(OH) vitamin D3, it causes the body's immune function to decline or even infection. This is mainly because 25-(OH) vitamin D3 can induce the expression of antibacterial peptides that resist bacterial and viral infections by binding to vitamin D receptors on the monocyte membrane, thus playing an immune role. At the same time, it can promote the differentiation of mononuclear cells into phagocytosis cells and enhance the body's resistance. In addition, 25-(OH) vitamin D3 can regulate the differentiation of antigen presentation cells, the proliferation of lymphocytes and the secretion of cytokines [35].

When the body is attacked by pathogenic microorganisms, 25-(OH) vitamin D3 can accelerate the secretion of anti-inflammatory cytokines and devour pathogens to protect the body from infection.

Because Kawasaki disease has obvious differences between races and regions, genetic factors may also play an important role in the pathogenesis of KD. At present, the most extensive research related to KD includes inositol 1,4,5-triphosphate 3 kinase (ITPKC), cystatase 3 (CASP3), B lymphocyte kinase (BLK), CD40, Fc fragments of HLA, TGF-β, and IgG [15], these factors Various pathways can be used to participate in the activation of immune cells such as T cells, B cells and dendritic cells, thus participating in maintaining the corresponding pro-inflammatory and anti-inflammatory balance [20]. Sun Ting [36] and others analyzed DNA methylation chips and gene expression chips by integrating bioinformatics, and found that most of the methylation genes related to Kawasaki disease were in a low methylation state, mainly participating in resonance reactions, inherent immune responses, coagulation and chemokine signaling pathways, and appropriate vitamin D supplementation. It can improve its whole genome methylation level [37], and research on vitamin D and epigenomes also shows that immune-related genes are usually significantly increased by vitamin D, while genes involved in cell metabolism are less sensitive to nuclear hormones. It can be seen that vitamin D can be raised in humans at a certain level. The epigenetics of Kawasaki disease affects the pathogenesis and return of Kawasaki disease.

Therefore, when vitamin D is deficient, the release of inflammatory factors can be promoted through the abovementioned mechanisms, thus damaging vascular endothelial cells, increasing vascular permeability and inducing the occurrence of vasculitis.

IV. PREDICTION OF VITAMIN D ON KAWASAKI DISEASE CORONARY ARTERY DISEASE

According to studies such as Zhang Yuanda [1], the level of 25-(OH)D3 in children with K D is significantly lower than that of healthy children. Considering that the decline in the level of 25-(OH)D3 is involved in the pathological process of KD. Most studies believe that children with a significant decline in 25-(OH)D3 levels are more likely to have coronary artery damage [38][39]. It can be seen that the degree of decline in 25-(OH)D3 levels may be related to whether children with KD have coronary artery damage. Therefore, serum 25-(OH) D3 levels in the acute stage of Kawasaki disease are of great predictive significance for CAL formation. However, the average low vitamin D water level of all Kawasaki patients decreased. Some studies have shown [12] that the serum 25-(OH) D3 levels of children with Kawasaki disease combined with CAL was significantly higher than that of non-CAL groups, and the acute 25-(OH) D3 levels increased and CAL occurred. There is a correlation. The diagnostic fold point is 64ng /mL or 65ng /mL, which may cause coronary artery hypercalcification, stimulate increased expression of cytochromease CYP27B1, resulting in an increase in blood 25-(OH) D3 levels [40], and due to inflammation It should be violent, leading to an increase in the number of receptors, resulting in an increase in the level of 25-(OH) D3 [41].

However, whether the vitamin D level is increased or decreased, the above studies have pointed out that serum 25-(OH) vitamin D3 levels in the acute stage are of great predictive significance for the formation of Kawasaki disease combined with CAL.

Conclusion: Vitamin D is closely related to children's Kawasaki disease due to its many effects of immune regulation and anti-inflammatory. Vitamin D deficiency may affect the return of Kawasaki disease and is closely related to Kawasaki disease complicated by coronary damage. However, some children with Kawasaki disease also show elevated vitamin D, which may be related to severe inflammatory reactions, excessive coronary artery calcification, and stimulating increased expression of cytochromease CYP27B1. Because the pathogenesis of Kawasaki disease and vitamin D are mostly adjuvant treatments in the prevention of coronary artery damage of Kawasaki disease, some large-scale clinical trials are still needed for further exploration and confirmation.

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FEATURES OF THE CLINICAL COURSE OF DIABETES MELLITUS IN ADOLESCENTS

BEGENCH H. ANNAYEV
(Ashgabat, Turkmenistan)

At the present time, complications of diabetes mellitus are one of the most common disorders of the endocrine system. This condition is caused by an increase in the number of pregnant women with gestational diabetes, as well as an advancing of the quality of diagnosis of diabetes mellitus among adolescents. Identification of women and children at high risk, timely diagnosis and treatment of diabetes mellitus is the main problem of modern endocrinology.

The purpose of scientific work – improvement of measures for the early detection of diabetes mellitus and metabolic disorders in the high-risk group for its development in adolescents and the prevention of complications of this disease.

Materials and methods: In the department of therapy of the Scientific and Clinical Center for Maternal and Child Health Protection, among 900 children who received inpatient treatment between 2018-2020, 76 adolescents underwent a more thorough analysis in terms of diagnosis, prevention and treatment of diabetes mellitus. Of these, there were 40 girls and 36 boys. The patients were 12-15 years old. Observed patientsunderwent a glucose tolerance test, studies of glycated hemoglobin and insulin levels in the blood, as well as complete clinical studies (complete blood count, urine analysis, biochemical analyzes, ultrasound, ECG and X-ray studies). Some patients also underwent an electroencephalogram of the brain.

The indicators of quality of life and the level of compensation for carbohydrate metabolism were assessed on the basis of international questionnaires according to the recommendations of ADA, ISPAD (2009).

Overview of the results. When assessing the level of carbohydrate metabolism compensation, 23.4% of adolescents noted full compensation, 19.8% had subcompensation, and 56.8% had chronic decompensation.

The analysis of the results of the quality of life showed a significant difference in patients with compensation and decompensation of diabetes mellitus. That is, the longer the compensation, the higher the indicators of the quality of life of patients.

Fully compensated adolescents have much higher quality of life indicators, which allows them to be more active, with an interest in participating in school, in creative and sports activities. This, in turn, improves the physical, emotional, mental and social well-being of adolescents.

The analysis of indicators of the quality of life of children showed that the first year of illness with diabetes is the most difficult for them. Since, almost all patients with diabetes mellitus are under certain stress during the first year. During this period, it becomes necessary to carry out additional measures for the rehabilitation and treatment of emotional disorders.

Evaluation of the functional state of the brain of adolescents with diabetes and the diagnosis of cerebral disorders were carried out by electroencephalographic studies of the brain. Various cerebral disorders were found in 49.4% of patients.

Examination of patients with type 1 diabetes mellitus revealed the following cerebral disorders: autonomic dysfunction in 63.7% of patients, neurosis-like disorders in 36.3% of patients, disturbances of emotions and behavior in 43% of cases. Signs of depressive syndrome were diagnosed in 28% of children.

The revealed disorders could not in all cases be attributed to manifestations of diabetic encephalopathy, since in 25.1% of patients there were indications of the onset of neuropsychiatric symptoms. The frequency of cerebral disorders in adolescents with diabetes mellitus type 1 depended on the degree of compensation for carbohydrate metabolism.

Clinical manifestations of cerebral disorders in patients with optimal metabolic compensation were 1.6 times less common in comparison with subcompensation and 2 times less often than in patients with decompensated diabetes mellitus.

Along with the clinical manifestations of autonomic dysfunction, 58% of adolescents with type I of diabetes mellitus showed a high level of personal anxiety, which indicates their constitutional susceptibility to stress and a tendency to experience negative emotions much more sharply than children with a low level of anxiety.

In children with subcompensation and decompensation of diabetes mellitus, the level of personal anxiety was significantly higher (2.96 ± 0.24 points and 3.32 ± 0.35 points, respectively) than in children with optimal compensation for carbohydrate metabolism (2.04 ± 0, 23 points).

Thus, in adolescents with diabetes mellitus type 1, metabolic parameters are a reliable factor in improving the quality of life. Patients who control their disease by themselves are able to fully compensate for metabolic disorders, just like healthy adolescents. Also this brings the quality of life of adolescents with diabetes mellitus closer to healthy people and increases the role of therapy.

Conclusions. The results found have created the possibility of developing individual and complex treatment, rehabilitation of patients with diabetes mellitus type 1, as well as the use of modern methods of insulin therapy, finding new, more effective ways of treating cerebral disorders, carbohydrate metabolism disorders.

DIFFERENT

RESEARCH PROGRESS OF ANGIOTENSIN-CONVERTING ENZYME 2 IN COVID-19 IN CHILDREN

JIAO FUYONG,
Xi'an Medical University, Xian,710068

LIU JING,
Department of Pediatrics, Shanxi Provincial People's Hospital, Xian Shanxi, 710001

Corresponding author: JIAO FUYONG
E-mail: 3105089948@qq.com

ABSTRACT

With the prevalence of SARS-CoV-2, 2019 in the world, the number of children infected with SARS-CoV-2, 2019 is increasing. Through angiotensin-converting enzyme 2 (ACE2) as one of the binding sites of SARS-CoV-2 infection, studying the role of ACE2 in the process of novel coronavirus infection is helpful to understand its pathogenic mechanism, better develop drugs, provide reference for the prevention and treatment of COVID-19 in children, and start treatment as soon as possible. This paper summarizes the clinical characteristics of COVID-19 's children and the role of ACE2 in the process of SARS-CoV-2 virus infection, aiming to provide reference for clinical diagnosis and treatment.

key words: *SARS-CoV-2; Coronavirus Disease 2019 (COVID-19); angiotensin-converting enzyme (ACE)2*

In December 2019, a case of pneumonia of unknown cause was found in Wuhan City, Hubei Province, China. The pathogen causing this disease was officially named "severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and SARS Coronavirus 2 (SARS Coronavirus 2). World Health Organization named the infectious pneumonia caused by this virus as "2019 coronavirus disease (COVID-19)" [1].SARS-CoV-2, a single-stranded positive-strand RNA virus, is a β-coronavirus [2], It has become a new pathogen causing a global pandemic. Until April 18, 2020, the global COVID-19 pandemic has caused about 2.3 million cases and more than 157000 deaths. In the United States, there have been 374329 confirmed cases and 12064 deaths. Of the 149082 reported cases, only 2572 (1.7 %t) were children, of which 398 (0.2 % were infants under 1 year old, with a total of 3 deaths reported [3].

1. CLINICAL FEATURES OF COVID-19 IN CHILDREN:

At the beginning of the epidemic, COVID-19-related cases were mainly reported in middle-aged and elderly patients, with few cases in children. As of February 11, 2020, of the 72314 cases of SARS-CoV-2 infection reported in China, children under the age of 19 accounted for only 2% [4]. The number of children under 3 years old is even less, with the development of the epidemic, the number of children is gradually increasing, and the virus infection affects premature infants, infants and young children[5,6,7]. SARS-CoV-2 was susceptible in all age groups, and there was no significant gender difference [8,9]. Children patients often get sick because of close contact with infected people or asymptomatic recessive infected people [10]. The most common symptoms after infection are fever, cough, runny nose and other upper respiratory tract infection symptoms [11,12]. There are also some asymptomatic infections. Chest CT showed ground glass changes or lung texture enhancement, and pharyngeal swabs were positive for 2019-nCoV nucleic acid. Compared with adults, the symptoms were usually mild, less common in severe cases, and mostly recovered after 1 week [12,1314]. There are also a small number of patients with upper respiratory symptoms and gastrointestinal symptoms. The proportion of asymptomatic infection is higher. Asymptomatic infection, as one of the sources of infection, is the difficulty of prevention and control [15]. Therefore, although the majority of mild patients, but also need to achieve early identification, early isolation, early diagnosis and early treatment.

Some studies [16,17] have proved that the mild symptoms of children after illness may be related to the immature immune function of children and the low level of immune response induced by virus infection, so it does not cause serious immune damage. Some studies [18] suggest that children may have mild symptoms because of insufficient expression of ACE2 protein or immature development and function.

For infants, studies have shown that SARS-CoV-2 virus proteins (orf1ab, ORF10 and ORF3a) can break down the 1-β chain of hemoglobin to form iron porphyrin [19]. Moreover, it can inhibit the normal metabolic pathway of heme and interfere with the normal synthesis and metabolism of heme in human body. Newborns have up to

80% fetal hemoglobin, which is composed of alpha and gamma chains, which can protect the body against SARS-CoV-2 infection. 15 Cross-immunization with other viruses may also provide protection for children [20]. Children under the age of 6 are likely to have an average of 8 to 12 upper respiratory tract infections per year, while adolescents and adults are only likely to have an average of 2 to 4 infections per year [21]. Children's young immune system and its effective T cells may have easier clearance of SARS-CoV-2 virus [22].

2. ANGIOTENSIN 2 (ACE2)

ACE2 is a key element in Renin-Angiotensin-Aldosterone System (RAAS)-[23,24]. It was discovered 20 years ago, and the metalloproteinase catalytic domain of ACE2 and ACE has 42% homology [24]. ACE2 is a glycoprotein metalloproteinase that exists in two forms: membrane binding and solubility[25,26]. Membrane-bound protein is a transmembrane protein with extracellular domain, which is the receptor of SARS-CoV-2 spinous process protein. The other is the soluble form of circulating ACE2, which can be cut and secreted as the outer domain of the N-terminal, and its low concentration can be found in the cycle, but the significance of soluble ACE2 is not clear.

ACE2 is mainly expressed in epithelial cells of lung, intestine, kidney, heart and blood vessels, as well as in ovary and testis. Both ACE and ACE2 belong to the ACE family of dipeptidyl carboxydipeptidases and have important physiological functions such as regulating blood pressure [27]. However, the active sites of ACE and ACE2 are different, so ACE inhibitors do not inhibit the activity of ACE2 [28]. The function of ACE2 is to convert angiotensin I (Ang I) into angiotensin-(1-9), and to degrade angiotensin II (AngII) into angiotensin-(1-7). When angiotensin 1-9 binds to Mas receptors, it antagonizes the classical RAS system, thus playing the role of anti-inflammation and reducing organ damage [27].

2.1 ACE2 and SARS-CoV-2.

ACE2 is the invasion target of SARS-CoV-2, and its S protein can trigger infection after binding to ACE2[29]. When the virus infects cells, it will cause the production of many inflammatory factors, such as interleukin-1 (IL-1), interferon-gamma (IFN-γ), tumor necrosis factor (TNF) and so on. At the same time, some studies have found that IL-4 and IFN- γ can down-regulate the expression of ACE2 [30]. When the expression of ACE2 is down-regulated, the renin-angiotensin (RAS) system is activated, resulting in damage to the heart, lungs, intestines and other organs.Therefore, the difference in the expression or function of ACE2 in the population, drug RAS blockers may increase the level of ACE2, increase the effective substrate of SARS-CoV-2 infection in some organs (such as lung and heart), and then increase the possibility of SARS-CoV-2 infection or the severity of infection. Although angiotensin enzyme inhibitor (ACEIs) does not directly regulate ACE2, both ACEI and angiotensin receptor antagonist (ARBs) can indirectly increase the expression of ACE2 [31] and activate ACE2, to maintain its binding to Ang II, which may delay the binding to SARS-CoV-2. Animal studies[31,32] have shown that the expression of ACE2 in ACEIs/ARBs-treated mice is significantly increased. In another study, diabetic patients treated with ACEIs had elevated circulating ACE2 levels [33].

There is evidence that SARS-CoV-2 infection may down-regulate ACE2 [34], leading to excessive accumulation of angiotensin II, leading to acute respiratory distress syndrome and fulminant myocarditis. A recent study showed that serum angiotensin II levels in patients with COVID-19 pneumonia were significantly higher than those in healthy people, and were linearly correlated with viral load and lungs [35]. Based on this, it can be speculated that the combination of SARS-CoV-2 and ACE2 may weaken the residual activity of ACE2, make the balance of ACE/ACE2 out of balance and increase the activity of angiotensin II, resulting in pulmonary vasoconstriction and organ damage caused by oxidative stress, thus increasing the risk of (ALI) in acute lung injury.

At the same time, ACE2 gene is a Xp22.2 linked gene [36], which may also be the basis of female sexual protection observed in COVID-19.

2.2 SARS-CoV and SARS-CoV-2.

The three-dimensional structure of the S protein of SARS-CoV-2 is similar to that of SARS-CoV in the receptor binding domain, so SARS-CoV-2 can also mediate the entry of virus into cells through the binding of S protein on the surface of virion to ACE2 on the surface of pulmonary epithelial cells[37,38]. In SARS-CoV, overexpression of ACE2 can promote the virus to enter the body and replicate in cells that are resistant to the virus [39]. A similar pathogenesis has been found in SARS-CoV-2, and it has recently been confirmed that its entry into host cells is also dependent on ACE2, and that the affinity of SARS-CoV-2 spinous process protein to ACE2 may be 10 to 20 times higher than that of SARS-CoV spinous process protein to ACE2[40]. This shows that SARS-CoV-2 can target the same kind of cells targeted by SARS-CoV. In fact, SARS-CoV is mainly located in lung cells and macrophages [41]. For the animal model of SARS-CoV, the expression of ACE2 in viral infection was down-regulated, resulting in inflammatory response associated with acute lung injury and impaired myocardial contractility [42]. Then if the same mechanism exists in SARS-CoV-2, it may be the basis of ARDS, myocardial injury and fulminant myocarditis. Similarly, acute respiratory distress syndrome ((ARDS)) is highly prevalent in SARS, which may also be due to the pulmonary tropism of the virus. In addition, the extrapulmonary manifestations of COVID-19, such as early gastrointestinal manifestations such as nausea and vomiting, may be related to the systematic distribution of ACE2 in multiple organs.

3. PROSPECT

The mortality of severe COVID-19 is high, so it is very important to prevent and improve the damage of heart, kidney, liver and other organs caused by SARS-CoV-2. There is a certain potential to find the therapeutic drugs and methods of COVID-19 from the invasion target ACE2. Some studies have shown that inhaling recombinant ACE2 in mice with acute respiratory failure can improve the related indexes of lung function in mice [43]. Animal experiments have also confirmed that attenuated vaccinia virus expressing SARS-CoVS protein can induce mice to produce protective neutralizing antibodies and play a role in preventing SARS, while parainfluenza viruses expressing SARS-CoV-2 protein can also induce African green monkeys to produce protective neutralizing antibodies [44, 45]. This suggests that antibodies against S protein may play a role in the treatment of SARS-CoV-2 and even improve the prognosis.

At present, there are relatively few cases of COVID-19 in children, coupled with the special physiological characteristics of children, clinical trials of drugs specifically for COVID-19 in children have not been carried out. The current guidelines all point

out that there are no specific antiviral drugs for the treatment of COVID-19 in children. It is recommended that interferon and lopinavir / ritonavir should be tried early, or ribavirin can be added. Interferon-α and lopinavir / ritonavir are more commonly used in clinical practice [46]. It is expected that more clinical trials of drugs will be carried out in the near future to confirm the efficacy and safety of more drugs in the treatment of COVID-19 in children.

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RESEARCH PROGRESS OF POST-TRAUMATIC STRESS DISORDER (PTSD) IN CHILDREN AND ADOLESCENTS

WENYAN JIAO,
Psychological department, shaanxi Provincial people's Hospital. Xi'an China

TUNGALA OSGONBAATAR,
Association of Pediatric Researchers of Mongolia

WEN HIE,
Department of Pediatrics, Chang'an Hospital, Xi'an China

ABSTRACT

Post-traumatic stress disorder (PTSD) in Children and teenagers is a disease that seriously affects children's physical and mental health. in this paper, the etiology, clinical manifestation, diagnosis and treatment methods and especially the clinical medication, cognitive, psychological treatment and prevention were summarized, hope to have promote role for diagnosis and treatment and children's health.

INTRODUCTION

Post-traumatic stress disorder (PTSD) is defined as the result of a child or adolescent experiencing, witnessing, or experiencing one or more actual deaths, threats of death, serious injuries, or threats to physical integrity involving themselves or others. The individual's delayed appearance and persistence of mental disorders. The incidence of PTSD has been reported variously, with women more likely to develop PTSD than men. Shortly after the inclusion of POST-traumatic stress disorder (PTsD) in the DIAGNOSTIC and Statistical Manual of Mental Disorders (DSM-DSM-III), researchers at Terr conducted one of the first such studies in children, and numerous subsequent studies have shown that exposure to a range of stress factors can lead to severe PTsD in children and adolescents. Child mental health workers are also becoming increasingly aware of the serious consequences of child exposure to traumatic events, including not only acute stress disorder, but also serious, long-term psychiatric sequelae.

PATHOGENE

PTSD in children and adolescents is associated with a number of factors, These factors mainly divides into the family and social psychological factors (such as gender, age, race, marital status, family, environmental conditions, education level, stressful life events, personality, defense style, childhood trauma, family violence, war, social support, etc.) and biological factors, such as genetic factors, neuroendocrine factors, nerve and biochemical factors, etc.). Major traumatic event is the basic condition of PTSD, which has great unpredictability.

CLINICAL PICTURE

There are three core symptoms of PTSD that are common in adults: traumatic reexperience symptoms, avoidance and numbness symptoms, and increased alertness. The symptoms of PTSD in children differ from those in adults.

1. Traumatic reexperience symptoms

It is mainly manifested as that the patients' thinking, memory or dream repeatedly and involuntarily emerge with the situation or content related to trauma, and there may also be a serious scene reaction, and even the traumatic event seems to happen again.

2. Symptoms of avoidance and numbness

It is mainly manifested in patients' long-term or persistent efforts to avoid events or situations related to traumatic experience, refusal to participate in relevant activities, avoidance of traumatic locations or people or things related to trauma, and some patients even appear selective amnesia, unable to recall the details of events related to trauma.

3. Increased alertness symptoms

The main manifestations are excessive vigilance and the enhancement of jump response, accompanied by inattention, increased irritability and anxiety.

OTHER SYMPTOMS

Some patients can also show the abuse of addictive substances, aggressive behavior, self-injury or suicide behavior, etc., these behaviors are often the manifestation of the patient's psychological behavior coping style. Depressive symptoms are also common in many PTSD patients.

5. Symptoms and characteristics of children with PTSD

Traumatic reexperience symptoms of children can be shown as nightmares, replaying traumatic events repeatedly, playing trauma-related theme games, emotional excitement or sadness when faced with relevant prompts, etc. Avoidance symptoms in children are often manifested as separation anxiety, clinginess, and unwillingness to leave their parents. Hypervigilance symptoms in children are often shown as excessive startles, high vigilance, attention disorders, irritability or rage, difficulty in sleeping, etc. And PTSD may manifest differently in children of different ages.

Typically, as children mature they show more and more adult-like symptoms of PTSD. So adolescents with PTSD may meet the DSM iv criteria for repetitive experiences, avoidance, apathetic feelings, and hyperarousal. Adolescents with chronic PTSD who experience chronic or repetitive stressors may also exhibit severe dissociative traits, including derealization, depersonalization, self-harming behavior, substance abuse, and intermittent outbursts of anger or aggression. Children are more likely than adolescents to exhibit traumatic re-enactments in play, painting, or verbal expression. Sleep disturbances may be particularly common in pre-adolescent children.

Infants, toddlers, and preadolescents may exhibit generalized anxiety symptoms (fear of separation, stranger anxiety, and monster or animal fear), avoidance of scenes that may or may not have an obvious connection to the original trauma, sleep disturbances, and memorization of words or symbols that may or may not have an obvious connection to the traumatic event.

DIAGNOSIS

According to DSM-iv-TR, the diagnostic criteria for PTSD are as follows:

1. The standard A

The individual has been exposed to both traumatic events: ①A1 The individual has experienced, witnessed, or experienced one or more actual deaths involving himself or others, or has been threatened with death, serious injury, or physical integrity has been threatened. ②A2 The person's reactions include intense fear, helplessness, or panic. Caution: In children, this may manifest as chaotic or provocative behavior.

2. Criteria B

Traumatic events are continually re-experienced in one (or more) of the following ways: ①B1 Repeated, intrusive, distressing memories of the event, including images, thoughts, or perceptions. Note: In young children, repetitive play can present themes or aspects of traumatic events. ②B2 Repeated troubled dreams about the event. Note: In children, frightening dreams may occur but have no identifiable content. B3 appears or feels as if the traumatic event has recur (including reexperiencing the traumatic experience, delusions, hallucinations, dissociative flashbacks, including those occurring during waking or poisoning). Note: Trauma-specific re-enactments may occur in young children. ④B4 Intense psychological distress when exposed to internal or internal cues that symbolize or resemble some aspect of the traumatic event. ⑤B5 Physiological response to exposure to internal or internal cues that symbolize or resemble some aspect of a traumatic event.

3. The standard C

Persistent avoidance of stimuli associated with the trauma, numbness in response to general things (which did not exist before the trauma), such as three or more of the following: ①C1 Avoidance of trauma-related thoughts, feelings, or dialogue efforts. (2) C2 avoidance triggers the recall of the traumatic activity, place, or person. C3 cannot recall important aspects of this trauma. ④C4's interest in or participation in important activities decreased significantly. ⑤C5 the feeling of alienation from others. ⑥C6 Emotional limitations (e.g., inability to feel love). ⑦ The feeling of a shortened future (e.g., not expecting to have a career, marriage, children or a normal life).

4. D

The symptoms of increased alertness (which did not exist before the trauma) are 2 or more of the following: ①D1 Difficulty falling asleep, or difficulty sleeping. D2 is irritable or irritable. D3 concentration difficulty. ④D4 hypervigilance. ⑤D5 excessive startle response.

5. Standard E

The above disorders (symptoms of B, C and D) lasted for more than 1 month.

6. Standard F

These disorders result in clinically significant distress or impaired functioning in social, professional or other important ways.

TREATMENT

Children and adolescents with PTSD can use either psychotherapy or physical therapy, or a combination of both. Available research data show that. Behavior therapy known good king other values of psychological treatment: the medication is not the best way to treatment effect, usually at the beginning of the all treatment should be carried out include patients with parents, psychological education, data also showed that individual therapy, family therapy and the effect of no significant difference between group therapy, but at present most of the more individualized treatment. In many cases, for abused children, individualized therapy may begin, with practice with parents slowly complementing the treatment process to enhance outcomes. For children and adolescents who experience other relatively common traumatic events, like hurricanes or school shootings, group therapy in schools is appropriate,

According to the current evidence-based medicine, psychotherapy is the most effective method for the radical treatment of PTSD. The psychotherapy commonly used for PTSD includes cognitive behavioral therapy, hypnosis therapy, eye movement desensitization and reprocessing, and psychoanalysis therapy. Drug therapy has a positive effect on alleviating patients' symptoms and strengthening psychological therapy, and the combination of the two should be the first choice. At present, SSRIs are the preferred treatment drugs, among which sertraline, paroxetine and fluoxetine have good efficacy.

Many remarkable findings indicate that many key psychobiological systems are maladjusted and disordered in PTSD patients. Evidence-based medical evidence suggests that adrenal energy and changes in the hypothalamic pituitary adrenal axis enhance physiological responses and disorders. Abnormalities associated with PTSD have also been shown to be associated with serotonin, opioids, dopamine, thyroxine, corticotropin-releasing factor, and glutamine. Finally, this extremely common disorder of comorbid pharmacological responses to PTSD (e.g., major depression, extreme anxiety) has made pharmacological treatment of PTSD an important therapeutic concept.

Despite the overwhelming scientific evidence. But medication for PTSD is still largely empirical, that is, specific

Drugs are often effective only for one particular symptom. In fact, of all current psychiatric disorders including PTSD.

There is little data linking disorders in the psychobiological system with specific drugs. In research including clinical practice, almost Each group of psychiatric drugs has been used to treat PTSD. The most studied effective medications for PTSD include antibiotics.

Suppressors: Selective 5-tryptamine reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), dichyclic antidepressants (TCAs), and other 5-hydroxytryptamine drugs (trazodone and nefazodone). Antiadrenergic drugs include A receptor agonists (Clonidine and guanfacine) and B receptor antagonists (propranolol). Research into mood-soothing antiseizure drugs (carbamazepine and valproate) was initially based on their anti-epileptic properties. Other drugs being studied include diocins, anti-anxiety drugs and antipsychotics.

- Psychological treatment
- Cognitive behavioral therapy A
- Eye movement desensitization and reconstruction of BC
- Psychodynamic therapy D
- Family therapy E
- Group therapy E
- Art Therapy E
- Drug treatment
- propranolol
- Clonidine B
- S - hydroxytryptamine and then extract preparation C
- Tricyclic antidepressants D
- Eurpirone D
- Traditional antipsychotic E

1, drug treatment, use drug therapy can effectively alleviate the patient, at the same time to strengthen the psychological treatment work, a combination of both can be as the preferred treatment, now the preferred treatment including SSRIs, patients can take paroxetine in accordance with the doctor's advice, sertraline and fluoxetine, all can have good curative effect, reduce the condition of patients with the disease.

2, other treatment, combined with the current evidence-based medicine, the therapy is to effect a radical cure traumatic psychological stress disorder, this is a remarkable curative effect treatment, commonly used method is hypnosis therapy, cognitive behavior therapy and psychoanalysis, need to combine the patient's physical condition, adopt the method of appropriate treatment, help the recovery of illness, Greatly reduce the harmfulness of disease. Most patients recover within a year, while individual patients remain unhealed for many years and develop persistent psychosis.

3, nursing, for conscious patients, should ignore setbacks and mental pain, for traumatic events do not perceive, do not contact, not to recall. Patients can take a walk outdoors, exercise and listen to music and other ways, can effectively transfer the attention of the stress source, the patient's diet to keep light, should not eat stimulating food is too serious.

Treatment for traumatic psychological stress disorder is very important, early treatment can control the patient's illness, treatment of hope that the above measures, can alleviate the patient's condition, pay attention to more rest during treatment, patients with friends to keep a good state of mind, with the friend's treatment work, improve the quality of life in onset period, is helpful to the recovery of health, And can reduce the harmfulness of the disease.

THE PREVENTION

PTSD typically develops within a few days to six months after a traumatic event, and lasts at least a month, months or years, and in some cases decades. Acute PTSD occurred within 3 months, chronic PTSD occurred more than 3 months, and delayed PTSD occurred at least 6 months after the traumatic event. If some psychological assessment tools can be used to assess the mental health status of individuals after traumatic events, it will be helpful to screen out high-risk groups for PTSD, and thus provide effective intervention strategies for high-risk groups.

A RESEARCH PROGRESS ON THE PATHOGENESIS OF JUVENILE IDIOPATHIC ARTHRITIS

FUYONG JIAO,
Children's Hospital, 3rd Affiliated Hospital of Xi'an Jiaotong University

CUIXIANG XU,
Shaanxi Provincial Key Laboratory of Infection and Immune Diseases

JING YUAN,
Xi`an Medical University

JIANYING FENG,
Children's Hospital, 3rd Affiliated Hospital of Xi'an Jiaotong University

Corresponding author: JIAO FUYONG,
E-mail 3105089948@qq.com

ABSTRACT

Juvenile Idiopathic Arthritis (JIA) pathogenesis is not very clear, but it may be associated with specific components of various infectious microorganisms as foreign antigens for people with a genetic background, activate immune cells, and trigger an abnormal immune response by directly damaging or secreting cytokines, autoantibodies. Cause damage and degeneration of our own organization. Especially certain bacteria, viruses, special components (such as HSP) can be used as superantigens, T cells are activated directly by binding to T cell receptors (TCR) with a special variable region β chain (chain) structure and stimulate immune damage. Self-tissue denaturing components (endogenous antigens), can also be used as an antigen to trigger an immune response to its own tissue components. Further aggravate the immune damage.Intestinal microbial groups and environmental factors may also play an important role in the pathogenesis of JIA.

Juvenile idiopathic arthritis is a common rheumatic disease in childhood and adolescence, characterized by chronic synovitis with systemic multiple organ dysfunction,causes serious harm to the physical and mental health of children and adolescents.It is an important cause of disability and blindness in childhood. The disease has many names, such as in juvenile rheumatoid arthritis(RA), juvenile chronic arthritis (JCA), juvenile arthritis (JA), etc. In order to facilitate the study of the genetics, epidemiology, outcome and implementation of treatment programmes for such diseases by the international collaborative group, 2000 Expert Meeting of the International Association of Rheumatology Societies (AR) Committee of Science and Technology, " Persons with unexplained joint distention and pain in childhood and adolescence (under 16 years of age) for more than 6 weeks ", named juvenile idiopathic arthritis (JIA).Divided into (1) systemic arthritis (systemic JIA); (2) Multiple joint type: rheumatoid factor negative (polyarticular JIA,); and JIA RF negative); (3) Multiple joints: rheumatoid factor positive (polyarticular JIA RF positive); (4) Less joint type (oligoarticular JIA); (5) Arthritis (enthesitis related JIA,) associated with inflammation at the attachment site ERA); (6) psoriatic arthritis (psoriatic JIA); (7) Unidentified juvenile idiopathic arthritis (undefined JIA): arthritis that does not meet either or more of the above categories.[1]

Systemic juvenile idiopathic arthritis (sJIA) is an autoimmune disease characterized by fever, rash, hepatosplenomegaly, lymphadenopathy, and serositis. Elevated levels of cytokine secretion are typical features of sJIA. IL-6 plays an important role in the pathogenesis and clinical manifestations of sJIA.The pathogenesis of the disease is considered to be the result of the combination of host genes and environmental factors.

THE ETIOLOGY AND PATHOGENESIS ARE STILL UNCLEAR AND MAY BE RELATED TO MANY FACTORS

1. infection factors

There are many reports of bacterial (Streptococcus, Yersen, Shigella, Campylobacter jejuni, Salmonella spread, etc.) viruses (parvovirus B、rubella virus and EB viruses and mycoplasma and chlamydia infections associated with the disease, but none of them can be confirmed as the direct cause of the induction of the disease.

2. genetic factors

A lot of information confirms JIA genetic background, the most studied human leukocyte antigen (HLA with HLA-DR4(especially DR1*0401), dr8(especially DRB1*0801), and DR5(especially DR11104) loci are the JIA susceptible populations. Other HLA sites related to JIA pathogenesis are HLA-DR6、HLA-A2. Other HLA sites were also found to be associated with JIA onset.

The occurrence of genetic factors JIA has a certain genetic tendency, and the types of JIA between different populations are also different. The reason may be related to some genetic structural characteristics or polymorphisms.

Genetic factors are helpful to determine the high-risk population and provide basis for JIA prevention and treatment. The relationship between human HLA and JIA is almost clear. I and II HLA allele changes are associated with JIA pathogenesis.Studies of siblings (sisters) with JIA in the same family show that some HLA genes have structural characteristics, such as DRB1 0801, DQB1 0402, etc.) resulting in a susceptibility to JIA of 0. Children with ankylosing spondylitis are the same as adults, HLA -B27 positive ratio reached more than 90%. The positive rate of HLA -B27 in children with less articular JIA complicated with iris ciliary body inflammation was also significantly higher than that in normal population. From a clinical perspective, the prognosis of HLA -B27 positive children was not as good as that of HLA -B27 negative children.The current study of HLA genetic structural characteristics is not enough to provide sufficient evidence related to various types of JIA.

Polymorphisms of Other Genes Many individuals have HLA susceptible alleles but do not JIA, them and many types of JIA families are rare indicate that polygenes may have an impact on JIA pathogenesis. There are many other candidate genes, because the JIA is mainly inflammatory,thus most of the studies are cytokines in the process of immune response. Proinflammatory cytokines include tumor necrosis factor-interleukin (IL)-6, IL -1, etc. The important role of TNF -o and its receptors in JIA pathology has been confirmed by many studies. Genetic analysis showed that, the polymorphism of some sites of TNF -o[promoter may be related to the onset of systemic JIA, TNF -o[promoter polymorphism sites involved include I308, I238, I1031, I863, I857, etc; Besides, TNF -o[microsatellite alleles may also be associated with JIA pathogenesis. The expression of IL-6 in sJIA serum is also abnormally high.Recently found IL-6 promoter-174 polymorphism may be the cause of IL-6 overexpression [3]. But the outcome is controversial. Contrary to proinflammatory cytokines, IL -10 with anti-inflammatory properties decreased serum levels in severe JIA children. This phenomenon may be attributed to the formation of "ArA" IL 10 haplotypes (haplotype) IL -10 promoters I1082, I819 and I592, but there are opposite results. Polymorphism in the regulatory region of cytokine expression affects cytokine expression, these factors with HLA specific alleles, may be JIA multiple influencing factors.

3. Immunological factors

Many studies have confirmed that JIA are autoimmune diseases: some children have rheumatoid factor (RF) in serum and synovial fluid autoantibodies such as anti-denaturing IgG antibodies) and anti-nuclear antibodies (ANA); Rheumatoid arthritis cells present in synovial fluid, RAC); Serum IgG、I gM and I gA increased in most children; 4 Peripheral blood CD4T cell amplification; Serum inflammatory cytokines increased significantly.

T cells T cells are thought to play an important role in JIA pathogenesis. The relationship between JIA and HLAII antigens indicates that CD4T cells play a prominent role in JIA pathogenesis. JIA T cell subsets and dysfunction, if the polyarticular and sJIAT cell proliferation response is reduced, T cell reduction, etc. T cell function is mainly reflected by the abnormal secretion of cytokines. JIA T1/T2 immune response was abnormal. Contrary to allergic diseases, autoimmune diseases include JIA types of immune responses, T1 response enhancement, T2 response weakened,and this cytokine response was also observed in JIA children. But deep research shows that the problem is not so simple. At different stages of the disease, T1/T2 types of response may vary. A recent study found that apart from T1/T2 reactions, T cells also affect the immune response to disease, JIA CD4、CD; with less joint type T cell reduction may suggest poor prognosis. JIA the synovial fluid, T cells are activated, also indicates that T cells play an important role in joint damage.

B cell JIA are considered to be autoimmune diseases, especially some types JIA the presence of rheumatoid factors (RF) or occult types RF, and the presence or absence of RF is also associated with the prognosis of JIA.B cells and their secreted antibodies also play an important role in JIA pathological processes. The relationship between antinuclear antibody (ANA) and less articular JIA and uveitis is very clear. Studies have found that blocking signaling between T cells and B cells by antibody binding CD or its ligands can alleviate the clinical symptoms of human rheumatoid arthritis. However, whether it can play a role in clinical practice needs further study and confirmation. The relationship between JIA and CD、CD ligands has not been studied.Most JIA children have not found characteristic autoantibodies in their bodies. Some special types of arthritis, such as x linkage without C globulinemia, are prone to autoimmune diseases, mainly arthritis. Its clinical manifestation is consistent with systemic JIA.A large amount of monocyte and granulocyte infiltration can be seen around the vessels in the early stage of sJIA involvement of joint inflammation, lymphocytes are almost absent. JIA infiltrating polymorphonuclear neutrophils (PMN) and mononuclear cells in the synovium during the course of the disease can release proinflammatory cytokines to cause synovial inflammation. Among them, important cytokines are IL -1、TNF -0t and so on. Under these cytokines, it can stimulate the release of metalloproteinases by neutrophils, phagocytes and so on. Aggravate joint damage, removal of neutrophils can completely block or reverse joint inflammation. The study found, in the affected joint, activation of proinflammatory factors by local immune complexes with activated complement fragments, damaged tissues, or fear cross-linked mononuclear cells, such as IL -1B and INF -0t, they can induce lower levels of neutrophil recruitment. These little activated neutrophils ooze blood vessels and back into the joint to form a proinflammatory environment. This is necessary for the persistence and expansion of arthritis. Except for local effects, in recent years, different from other rheumatic diseases SLE、Kawasaki disease, different types of peripheral blood neutrophils exist in different types of JIA, activation of peripheral blood neutrophils during active JIA especially sJIA neutrophil activation is very obvious.

4. involvement of gut microbiota in JIA pathogenesis

The pathogenesis of the disease is considered to be the result of the combination of host genes and environmental factors.But what causes the body's sensitivity to JIA is unclear. Microbiome has received increasing attention as a potential enabler of immune-mediated disease development, including inflammatory bowel disease [5], type 1 diabetes, and rheumatoid arthritis. Also in JIA, there is growing evidence that the composition of the microbiome is different from that of healthy individuals. There is growing evidence that the microbiome may influence the development of the immune system, the integrity [6] of the intestinal mucosal barrier, and the differentiation of T cell subsets. which may lead to dysregulation of the immune system and thus may play a role in JIA development.Controlling the effects and effects of altered microbial groups, such as fecal microbial transplantation, may provide prospects for future therapeutic interventions.A report suggests that the microbiome is involved in JIA pathogenesis, and the microbiome affects autoimmune development in general and micro-local.[2][7]

5. Research Progress of High Migration Rate B1 in Children with Rheumatoid Disease [4]

High migration rate group protein B1 as a non-histone expressed in eukaryotic nucleus, can promote inflammatory response after release to extracellular, participate in the positive feedback loop of cytokines, and are closely related to the pathogenesis of many autoimmune and inflammatory diseases. Recent studies have found that it may become a serum marker of purpura nephritis and lupus nephritis, and may predict the prognosis of juvenile idiopathic arthritis and the lack of response to intravenous gamma globulin in children with Kawasaki disease.

6. Environmental factors

The effect of environmental factors on the incidence of rheumatism is not very clear. It is generally believed that families with relatively poor socioeconomic conditions are at increased risk of rheumatic diseases.Growth in cold and humid areas of the disease is relatively more.As with other rheumatic diseases, the incidence of JIA population has increased in recent years. The reasons for the increase in the incidence of this population are unclear. According to one view, environmental factors and lifestyle may be the cause of increased JIA morbidity. The environmental one gene interaction (environmental-genet—ieinteraction) hypothesis suggests that environmental factors may make phenotypes (phenotype) different under the same genotype (genotype) premise. But at present, this only exists in the conceptual and theoretical stage, and needs careful and in-depth research data support. The increase in the incidence of rheumatic diseases is related to the abnormal immune response caused by environmental factors, which is similar to the "hygiene hypothesis" in allergic diseases: environmental factors cause not only T2 response tendency, but also T1 response. Recent epidemiological studies suggest that the evidence for this hypothesis is inadequate.

While infection has been thought JIA may be associated with infection, infection as a JIA cause has not been confirmed. The causes of association JIA and infection include: Lyme disease, reactive arthritis and so on, which are infected by pathogenic microorganisms, are very similar to JIA, and some studies have shown that epidemiological and serological antibody tests suggest that some JIA children have a history influenza virus infection. Studies of infection are not well documented, possibly because infection often occurs early and is systemic rather than intra-articular, whereas arthritis is due to subsequent autoimmune responses.

CONCLUSION

To sum up, the pathogenesis of JIA is not very clear, but it may be associated with specific components of various infectious microorganisms as foreign antigens for people with a genetic background, activate immune cells, and trigger an abnormal immune response by directly damaging or secreting cytokines, autoantibodies. Cause damage and degeneration of our own organization. Especially certain bacteria, viruses, special components (such as HSP) can be used as superantigens, T cells are activated directly by binding to T cell receptors (TCR) with a special variable region β chain (chain) structure and stimulate immune damage. Self-tissue denaturing components (endogenous antigens), can also be used as an antigen to trigger an immune response to its own tissue components. Further aggravate the immune damage.Intestinal microbial groups and environmental factors may also play an important role in the pathogenesis of JIA.

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ABOUT OF SOME PECULIARITIES OF EXPRESSION OF THE GENES

DAVIT TSKHOMELIDZE

ABSTRACT

Within the existing ecosystem, there are probably many biological programs operating in the human body. Many of them are highly dependent on environmental factors, although often it is important to work with environmental factors to identify the epigenetic mechanisms hidden under some of these programs. I would also like to mention that in this paper I had to use a new term - უფროსი მშობლები, because I could not find a special singal word in Georgian that would be appropriate for English- Grandparents.

All humans have two parents (there is one exception at least for now, when newborn had two mothers and one father) and usually four distinct grandparents. Genetically you are a recombination of four separate individuals, but that does not mean you have an equal contribution from four separate individuals. Exactly half of your genome derives from each parent. But while the proportion of one`s inheritance from parents is fixed exact necessity, the fraction from grandparents is governed by chance. take into account the amount you inherit from a Grandparent is slightly random. These affect a wide range of traits, and it would be extremely difficult to know exactly what the grandparent passed on. These genes would also be present in your corresponding parent, but might not be expressed. Genes that "skip a generation" don`t technically because of this. They are present in the parents, but they might be a recessive gene, or the trait might only be expressed in another gene is present. This way you could get a trait maybe hair color for example that was the same in the child and grandparent, but not in the parent in between the two.

The idea that our environment and lifestyle can alter how our genes behave is part of the new field of science called Epigenetics.

Epigenetics is the study of heritable changes in gene expression that do not involve changes to the underling DNA sequence - a change in phenotype without a change in genotype which in turn affects how cells read the genes. Epigenetic changes modify the activation of certain genes, but not the genetic code sequence of DNA. In simple terms it`s a mechanism that describes how genes can be switched on or off by chemical signals, a bit like a dimmer switch on light, without altering the DNA structure. These signals can alter the way genes produce proteins or signal other genes and importantly, they can last months or years and are potentially reversible. These epigenetic switchers are triggered by many factors such as our lifestyle, environment, disease state and our age, and as the development of a growing foetus in the womb is totally dependent on these signals, it can alter the function of its cells. This can come in many forms and shows just how important these finely controlled mechanisms are for normal life. The one most easily studied is methylation, in which a methyl chemical group is added or removed from the DNA. Other changes include how DNA strands are folded tightly or loosely around chromatin. The method that determines which traits are inherited from each parent by the offspring is known as homologous recombination.

As concern the relationship between grandparents and grandchildren according to many reports, grandparents have a favorite grandchild. It completely relies on the genetical composition of grandchildren that is inherited from their grandparents. They can inherit physical feature from their grandparents too. For example, one young man has his grandfather`s (paternal) face shape and he walks like his grandpa. He is a fan of a football team whose fan is also a grandfather. They both love animals. While the boy's father has an allergy to animals and is not even interested in football. Anyway, I did research and interviewed too many older parents (grandparents) and came to the conclusion recombination of genes is not always done in such a way that it is random. Moreover, genes that are very important to humans sometimes specially do not work in children and, conversely, are often activated in grandchildren, which strengthens love for grandchildren and consequently increases the quality of care. At the same time close relationship benefits the health and well-being of both grandparent and grandchild. For grandchildren, the biggest gift of this all-important bond is the endless supply of love, acceptance, patience and unwavering support that grandparents uniquely have to offer. This extra layer of support can have lasting positive effects on the child`s emotional well-being. But becoming a grandparent can be life changing-an adrenaline shot that restores your energy, optimism and so on. Moreover, when grandchildren and grandparents have a close relationship, they can expand each other`s knowledge base. Grandparents can teach their grandchildren life lessons and tell them stories about their lives and the rest of the family. The grandchildren can also teach their grandparents a lot by keeping them up to date with what teaches new and help them with technology. This event is also important in the sense that it makes the lives of grandparents more purposeful. I do not rule out that this will increase their life expectancy, which is probably a biological program that has been working so successfully for centuries to preserve the human condition.

MALARIA AS A UNIQUE PARASITIC DISEASE

DAVIT TSKHOMELIDZE, NATALIA CHILADZE,
EKA MCHEDLISHVILI, ANUKA GOGOSASHVILI
Tbilisi, Georgia

ABSTRACT

We surveyed an Anopheles gambiae population in a West African malaria transmission zone for naturally occurring genetic loci that control mosquito infection with the human malaria parasite, Plasmodium falciparum. The strongest Plasmodium resistance loci cluster in a small region of chromosome 2L and each locus explains at least 89% of parasite-free mosquitoes in independent pedigrees. Together, the clustered loci form a genomic Plasmodium-resistance island that explains most of the genetic variation for malaria parasite infection of mosquitoes in nature. Among the candidate genes in this chromosome region, RNA interference knockdown assays confirm a role in Plasmodium resistance for Anopheles Plasmodium-responsive leucine-rich repeat 1 (APL1), encoding a leucine-rich repeat protein that is similar to molecules involved in natural pathogen resistance mechanisms in plants and mammals.

Malaria is an ancient disease and continues to exact a substantial toll of human life and sufferings, particularly in the tropics and subtropics. 10 % of genome of malaria consists of from genetical material of plants and produced 500 proteins of plants. Billion-year-old drama explains how Malaria came to be a green disease. Some ancient eukaryote swallowed aphotosynthesizing bacteria and became a sunlight-gathering alga. Millions of years later one of these algae was devoured by a second eukaryote and this new host gutted the alga, casting away its nucleus and its mitochondria, keeping only the chloroplast. That Thief of a thief was the ancestor of plasmodium.

Malaria parasite passes its life cycle in two hosts:

1. Definitive host: female Anopheles mosquito (sexual phase)
2. Intermediate host: human (asexual phase)

Asexual phase

In this stage, the malaria parasite multiplies by division or splitting a process designated to as schizogony.

In humans, schizogony occurs in two locations- in the red blood cells (erythrocytic schizogony) and in the liver cell (exoerythrocytic schizogony or the tissue phase). The products of schizogony, whether erythrocytic or exoerythrocytic, are called merozoites.

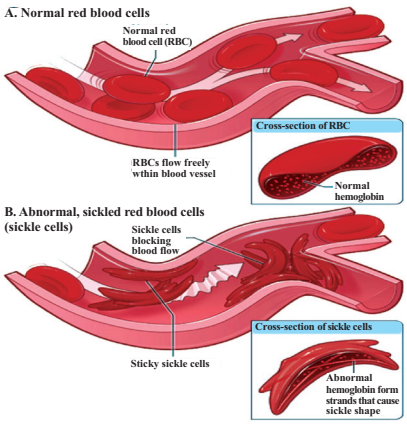
Female Anopheles mosquito represents definitive host, in which sexual forms take places. although the sexual forms of the parasite (gametocytes) originate in human RBCs.

Maturation and fertilization take place in the mosquito, giving rise to a large number of sporozoites.

Causative agents of human malaria

1. Plasmodium vivax: Benign tertian malaria
2. Plasm falciparum: Malignant tertian malaria
3. Plasmodium ovale: Benign tertian malaria
4. Plasmodium malariae: Benign tertian malaria

The red blood cells have some unusual construction- Erythrocytes lack nuclei and organelles, but contain Hemoglobin, which is so important food for all of species of P. Malaria. P. falciparum is responsible for most cases of human malaria worldwide (80 %) The plasma membrane of infected erythrocyte by P. falciparum undergo alteration that causes them to adhere to the walls of capillaries. But P. falciparum infects erythrocytes of any age indiscriminately. Multiple infections of single erythrocytes are common, and the presence of more than one ring trophozoite in a cell is not unusual. As concern P. vivax and P. ovale a diagnostically significant characteristic is the larger size of these infected erythrocyte, probably due to the fact that parasites prefer to invade relatively larger reticulocytes. At the same time a red blood cell is a good place to hide, because they don`t have genes, they can`t make any MHC molecules, so they have no way of showing the immune system what`s inside them and for a time Plasmodium can enjoy perfect camouflage inside the cell. Parasite divides and fills the cell it has to start supporting the membrane with its own proteins. To avoid being destroyed in the spleen, it builds knobs on the surface of the cell. They contain a littl latches that can snag onto the walls of blood vessels

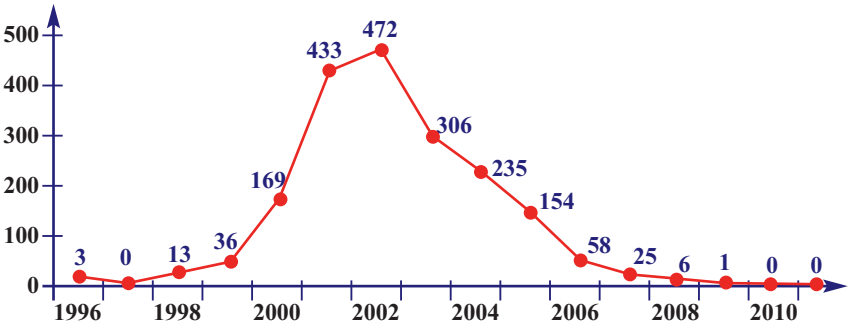


Sickle cell mutation

Hemoglobin is essential for the parasite`s development, although it is uncertain precisely which components are required. It is known that the parasite digests hemoglobin intracellularly, producing an insoluble by-product, hemozoin. The malaria parasite depends on host erythrocytes for many essential molecules and it does have the ability to synthesize folic acid, a key compound in pyrimidine acid.

Our aim was to show that unfortunately, many gaps remain in the understanding of several metabolic aspects of the intracellular stages of the life cycle due, in part, to the fact that, until recently, there was no culture technique for reproducing these stages in vitro. Besides of this, it has long been known that victims of P. vivax or plasmodium and P. ovale, after apparent recovery, may suffer relapse. Originally, such relapse was thought to be due to populations of cryptozoites entering the exoerythrocytic cycle. Now, it is recognized that long prepatent sporozoites or hypnozoites remain dormant in the hepatocytes for an indefinite period. When a stimulus, such as the physiological fluctuation activates hypnozoites into the exoerythrocytic cycles, relapse occurs.

Sickle cell anemia is actually just one of several blood disorders created in the fight between humans and malaria. The lack of Duffy antigens in the plasma membrane of the erythrocytes as a special genetical programs invented by human organisms for protection against malaria. Plasmodium vivax (P. vivax) causes approximately between 70 and 80 million cases of malaria per year and is the most amply distributed human malaria in the world. At the same time The Duffy glycoprotein is a receptor for chemicals that are secreted by blood cells during inflammation. It also happens to be a receptor for Plasmodium vivax, a parasite that invades red blood cells (RBCs) and causes malaria. RBCs that lack the Duffy antigens are relatively resistant to invasion by P. vivax. Individuals with the Duffy-negative phenotype are resistant to P. vivax invasion, and the molecular mechanism that gives rise to the phenotype Fy (a - b -) in black individuals has been associated with a point mutation - 33TC expressed in homozigosity in the FYB allele [5].



As concern our country, Georgia became the first country in the European region that was granted by the Global fund for Malaria. As the result of the project, consistent reduction of malaria cases have been achieved in the country since 2004. Malaria as an endemic disease in Georgia has been eliminated since 2010.

PRACTICING PHYSICIANS

CORONARY ANEURYSM FORMATION IN INFANTS WITH FEVER AT 3 DAYS

JIAO FUYONG, WANG WENHUI
Shaanxi Kawasaki Disease Diagnosis and Treatment Center; Xi 'an Medical College 2016

ABSTRACT

The clinical data of a child with Kawasaki disease admitted to Shaanxi Provincial People's Hospital were retrospectively analyzed. The patient, male, more than 3 months old, presented with fever and rash. Cardiac ultrasound showed coronary artery widening and formation of coronary aneurysm only 3 days after onset. After receiving anti-infection, proglobulin + dexamethasone to suppress the immune response and protect the liver, the child did not develop fever and was discharged from hospital after symptoms disappeared. Kawasaki disease is an acute febrile and eruptive pediatric disease characterized by systemic vasculitis. The etiology of Kawasaki disease is not yet clear. The disease is prevalent and endemic to a certain extent. The clinical manifestations include fever, rash, etc., which may be related to infection. It is believed that multiple agents may be involved, including Epstein-Barr virus, retrovirus, or streptococcal or propionibacterium infections. Early symptoms are similar to acute infection, it is difficult to distinguish, the symptoms are serious, so it should be paid attention to in clinical work.

Key words: *Kawasaki disease; Infant; Diagnosis; Treatment; Prognosis* DOI:

Kawasaki disease, also known as mucocutaneous lymph node syndrome (MCLS), was first reported by Nagasaki Fuzuo in 1967 and named after him. Kawasaki disease is an acute systemic vascular inflammatory disease, which mainly involves the coronary artery and occurs in children under 5 years old. In addition to the cardiovascular system, it is also easy to involve other systems. There are many complications and the diagnosis is relatively difficult. [1] Clinical manifestations include fever, rash, cervical non-suppurative lymphadenopathy, conjunctival congestion, diffuse congestion of oral mucosa, bayberry tongue, palmoplantar erythema, and hand-foot edema. Due to the occurrence of severe cardiovascular complications, the incidence of untreated children can be as high as 20 % -25 %, which is the primary cause of acquired heart disease in children in developed regions. In order to further improve the understanding of Kawasaki disease, especially for the case of coronary aneurysm formation and thrombosis, this paper summarizes and reports the clinical characteristics and treatment process of aneurysm formation in a KD infant.

1. CLINICAL DATA

The child, male, aged 3 months, was admitted on behalf of ' fever with rash for 2 hours '. There was no obvious cause of low fever with rash, the fever peak was 37.7°C, no convulsions, chills, no cough, expectoration, no lip cyanosis and dyspnea, and no treatment. The patient was treated in Shaanxi Provincial People ' s Hospital. Routine blood test showed that white blood cells 12.73×109 / L, neutrophil ratio 0.75, absolute neutrophil value 8.97×10⁹ / L, lymphocyte ratio 0.189, monocyte ratio 0.093 red blood cells

4.81×10¹²/L hemoglobin 133 g / L, platelet 199×10⁹ / L, high-sensitivity C-reactive protein quantification > 5 mg / L, C-reactive protein 23.1 mg / significantly increased. Considering ' sepsis, upper respiratory tract infection, rash to be examined ', after excluding new coronavirus pneumonia, hospitalized. Physical examination: body temperature: 37.4ºC, pulse: 145 / min, breathing: 36 / min, blood pressure: 68 / 55mmHg (1mmHg = 0.133kPa), weight: 7.00Kg. Whole body trunk and limbs visible scattered rash, red papules, slightly prominent in the skin, pressure fade, part of the fusion into pieces. The superficial lymph nodes of the whole body did not touch swelling. No deformity of the head shape, free eye movement, yellow secretions in the corners of the eye, no congestion and pale eyelid conjunctiva, sclera without yellow staining, lips red, buccal mucosa without Cholera, pharyngeal congestion. Hearing breath sounds slightly coarse, not smell dry, wet rales. There was no obvious abnormality in abdominal examination. The physiological reflex of nervous system exists, and the pathological reflex is not introduced. Limb muscle tension is normal.

After admission, symptomatic treatment of anti-infection such as cefoxitin and atomizing inhalation of interferon was given. The body temperature of the children increased repeatedly, and the peak of fever was significantly higher than that before, up to 39.5ºC. There was restlessness, crying, milking, abdominal distension, and cold hands and feet. The rashes on the trunk and limbs increased significantly and fused into slices. On the second day of admission, the child was still repeatedly high fever. Physical examination showed that systemic rash was alleviated, and the face and trunk were more obvious. The scar was red, and the hand and foot were red and swollen. Bilateral conjunctival congestion, lip red, slightly dry cleft, bayberry tongue, perianal redness (Fig. 1). Test results after admission: PCT 7.676ng / ml. Liver and kidney function electrolyte ALT119U / L AST54U / L TP49.3g / L ALB30.6g / L Cl93mmol / L, the remaining normal. Urine routine white blood cell 3 + 582.6ul protein +. The five indicators of humoral immunity were low. Myocardial enzyme, EB virus antibody, peripheral blood smear, TORCH, nine respiratory pathogens, fecal routine, eight items before blood transfusion, vitamin D determination were basically normal. Chest radiographs showed pulmonary inflammation. Considering the possibility of diagnosis of ' sepsis, bronchial pneumonia ', ' Kawasaki disease, urinary tract infection ', it is necessary to replace antibiotics with Rosfen to strengthen anti-infection, and add symptomatic treatment such as ' Compound Glycyrrhizin'liver protection and fluid infusion. The inflammatory indexes were further reviewed, and the condition was further clarified by echocardiography and urine culture. Three days after admission, echocardiogram showed: right coronary artery widened and coronary aneurysm formation, thrombosis suspicious (Fig. 2). Blood routine examination after 3 days of admission: white blood cell 12.76×10⁹ / L, neutrophil ratio 0.825, neutrophil absolute value 10.52×10⁹ / L, lymphocyte ratio 0.067, monocyte ratio 0.045 red blood cell 3.67×10¹² / L hemoglobin 96 g / L, platelet 277×10⁹ / L. ESR 44mm / h. CRP, complement C3, C4 were in normal range. Coagulation function: blood D-dimer quantitative 9.62mg / L, fibrinogen degradation products25.6mg / L, so Kawasaki disease diagnosis. The patient was young, and the course of the disease was only three days. The disease progressed rapidly, and the immune response in vivo was considered to be strong. Therefore, after the results of echocardiography were returned, the infusion of human immunoglobulin (2 g / Kg) was immediately given to block the immune response process and reduce further coronary damage. Since the course of disease has not been more than five days, the second dose of gamma globulin may be insensitive to gamma globulin. After informed of the family's consent, the children were infused with human immunoglobulin. At the same time, aspirin and dipyridamole anticoagulant therapy were taken orally. After the infusion of the first dose of gamma globulin, the patient's condition was improved for a time, and the body temperature was normal. The signs of Kawasaki disease were relieved, but no more than 24 hours later, repeated fever occurred again. The signs of Kawasaki disease were aggravated again, and the rash reappeared. The signs of lipstick, bayberry tongue, conjunctival congestion and so on. The blood routine examination (3 days from the last interval) showed that WBC was 16.66x109 / L, NEU was 0.64, RBC was 3.41x10¹² / L, HB was 89 g / L, and PLT was 367x109 / L. Coagulation function: FDP 12.6mg / L, DD 7.2mg / L. Liver function: ALP 132U / L GGT 211U / L total protein 52.8 / L albumin 21.1g / L. ESR 35mm / h, PCT 1.777ng / ml, CRP 41.17mg / l. Blood lipid, myocardial enzyme normal range. Considering the possibility of gamma globulin tolerance, the second dose of gamma globulin (2 g / Kg) was infused, and the hormone was added to inhibit the immune response. The children did not have fever, the rash subsided, the conjunctiva was not hyperemia, the perianal and scars were not red, and the skin at the finger toe end and the nail moved to the membrane (Fig. 3). There was no obvious abnormality in cardiopulmonary examination. The blood routine examination of inflammatory indexes showed that WBC 10.23 x 10⁹ / L, NEU 0.32, RBC 3.5 x 10¹² / L, HB 94 g / L, PLT 770 x 10⁹ / L. ESR 40mm / h. CRP, PCT, coagulation function is normal. The reexamination of echocardiography 10 days after admission (1 week from the first echocardiography) showed that: (Figure 4), the patient was discharged from hospital. Regular follow-up was conducted after discharge according to the management plan formulated by the Kawasaki Disease Cooperation Group of the Pediatric Branch of the Chinese Medical Association and the relevant guidelines of Japan and the United States [2, 4, 7]. Up to now, children have been re-examined for three times, and they have been re-examined in our hospital at 2, 4 and 5 weeks after discharge, respectively. The recurrent inflammatory indexes were all normal, and the number of platelets decreased gradually. The results of echocardiography are shown in the figure.

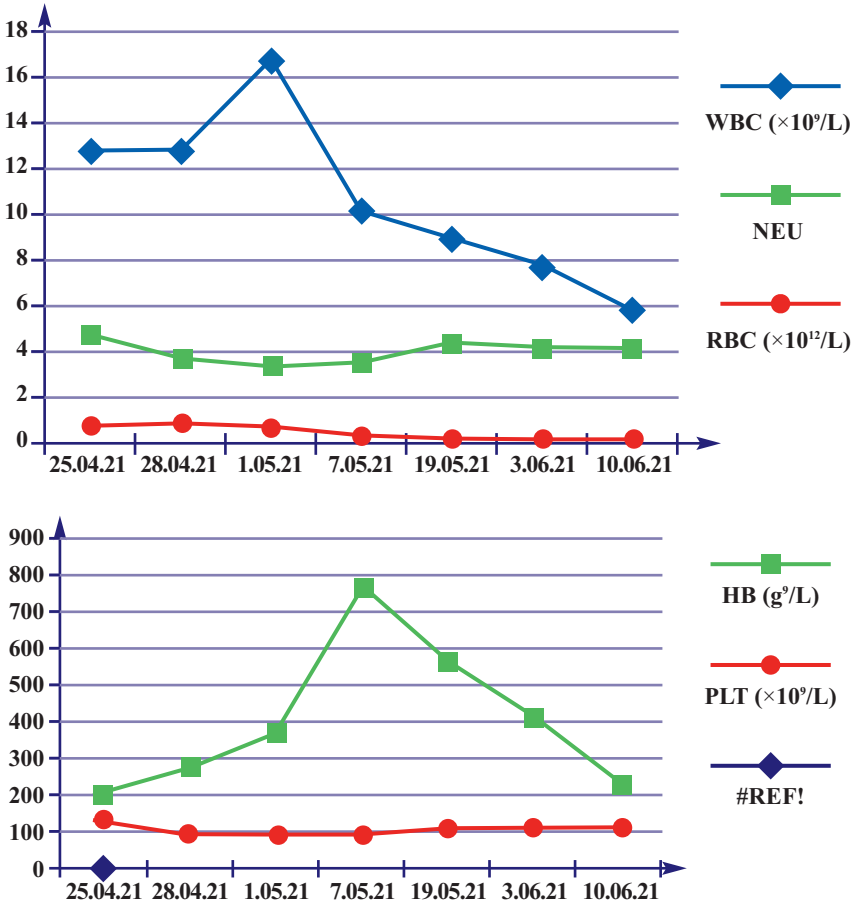
	WBC (×10⁹/L)	NEU	RBC (×10¹²/L)	HB (g/L)	PLT (×10⁹/L)
2021.4.25	12.73	0.75	4.81	133	199
2021.4.28	12.76	0.825	3.67	96	277
2021.5.1	16.66	0.64	3.41	89	367
2021.5.7	10.23	0.32	3.5	94	770
2021.5.19	8.87	0.121	4.24	111	568
2021.6.3	7.66	0.094	4.13	109	412
2021.6.10	5.73	0.07	4.18	109	225

2. DISCUSSION

Kawasaki disease is an acute, self-limiting, fever rash disease, mainly in-

volving small and medium arteries of acute systemic vasculitis. The incidence of Kawasaki disease is high in children under 5 years old. Since the first report of Kawasaki disease in 1976, the incidence has been on the rise. The incidence reported recently in Japan was 306 / 100 000[5]. The incidence of Kawasaki disease reported in Beijing in 2000 and 2004 was 40.9 / 100 000 and 55.1 / 100 000, respectively[6]. In 2014, the incidence was 116.6 / 100 000 [2]. In developed countries or regions, Kawasaki disease has replaced rheumatic heart disease and become the most common cause of acquired heart disease[7]. Due to the use of intravenous immunoglobulin (IVIG), the incidence of coronary artery complications in Kawasaki disease decreased from 20% to about 5%, but there are still about 0.1% of children with giant coronary artery aneurysm (GCAA)[4]. The most common GCAA in Kawasaki disease is the middle right coronary artery and the anterior descending left coronary artery. The incidence of cardiovascular events and mortality in children are high, and the prognosis is poor [17]. At present, the pathogenesis of Kawasaki disease is still unclear, which may involve immune activation, inflammatory factors, nuclear factor-κB, matrix metalloproteinase, vascular endothelial injury and many other factors. Aspirin combined with intravenous immunoglobulin is the main treatment of Kawasaki disease, which can effectively alleviate the clinical symptoms of Kawasaki disease and reduce coronary artery injury caused by Kawasaki disease. In recent years, clinicians have tried to use glucocorticoids and tumor necrosis factor-α blockers in the treatment of Kawasaki disease, further improving the prognosis of children with Kawasaki disease. This case is a male infant diagnosed with Kawasaki disease. It is also the earliest case of coronary artery damage in Kawasaki disease.

The early symptoms of Kawasaki disease are not typical, which often lead to missed diagnosis and misdiagnosis, thereby delaying treatment and causing coronary artery damage. The common symptoms were persistent fever, 5 ~ 11 days or longer (2 weeks to 1 month), bilateral conjunctival hyperemia, lip flush, chapped or bleeding, bayberry tongue, hard edema of hand and foot, palm and plantar early flush, 10 days after the emergence of characteristic finger toe large flake peeling, transient cervical lymph node swelling, systemic trunk



and limbs visible scattered rash, BCG vaccination site reproduction erythema or scab. The most serious complications were heart damage, coronary aneurysm, pericardial effusion, left ventricular enlargement and mitral insufficiency.

The first stage of Kawasaki disease is acute fever, with a general course of 1 – 11 days. The main symptoms appear gradually after fever, and severe myocarditis can occur. The second stage is subacute, with a general course of 11 – 21 days. Most patients have decreased body temperature, relieved symptoms, and membranous decortication at the finger toe. Severe cases are still sustainable fever, and coronary artery aneurysm can occur, which can lead to myocardial infarction and aneurysm rupture. Most patients enter the third stage in the fourth week, namely recovery period, with a general course of 21 – 60 days. The clinical symptoms are subsided, and gradually recover if there is no obvious coronary artery lesion. Coronary artery aneurysm is still sustainable development, and myocardial infarction or ischemic heart disease can occur. A small number of patients with severe coronary artery aneurysm enter the chronic phase, which can be extended for several years. Coronary artery stenosis, angina pectoris, cardiac insufficiency, and ischemic heart disease can be left behind, which can endanger life due to myocardial infarction.

This case of Kawasaki disease had fever, rash on the face and trunk of the whole body, scar red, and red swelling of hands and feet. Bilateral conjunctival congestion, lip red, dry fissure, bayberry tongue, perianal red, in line with the characteristics of Kawasaki disease. Clinically, coronary artery lesions in Kawasaki disease mostly occurred after 2 weeks of disease course, but the patient had fever for 3 days. Echocardiography showed that the diameter of left main coronary artery, proximal right coronary artery and left anterior descending branch increased, and the echo of wall was rough and enhanced. Coronary aneurysm was formed at the proximal start of the right coronary artery, with the exception of thrombosis. The conventional treatment of Kawasaki disease is recommended to use gamma globulin after 5 days of fever. However, due to the early occurrence of cardiac damage and the sever-

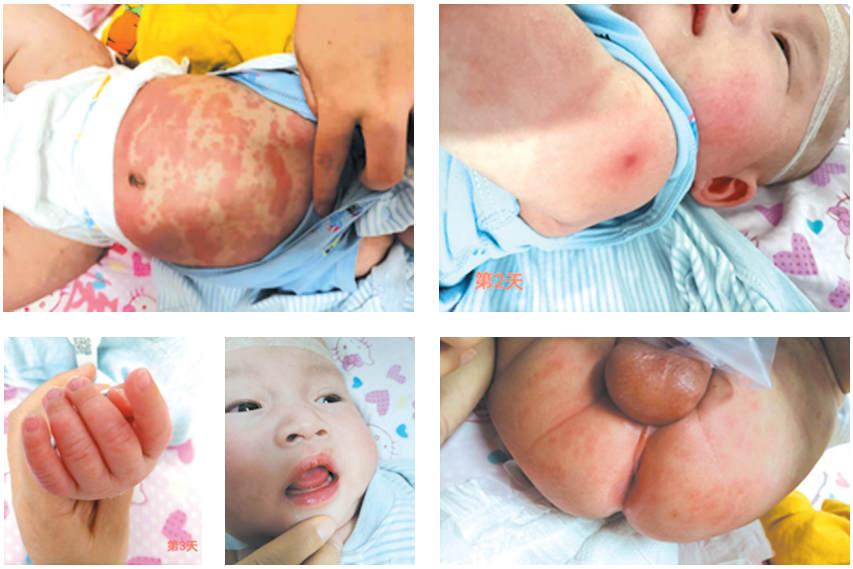


Fig 1 Signs on the second day of disease course

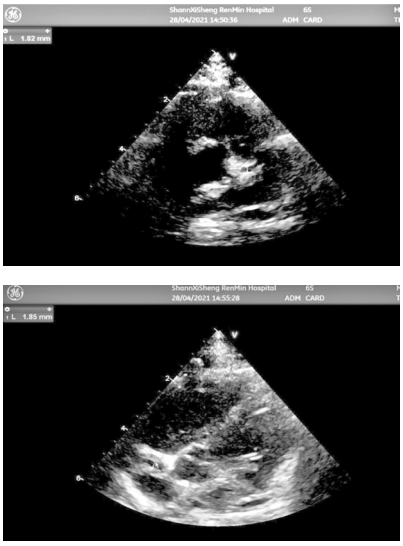


Fig. 2 Echocardiography on day 4 of course of disease

ity of the disease, the first dose of gamma globulin was immediately infused after the return of echocardiography results (the fourth day of the course of the disease), and the results showed tolerance and no remission of clinical symptoms. At present, the mechanism of gamma globulin tolerance is unclear, which is generally believed to be related to heredity and may be caused by the polymorphism of Fcγ receptor. [8] After early infusion of the second dose of gamma globulin combined with glucocorticoid, the symptoms were relieved and the patients were discharged. Therefore, when it is diagnosed or suspected that gamma globulin does not respond, the children can be given the second dose of gamma globulin intravenously for treatment. If the curative effect is still not good, glucocorticoid can be used intravenously for treatment [9]. Recent studies have also found that with the different timing of IVIG treatment, the incidence of CAL is also significantly different, suggesting that early use of IVIG is an effective method to inhibit systemic inflammation and prevent CAL [10].

Studies have reported that the time range of CAA reaching the maximum diameter in children with Kawasaki disease is 11 days to 87 days, and the median is 35 days (n = 195). The time of CAA regression varies from 41 days to 386 days, and the median is 136 days. [18]

Aspirin has anti-inflammatory and antiplatelet effects, and is widely used in clinical adjuvant therapy of Kawasaki disease. As for the application dose of aspirin, it is not the same in different countries and regions. In the acute phase of Kawasaki disease, the United States advocates high dose (80 – 100 mg / (kg. d)), while Japan and Western European countries mostly use medium dose (30 – 50 mg / (kg. d)), which is reduced to low dose (3 – 5 mg / (kg. d)) after 72 h of normal body temperature. The time and dose of aspirin are currently controversial. Recent studies have shown that compared with low-dose aspirin, medium and high doses of aspirin have no advantages in preventing CAL [11,12]. So the onset of young children, coronary artery damage occurred earlier and more serious, and what the consequence of aspirin dosage and treatment should be how ? Considering the formation of coronary aneurysm and suspected thrombosis, the medium-dose aspirin was used for a long time. After two weeks of discharge, the echocardiography was reviewed. The coronary artery lesion was not significantly improved, the thrombosis was still increasing, and the liver function and liver enzyme were significantly increased. Reinforc-

Fig 3 Manifestations of finger toe end membranous peeling on the 12th day of disease course

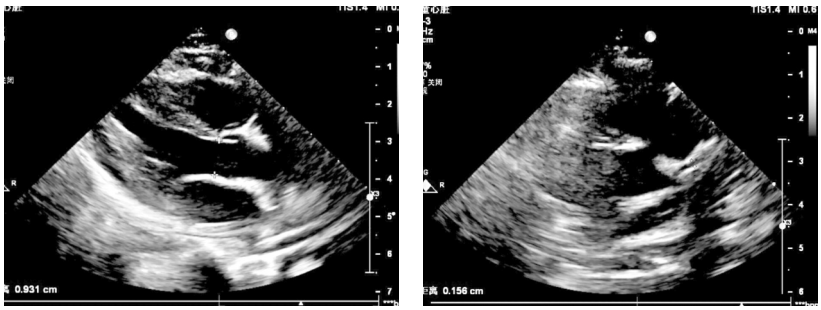


Fig 4 Echocardiography on the 46th day of disease course

Figure. 1 Sprinkled skin rash can be seen on the torso and limbs, conjunctival congestion on both sides, red and dry lips, red bayberry tongue and perianal redness **Figure. 2** Ultrasound examination of the heart showed coronary artery widening and formation of coronary aneurysm **Figure. 3** Systemic rash subsided, bulbar conjunctiva was not congested, perianal and card scar were not red **Figure. 4** Cardiac color ultrasound results were reexamined

ing hospital should be vigilant, improve the relevant examination and liver protection treatment, exclude Reinforcing syndrome, and improve and discharge after liver protection treatment. This has brought us some clinical thinking. The protective effect of medium and large doses of aspirin on coronary artery lesions in Kawasaki disease is not proportional to its dose, and the side effect is large. Long medication time can cause significant damage to liver function, and severe cases can cause RRS, which needs to be paid great attention to in clinic.

Anticoagulant therapy is particularly important for Kawasaki disease with coronary aneurysm, especially for children with thrombosis. Warfarin is currently recognized as a commonly used anticoagulant for the prevention and treatment of coronary artery thrombosis. It has the advantages of good oral absorption, fast onset, long half-life, and once a day [13]. However, its treatment spectrum is narrow, and there are adverse reactions such as bleeding. In clinical practice, dose adjustment should be carried out in combination with the severity of coronary artery lesions, and standardized management can increase the safety of warfarin treatment in children with Kawasaki disease, improve coronary artery lesions in children, treat thrombosis and prevent new thrombosis, and reduce the risk of bleeding[16].

Studies have shown that warfarin has a positive effect on the prognosis of coronary artery lesions and thrombosis in children with Kawasaki disease complicated with CAA [14].P=0.031). Conclusion The warfarin dose was adjusted according to the target range of INR 2.0 – 3.0 and the severity of Kawasaki disease combined with coronary artery aneurysm. Studies have also shown that 75% of children with Kawasaki disease without warfarin combined with thrombosis, while 14% of children with Kawasaki disease with warfarin still formed coronary thrombosis, suggesting that the application of warfarin can not completely avoid thrombosis. Thrombosis was found to increase in the course of reexamination, and moderate dose aspirin had no obvious effect on it[15]. Therefore, warfarin anticoagulation (0.09mg/kg) was adjusted to oral anticoagulation, and coagulation function was regularly rechecked to control plasma prothrombin international normalized ratio (INR) 1.5-2.5. After 1 week of oral administration, coagulation function was normal, and coronary aneurysm and thrombosis disappeared after reexamination of echocardiography (4 weeks after discharge), but left coronary artery dilatation continued to be consolidated by oral administration for 3 weeks.

This case suggests that not all Kawasaki disease coronary artery damage appear late, 3 days can also appear coronary artery damage, remind clinicians in the confirmation of Kawasaki disease should be early cardiac ultrasound examination. The best time for intravenous infusion of gamma globulin in Kawasaki disease is 5-10 days, but CAA occurs 3 days, and gamma globulin should be used as soon as possible.

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ADVERSE DRUG REACTIONS MONITORING IN GEORGIA

RUSUDAN G. JASHI, ***MD. PHD***
Georgian Society of Clinical Pharmacology and Rational Pharmacotherapy

PRIMUM NON NOCERE,
Department of Pharmacology Georgian National Section of EuroScience

During the last decades it has been demonstrated by a number of studies that medicine morbidity and mortality is one of the major health problems which is beginning to be recognized by health professionals and the public. It has been estimated that such adverse drug reactions (ADRs) are 4th to 6th largest cause for mortality in the USA. They result in the death of several thousands of patients each year, and many more suffer from ADRs. The percentage of hospital admissions due to adverse drug reactions in some countries is about or more than 10%: Norway 11.5%, France 13.0, UK 16.0%

In addition suitable services to treat ADRs impose a high financial burden on health care due to the hospital care of patients with drug related problems. Some countries spend up to 15-20% of their hospital budget dealing with drug complications. Beside ADRs, medicine-related problems include also – drug abuse, misuse, poisoning, therapeutic failure and medication errors.

Drug monitoring researches focusing on adverse drug reactions, rationalization of drug prescription and consumption, promotion of concept of essential drugs and precise reporting system are likely to be particularly cost-effective. There is very limited information available on ADRs in developing countries and countries in transition. However, one may expect that the situation is worse rather than better. This problem is also caused by a lack, in some countries, of legislation and proper drug regulations, including ADR reporting, a large number of substandard and counterfeit products circulating in their markets, a lack of independent information and the irrational use of drugs that absolutely coincides with Georgian situation. There are developed publications with this regard both for Georgian and international scientific editions.

We don't have statistically reliable data concerning ADRs in Georgia, but several studies confirm that the situation is quite poor and sometimes morbidity and mortality is disguised by the name of nosology ADR had caused. Due to existing in our country epidemiological situation it is of urgent necessity implementation of pharmacovigilance system in our country.

WHO defines pharmacovigilance as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine_ related problem

Our aim is establish and maintain country specific, scientifically proved ADRs control system - the system of Pharmacovigilance in Georgia, based on WHO and Uppsala recommendations on ADR management. The pharmacovigilance system, established by the recommendations of European countries will improve the treatment of the patients and will help to reveal, evaluate and prevent ADRs. Our aim is establish and maintain country specific, scientifically proved ADRs control system - the system of Pharmacovigilance in Georgia, based on WHO and Uppsala recommendations on ADR management.

The main aim will be reached by resolving the following problems: reveal new (not known) ADRs; reveal the rising the incidence of (known) serious ADRs; identify the risk-factors and reveal the mechanisms which cause ADRs; evaluate the quantitative indicators of the risk and benefit of drugs, which is necessary for State regulation and improvement of quality of prescriptions; search of social aspects of drug provision; prepare specialists in the field of pharmacovigilance; patient education on ADR risk-factors and expected complications;

The major sources of information will patient's medical record. Hospitals and physicians will be guaranteed with the confidentiality of the data and all publications. The clinics will receive the reports on ADRs. The evaluation of questionnaires will be carried out using methodologies, recommended by WHO and tested in European countries, which are simple for implementation, cheap and optimally informative.

we reckon to create the center of Pharmacovigilance Scientific-Research-Methodology Center together with Department of Pharmacology Georgian National Section of EuroScience and Society Promotion of Clinical Pharmacology and Rational Pharmacotherapy – Primum non Nocere (PNN) for the implementation of adverse drug reactions monitoring in Georgia.

For the first time in Georgian clinics it will be evaluated the real situation concerning ADRs. Data derived from this may have greater relevance, educational value and will be used to increase awareness of medical society, medical students and the population. Thus the potential users of results will be health professionals and the population of Georgia. This may encourage national regulatory decision-making to make National Center of Pharmacoviligance in Georgia.

The management Pharmacoviligilance will be studying in Medical Universities and during postgraduate education. The obtained data will inspire graduate students to elaborate new ideas. The physicians will be given methodological guidelines, treatment protocols and standards, including schemes of new drugs application. This will help to reveal ADRs on early stages, decrease drug-caused morbidity and mortality, and correspondingly Governmental and individual expenditures will be reduced.

It will promote achievement of the general goal – provide patients with safe, effective and affordable treatment.

USE OF BNP AND NT-PROBNP IN EARLY STAGE DIAGNOSIS OF ATHLETE'S CARDIOVASCULAR PATHOLOGIES: LITERATURE OVERVIEW

ILIA NADAREISHVILI,
AIETI Highest Medical School

GEORGE CHAKHUNASHVILI, *MD, PhD.,*
TSMU Pediatric Clinic Director Substitute

Brain natriuretic peptide (BNP), now known as B-type natriuretic peptide(also BNP) or GC-B, is 32 amino acid polypeptide secreted by the ventricles of the heart in response to excessive stretching of heart muscle cells (cardiomyocytes). BNP, originally termed brain natriuretic peptide, was discovered in 1988 from porcine brain by T. Sudoh et al. in 1988, but it was soon discovered that the highest concentration of the peptide is found in the atria, with the total ventricular amount of BNP being even higher due to greater mass (Minamino et al.1988).

BNP is co-secreted along with the remaining part of the prohormone, a 76 amino acid N-terminal fragment (NT-proBNP) which is biologically inactive. BNP binds to and activates the atrial natriuretic factor receptors Natriuretic peptide receptor A/guanylate cyclase A NPRA, or NPR1, and to a lesser extent NPRB, in a fashion similar to atrial natriuretic peptide (ANP) but with 10-fold lower affinity. NRP1 is a single membrane-spanning receptors with intrinsic guanylate cyclase activity. The vast majority of natriuretic peptide-dependent effects are mediated by elevations of intracellular cGMP concentrations. cGMP will then stimulate cGMP-dependent pro-tein kinase (PKG) which will then induce smooth muscle relaxation. This relaxation will decrease total periph-eral resistance which will in turn decrease venous return to the heart. The decrease in venous return to the heart will reduce the preload and will result in the heart having to do less work.

The physiologic actions of BNP are similar to ANP and include increase in natriuresis, decrease in systemic vascular resistance and central venous pressure, inhibition of renin and aldosterone production and of cardiac and vascular myocyte growth. Thus, the net effect of BNP and ANP is a decrease in blood volume and a de-crease in cardiac output.

The biological half-life of BNP, however, is twice as long as that of ANP, and that of NT-proBNP is even longer, making these peptides better targets than ANP for diagnostic blood testing. BNP accurately reflects cur-rent ventricular status. The half-life of NT-ProBNP is 1 to 2 hours vs. 20 minutes for BNP.

CLINICAL USE

The BNP assay has become one of the most important blood tests in cardiology.

The BNP test as well as the NT-proBNP one have already proved to be extremely useful in screening and diag-nosis of Congestive Heart Failure, and in establishing prognosis for heart failure patients. In addition, BNP helps physicians to make decisions hospitalization and evaluate effectiveness of therapy. A synthetic formula-tion of BNP (nesiritide) is used to treat decompensated heart failure, resulting in improved hemodynamics and symptoms.

There is also more and more evidence that the BNP test may play a major role in critical care medicine, in: pulmonary embolism, cardio-renal syndrome, septic shock, subarachnoid hemorrhage,

Cardiologic Pathologies: Congenital heart diseases, cardiomyopathies, mitral regurgitation, aortic stenosis, atrial fibrillation, acute coronary syndrome, myocardial infarction, chronic stable angina, rheumatic fever, aortic aneurism repair, cervical spine surgery,

Non-cardiologic pathologies: COPD, pulmonary hypertension, fibrotic lung disease, oncology (radiotherapy),

B-type natriuretic peptide appears to be a reliable predictor of future cardiac and all-cause mortality in diabetic patients. Bhalla et al. showed that combining BNP with other tools like ICG can improve early diagnosis of heart failure and advance prevention strategies. Utility of BNP has also been explored in various settings like preeclampsia, shock and End Stage Renal Disease.

TEST FEATURES

Biostatistics:

Negative predictive value is 96%, so heart failure can confidently be ruled out for patients in the normal range.

When BNP is over 100 pg per milliliter - sensitivity = 90%; specificity = 76%

When BNP is over 50 pg per milliliter - sensitivity = 97%; specificity = 62%

For patients with CHF, BNP values will generally be above 100 pg per milliliter; however, a more conservative interpretation of the BNP is that normal values are less than 50 pg per milliliter in order to achieve adequate sensitivity. There is a diagnostic 'gray area', often defined as between 100 and 500 pg/mL, for which the test is considered inconclusive. Values above 500 pg/mL are generally considered to be positive. This so called gray zone has been addressed in several studies and using clinical history or other available simple tools can help make the diagnosis.

The effect or race and gender on value of BNP and its utility in that context has been studied extensively

RESULTS

- BNP levels below 100 pg/mL indicate no heart failure
- BNP levels of 100-300 suggest heart failure is present
- BNP levels above 300 pg/mL indicate mild heart failure
- BNP levels above 600 pg/mL indicate moderate heart failure.
- BNP levels above 900 pg/mL indicate severe heart failure.
- 3000 During Nesiritide Infusion

BNP levels rise with age. Mean BNP levels are:

- 26.2 pg/ml in those aged 55-64 years.
- 31.0 pg/ml in those aged 65-74 years.
- 63.7 pg/ml in those aged 75 years and older.
- Women without CHF tend to have higher BNP levels than males of the same age.

A small difference was noted between the white and black racial groups (area under the curve = 0.888 and 0.903, respectively). In patients presenting to the ED with heart failure, the disconnect between perceived sever-ity of CHF and severity as determined by BNP levels is most pronounced in African Americans.

METHODS AND EQUIPMENT

A wide array of products now allows rapid measurement of BNP (or NT-proBNP) on a point-of-care or laboratory basis. These products use whole blood or serum samples and employ ELISA methods with photometric readout. They differ mainly on points of hardware size, CLIA-waived status, sample preparation, automation etc.

Usually, to test the BNP level, a small amount of blood (in case of the Montgomery et al. study it was fifteen milliliters of venous blood) is taken and placed in a machine that detects the level of BNP in blood. Blood thin-ner EDTA is used to prevent blood from clotting. The test takes about 15 minutes. Different machines can de-tect such low concentrations as 5pg/ml.

We conclude that the BNP test is a quick, inexpensive test which enhances current diagnostic assessment tools, and enables doctors to make the correct diagnosis of heart failure, prognosis and decisions regarding treatment. Future research is evaluating the use of BNP test to determine its role in many other conditions for screening, diagnosis, prognosis and treatment strategy determination purposes.

Cardiac enlargement in athletes was first reported over a century ago. But the debate whether this adaptation to regular high intensity exercise training is a purely physiological condition or has pathological consequences continues to this day. We are uncomfortable with widely accepted view that athletic left ventricular hypertrophy is a purely physiological adaptation with no pathological consequences, for several reasons. Firstly, although sudden cardiac death in competitive athletes under the age of 35 years is rare (according to the Minneapolis Heart Institute Foundation, which tracks deaths of young athletes in a registry, about 125 athletes under 35 die in the U.S. each year, mainly from cardiovascular problems), up to 18%of post-mortems of athletes dying dur-ing sport suggest a condition which has been termed idiopathic left ventricular hypertrophy, where no clear rea-son has been found for the increase in left ventricular mass. Some studies were not controlled for cardiovascular risk factors. The fact that left ventricular hypertrophy caused by endurance training regresses on cessation of regular exercise, merely confirms that athletic left ventricular hypertrophy acts the same way as other pathologi-cal conditions. Recent reports speculate that structural adaptations to exercise, particularly of the right ventricle (RV), may predispose to tachyarrhythmias and sudden cardiac death.

At present, the risk of myocardial damage by endurance exercise is under debate because of reports on exercise-associated increases in cardiac biomarkers troponin and B-type natriuretic peptide. Based on the determination of cardiac troponin (cTnT), brain natriuretic peptide (BNP), and echocardiographic measurements, recent inves-tigations have reported myocardial damage and reversible cardiac dysfunction after prolonged endurance exer-cise in apparently healthy subjects. Exercise-associated elevations of cardiac biomarkers can be present in elite and in recreational athletes, especially after prolonged and strenuous endurance exercise bouts (e.g., cycling, rowing, marathon, ultra triathlon and cross-country skiing). Athletic left ventricular hypertrophy does also occur in people with other kind of strenuous activities. However, it is still unclear if the exercise-associated appearance or increase in cardiac biomarkers in obviously healthy athletes represents clinically significant cardiac in-sult or is indeed part of the physiological response to endurance exercise. In addition, elevations in cardiac bio-markers in athletes after exercise may generate difficulties for clinicians in terms of differential diagnosis and may result in inappropriate consequences.

Although the idea of using the BNP or NT-proBNP test to assess athlete's heart was suggest some years ago, the present topic is still not studies well. It was noted by a number of authors that strenuous exercise leads to a plasma BNP/NT-proBNP concentration increase. (Table # 1) Some researches also shown, that the peptides' concentration is also elevated in healthy control individuals after physical exercise. Though the first such obser-vations and hypotheses about the exact mechanism of this elevation where done over a decade ago, there is still no commonly accepted insight on this problem. Different researches try to clear the meaning of these findings as well as explain them theoretically and experimentally. Recent echocardiographic investigations have shown a reversible diastolic and systolic dysfunction after long-lasting endurance events in trained individuals. It can be speculated that this exercise-induced myocardial dysfunction is pathogenetically responsible for an increase in BNP after such types of exercise. Thus, there is a reasonable background to claim for more information regard-ing the exercise-induced myocardial stress reaction in athletes, particularly with the third-generation assay for cTnT. Moreover, different exercise intensities and durations have to be considered. Aside from the already men-tioned problem regarding the cross-reactivity of the cTnT assay, an increase in postexercise cTnT levels or the marked rise in BNP were mostly observed after extreme ultra-endurance events. Although the authors reported that the majority of subjects investigated were well-trained endurance athletes, the question arises in how far any form of training can prepare the human organism and particularly the heart for such forms of exercise. In addition, some events took place under extreme environmental conditions or high altitude, thereby imposing additional cardiovascular stress.

Correct interpretation of the test could open new quick and easy ways to diagnose and screen for heart diseases in athletes. Some of the authors suggest that BNP/NT-proBNP tests can be very useful for differentiation be-tween physiological and pathological cardiac hypertrophy. Better knowledge of BNP behav-

ior under physio-logical conditions should be useful for proper assessment of load in athletes as well as for correct interpretation of BNP results after physical exercise.

It's interesting that at least one published work states that the NT-proBNP test can be useful in senior endurance runners screening. Sahlen et al. published two articles related to the problem: "Predisposing factors and conse-quences of elevated biomarker levels in long-distance runners aged >or=55 years" (2009) and "Magnitude, re-producibility, and association with baseline cardiac function of cardiac biomarker release in long-distance runners aged > or =55 years" (2008). The aim of both studies was to assess the magnitude and reproducibility of biomarker release in athletes aged > or =55 years. One hundred eighty-five participants where included (61.1 +/- 5 years; 29% women) at a 30-km cross-country race who were self-reportedly in excellent health. Before and after the race, the creatinine, N-terminal probrain natriuretic peptide (NT-proBNP), and troponin T were analyzed, and participation in the number of previous races and the race duration were recorded. NT-proBNP increased from 53 ng/L (interquartile range 31 to 89) to 121 ng/L (interquartile range 79 to 184) and troponin T from undetectable to 0.01 microg/L (interquartile range 0.01 to 0.04). The independent predictors of a large NT-proBNP increase were (1) greater levels present at baseline, (2) a greater increase in creatinine (both p <0.001), (3) older age (p = 0.01), and (4) a longer race duration (p <0.05). Troponin T elevation was independently pre-dicted by (1) older age (p = 0.01), (2) a greater increase in creatinine, and (3) participation in fewer previous races (both p <0.05). Of the 15 runners with an elevated (>194 ng/L) baseline NT-proBNP level (8.1% of 185), 4 were found to have serious cardiovascular disease (2.2% of whole sample). Of these 4 patients, 1 died from sudden cardiac death within months after the race. In conclusion, biomarker elevation occurs commonly in sen-ior runners. A high baseline NT-proBNP is predictive of a large release during exercise, suggesting that the fac-tors that control the at rest levels also determine its release with exertion. Troponin T elevation was seen in less-experienced participants. A small group of very ill runners were identified by NT-proBNP analysis. Long-distance runners aged > or =55 years released NT-proBNP and troponin T in a reproducible fashion. The mag-nitude of NT-proBNP release during the race was correlated strongly with NT-proBNP baseline levels and was associated with left ventricular mass and age. These findings may suggest a potential adverse effect of long-distance running on cardiac function in certain participants in this age group.

Whether the observed elevation represents a physiological adaptation reaction or a pathology is not clear yet. Here are some suggested hypotheses regarding this question.

Among authors who claim the BNP/NT-proBNP elevation is a physi-

Table N1

BNP test results before and after exercise, as obtained by some authors. Note we do not add exercise duration time and time past after the exercise, when the blood samples were taken.

Article	Peptide	Sports	Pre-Training Concentration	Post-Training Concentration
Effect of Professional Exercises on BNP (Sheikhani Shahin et al.)	BNP	Football Volleyball Water Polo Bodybuilding	26.3 +/- 12.9 19.1+/-11.8 9.5 +/- 2.1 12.0 +/- 5.9 pg/ml	48.5+/- 18.4 43.4+/- 30.6 12.4 +/- 4.3 15.7 +/- 5.6 pg/ml
Elevation of serum NT-proBNP after exercise is an index of myocardial damage or cytoprotective reflection? (Faviou et al.)	NT-proBNP	-	-	58.37+/-19.48 22.93+/-10.22 ng/L
GDF-15, endoglin and NT-proBNP induction in athletes participating in an ultramarathon foot race. (Tchou et al.)	NT-proBNP	Ultramarathon Foot Race	38.1+/-4.8 pg/ml	1280.6 +/- 259.0 pg/ml
Myocardial response to a triathlon in male athletes evaluated by Doppler tissue imaging and biochemical parameters (Leetmaa et al.)	Pro-BNP	Triathlon	7+/-2 pmol/L	27+/-21 pmol/L
Myocardial Stress after Competitive Exercise in Professional Road Cyclists (Koning et al)	BNP	Road Cycling	47.5+/-37.5 pg/ml	75.3 +/- 55.3 pg/ml
Magnitude, Reproducibility, and Association With Baseline Cardiac Function of Cardiac Biomarker Release in Long-Distance Runners Aged ≥55 Years (Sahlen et al.)	NT-proBNP	Running	42ng/L	191ng/L
Effect of Competitive marathon cycling on plasma NT-proBNP and CTnT in healthy recreational cyclists (Neumayr et al.)	NT-proBNP	Road Cycling	28+/-21 ng/L	278 +/- 152 ng/L
Independent elevation of NT proBNP and cardiac troponins in endurance athletes after prolonged strenuous exercise (Scharhag et al.)	NT-proBNP	Running marathon Mountain bike marathon		Increased by: 200ng/L 97ng/L 78ng/L
Predisposing factors and consequences of elevated biomarker levels in long-distance runners aged >or=55 years	NT-proBNP	Running	53ng/L	121ng/L
Biochemical and functional abnormalities of left and right ventricular function following ultra-endurance exercise (La Gerche et al.)	BNP	Triathlon	12.2 etag/L	42.5 etag/L

Table N2

Plasma BNP concentration was also found to be elevated after maximal exercise in healthy control individuals.

Article	Peptide	Sports	Before Training Concentration	Post-Training Concentration
The impact of exercise duration and intensity on the release of cardiac biomarkers (Serrano-Ostariz et al.)	NT-proBNP	Running	21-32 ng/L	38-67 ng/L
Effect of short-term maximal exercise on BNP plasma levels in healthy individuals (Krupicka et al.)	BNP	Bicycle Spiroergometry	19.4+/-2.5 pg/ml	30.6+/-4.7 pg/ml

ological response are J. Scharhag, A. Urhausen et al., who published the article titled "No difference in N-terminal probrain natriuretic peptide (NT-proBNP) concentrations between endurance athletes with athlete's heart and healthy untrained controls" in 2004. They still find that NT-proBNP and BNP tests can have important value as a tool to differentiate between pathological and physiological cardiac hypertrophy. Ten triathletes, 5 road cyclists and 5 long distance runners (age, 28 (4) years; height, 178(7) cm; weight, 69 (8) kg; heart volume, 14.5 (1.1) ml/kg; aerobic capacity VO2max, 68 (6) ml/min/kg; endurance training volume per week, 17 (6) hours; training history, 8 (4) years) and a control group of 20 healthy untrained males (group C) (age, 26 (4) years; height, 179 (6) cm; weight, 73 (8) kg; heart volume, 10.9 (0.6) ml/kg; VO2max, 42 (5) ml/min/kg) matched for age, weight and height with no his-tory of physical activity were included into the study. VO2max, CMR, and echocardiographic parameters were determined as described previously.5 Diastolic function was determined by pulsed Doppler spectral recordings in the four chamber view at the tips of the mitral leaflets and an E/A ratio > 1 was considered to be normal.

As a result of the research, no difference was found in diastolic or systolic function between groups. There was no difference in NT-proBNP values between endurance athletes and untrained control subjects (p = 0.56); endurance athletes, 24.7 pg/ml (10th, 25th, 75th, and 90th centiles: 9.9, 14.1, 37.3, and 49.4 pg/ml, respectively) and untrained control subjects, 28.9 pg/ml (10th, 25th, 75th and 90th centiles: 14.1, 16.7, 32.5, and 41.2 pg/ml, respectively)

It was stated, that NT-proBNP represents BNP in an equimolar manner. There was no difference between BNP concentrations in a small group of eight cyclists and their age matched controls. relation between LV mass and resting NT-proBNP concentration even when examining a greater number of subjects was not found.

The authors discuss relation of their findings to those of Montgomery at al. (which we will discuss next): "Therefore, the present results do not support the findings of Montgomery and colleagues, who observed an in-crease in BNP concentrations in angiotensin converting enzyme D-allele-positive healthy male British Army recruits with an increase in LV mass after 10 weeks of intensive strength and endurance training.3 As a marker of myocardial growth,3 the raised BNP concentrations reported by Montgomery might reflect acute cardiac stress and a beginning myocardial adaptation to the training stimulus (acute effect), whereas in endurance ath-letes with a longer history of training, the myocardium might be already adapted to endurance exercise bouts without further induction of relevant cardiomyocyte growth. Consequently, BNP concentrations do not remain elevated in endurance athletes with athlete's heart at rest (chronic effect)."

Scharhag et al. concluded, that repeated bouts of endurance exercise do not chronically alter myocardial integ-rity and that myocardial wall stress is not elevated in endurance athletes with athlete's heart. The results confirm the assumption that the athlete's heart represents a physiological hypertrophy to an increased volume load with-out ventricular overload. Therefore, under resting conditions, NT-proBNP (and BNP) might be a useful addi-tional tool to differentiate between physiological and pathological cardiac hypertrophy.

One of the first studies which pointed out, that BNP is elevated after strenuous physical load was the one by Montgomery et al. Although it was not focused on athletes, but army recruits, it gave some first vision of the presented problem. And it was also one of the first research projects, which used the BNP test not to diagnose CHF, but to describe the heart features related to the extremely strenuous long-term physical exercises.

Although the main aim of the project was determining the genotype, which is the most associated with the LV mass increase, it was there, where BNP test was used to assess cardiologic features and functions related to ex-treme exercise, among such others as Electrocardiography and Echocardiography.

"The study population comprised all 460 consecutive males recruited to the Army Training Regiment Bassing-bourn, UK, over a 9-month period. All were normotensive and free of cardiovascular disease and underwent an identical 10-week period of intensive strength and endurance training. At entry, height, weight, and the time taken to complete a standard 1.5-mile run at maximal exertion were recorded, and venous blood samples were drawn. On the first day of training (pretraining data) and again 10 weeks later (post-training data), BP (mean of three manual measurements after 5-minute supine rest, each 1 minute apart) was documented, and transtho-racic echocardiography was performed. In one random training cohort, blood was taken for assay of BNP, and a 12-lead ECG recording was performed before and after training. Only subjects who completed training without interruption were included in follow-up."

The results were:

One cohort of 84 participants was randomly selected at entry for assay of plasma BNP, of whom 49 completed training. Pretraining plasma BNP levels did not differ between genotypes. Levels increased significantly with training in the whole group (n=49; mean±SEM, 44.6±2.5 versus 66.4±4.7 pg/mL; P<.001), an effect strongly associated with ACE genotype (for rise in BNP levels,P<.05). Levels did not rise significantly for those of II genotype (47.0±5.6

versus 58.4±6.3 pg/mL), rising significantly only among those with 1 D allele (n=35; pretraining, 43.7±2.8 pg/mL; post-training,69.6±6.1 pg/mL; P<.0001). The rise was greatest for those of DD genotype (mean rise, 11.5±6.3 versus 56.0±17.3 pg/mL for II versus DD genotype, respectively; P<.01). Post-training BNP levels, unlike pretraining levels, were associated with ACE genotype (DD>ID and DD>II; P<.001 for both comparisons).

The data obtained by Montgomery et al. strongly support the association of ACE genotype with LV growth, with the rise in BNP levels with training being ACE genotype dependent. Confounding factors (eg, cardiac dis-ease) were eliminated.

The authors write: "Exercise has little influence on plasma BNP concentration; all blood samples were taken in the absence of recent exercise, and any such effect of exercise is likely to be short-lived due to the very short plasma half-life of BNP." This was later observed by the most researches of this topic. But the short-time eleva-tion in BNP levels rose even more questions later.

On the basis of the above mentioned BNP test results as well as electrocardiographic and echocardiography ones (which we don't add into our overview), the authors concluded that, exercise-induced LV growth in young males is strongly associated with the ACE I/D polymorphism.

"Does Cardiac Morphology Predict Plasma Brain Natriuretic Peptide Levels in Adolescent Athletes?" - the ar-ticle by authors Nilsson, Womack and co-authors, who's research found that plasma BNP levels in healthy ado-lescent athletes have no correlation to body mass index or LV mass, even when corrected for body surface area. Thirty healthy male adolescent high school football players (16.0 ± 1.1 years) were examined. Plasma BNP for this population was 11.9 ± 10.2 pg/mL. There was no correlation between BNP and mean arterial pressure (r = -0.09, P = 0.64), body mass index (r = 0.11, P = 0.57), interventricular septal thickness (r = -0.15, P = 0.44), left ventricular (LV) wall thickness (r = 0.00, P = 0.99), relative wall thickness (r = -0.04, P = 0.84), LV mass (r = 0.05, P = 0.79), or LV mass index (r = 0.11, P = 0.55).

Other articles: "B-Type Natriuretic Peptide Is Related to Left Ventricular Mass in Hypertensive Patients but Not in Athletes" by Susana S. Almeida et al. and "Plasma Brain Natriuretic Peptide In Endurance Trained Ado-lescents" by Nilsson et al., does also find no relation between BNP levels and LVM in athletes.

Mechanism of exercise induces BNP/NT-proBNP level elevation.

Despite the availability of some tens of published works related to the problem we study, there is not clear an-swer, what is the mechanism behind the BNP elevation.

Here is our overview of the article "Exercise-induced increases in NT-proBNP are not related to the exercise-induced immune response", J. Scharhag, T. Meyer and others.

Fourteen cyclists and triathletes (mean (SD) age 25 (5) years; height 180 (7) cm; weight 72 (9) kg; body fat 10.8 (2.5)%; heart volume 13.8 (1.7) ml/kg; VO2peak 67 (6) ml/min/kg) represented the study population. Inflammatory and cardiovascular diseases were excluded by physical examinations, routine blood parameters, an electro-cardiogram at rest and during cycle ergometry, and an echocardiography at rest.

In randomised order, athletes had to perform three 4-h constant load trials at an intensity of 70% of their indi-vidual anaerobic threshold on a 400 m track on three different days, using different carbohydrate beverages (6% or 12% carbohydrate or placebo; 50 ml fluid per kg body weight for each trial). In all three trials (placebo, 6% carbohydrate, 12% carbohydrate), 13 of 14 athletes demonstrated an exercise-induced increase in NT-proBNP concentrations, with a significant effect over time (p<0.001). No difference was found between trials for exercise-induced increases in NT-proBNP concentrations.

It is known, that in cardiovascular patients, levels of BNP and NT-proBNP are elevated due to a pathological increase in myocardial wall stress and, in addition, have been shown to be related to immune reactions.

Authors of the discussed article did not find significant correlations for increases between NT-proBNP and IL-6 (r =0.18; p=0.25), CRP (R=0.28; p=0.12), leucocytes (R=0.10; p=0.54), neutrophils (R=0.13; p=0.40), monocytes (r= 0.05; p=0.77), natural killer cells (R= −0.18; p=0.27), lactate (r=−0.02; p= 0.92), blood glucose (r=−0.16; p=0.32) or cortisol (r=0.16; p=0.32), or between the exercise-induced increase in NT-proBNP and the exercise heart rate at the end of exercise (r=0.09; p=0.60) or the heart volume (r=−0.42; p=0.14). A significant relationship was found between the exercise-induced increases in IL-6 and CRP (R=0.68; p<0.001), and there was a trend between blood glucose and IL-6 (r=−0.49; p=0.088).

The following text discusses the problem very well, so we place it here closely to the original one:

Although prolonged exercise in the present study induced a typical immune response (which could be attenu-ated by CHO supplementation), and a typical increase in NT-proBNP in healthy and well-trained endurance ath-letes after 4 h of moderate but strenuous exercise, no relationship between the exercise-induced immune re-sponse and the increase in NT-proBNP could be demonstrated. Therefore, exercise-induced increases in NT-proBNP or BNP in healthy athletes must be differentiated from increases in cardiovascular patients with sys-temic inflammation.

First, it has to be noted that the exercise-induced immune response in athletes is only transient and mild compared with the chronic systemic inflammation in cardiovascular patients with heart failure, cardiac allograft re-jection or other diseases. Although mean exercise-induced concentrations in IL-6 reached about 5 pg/ml in the present study, which is as high as resting values in patients with worsening heart failure, resting values in ath-letes were normal. Nevertheless, IL-6 has been shown to induce BNP gene expression in cardiac myocytes in vitro, and it has been assumed that the exercise-induced increase in IL-6 (which is produced by the contracting muscle to regulate substrate delivery and to maintain the metabolic homeostasis for glycogen-depleted myo-cytes during exercise in healthy athletes) is responsible for the exercise-induced release in BNP. However, in the present study, no relationship between the exercise-induced increase in IL-6 or other exercise-induced im-mune reactions and the release in NT-proBNP was found. Consequently, other reasons for the exercise-induced release of BNP in healthy athletes have to be considered.

Owing to the increase in cardiac work and arterial blood pressure during exer-

cise, elevated left ventricular wall stress on cardiomyocytes could be one stimulus for the exercise-induced increase in BNP release. In addition, it has been shown that catecholamines induce an increase in the gene expression and release of BNP in vitro and in patients with sepsis. As epinephrine and norepinephrine during 4 h of cycling at an intensity of 70% individ-ual anaerobic threshold are elevated about 1.5 to 2-fold, increases in catecholamines could further explain the exercise-induced increases in BNP or NT-proBNP in healthy athletes.

In conclusion, the exercise-induced immune response does not contribute to the exercise-induced increase in BNP or NT-proBNP in healthy athletes, which therefore has to be differentiated from (NT-pro)BNP elevations modulated by pro-inflammatory cytokines in cardiovascular patients with systemic inflammation.

In an other article "Independent elevations of N-terminal pro-brain natriuretic peptide and cardiac troponins in endurance athletes after prolonged strenuous exercise", Scharhag et al suggest, that the release of BNP during and after exercise may not result from myocardial damage but may have cytoprotective and growth-regulating effects. This conclusion was made after the researches "examined exercise-induced changes in NT-proBNP, cTnI, and cTnT in 105 obviously healthy endurance athletes (40 +/- 8 years) before and after prolonged strenu-ous exercise. Blood samples were taken before, 15 minutes, and 3 hours after a marathon (n = 46), a 100-km run (n = 14), and a mountain bike marathon (n = 45). RESULTS: Eighty-one of 105 athletes exceeded the upper reference limit of NT-proBNP (males/females 88:153 ng/L) after exercise. NT-proBNP increased in all 3 events (P <.001) with the highest increase in the 100-km runners (median increase 200 ng/L; 25th/75th percentile 115/770 ng/L), which differed from the increase in the marathon (97 ng/L; 36/254 ng/L) or the mountain bike marathon (78 ng/L; 37/196 ng/L) (P <.01). Cardiac troponin I exceeded 0.04 microg/L in 74%; cTnT exceeded 0.01 microg/L in 47% of athletes after exercise. NT-proBNP was not related to exercise-induced increases in cTnI or cTnT, but correlated with exercise time (r = 0.55, P <.001)."

In the article "Effect of Professional Exercises on Brain Natriuretic Peptide", H Sheikhani Shahin et al. (20 healthy professional athletes were studied, test results are in table 1) suggest four possible mechanism of BNP concentration rise. First it is "Myocardial Cell Injury", as the increase in BNP correlated to the elevation in cardiac Troponin-T after the run and was interpreted as the result of exercise-induced subclinical myocardial cell damage. Second version is – hemoconcentration, which is a result of exercise induced trans-capillary water passage. But as the authors write themselves, due to a quick Hct correction but longer BNP high levels, some other causes and factors should be suggested. The third hypothesis is ACE gene polymorphism which we have already discussed under Montgomery's article overview. And the final possible mechanism suggested by Ira-nian scientists is "Volume-related stimulus". The authors also have same theory as that of Scharhag et al., that the elevation may represent a cyto-protective mechanism.

La Gerche does also conclude that BNP rise is due to myocardial damage (article "Biochemical and functional abnormalities of left and right ventricular function following ultra-endurance exercise"). This study was aimed to quantify the extent and duration of post-exercise cardiac injury with particular attention to right ventricular (RV) dysfunction. The team tested 27 athletes (20 male, 7 female) one week before, immediately after, and one week following an ultra-endurance triathlon. Tests included cardiac troponin I (cTnI), B-type natri-uretic peptide (BNP) and comprehensive echocardiographic assessment. Results 26 athletes completed the race and testing procedures. Post-race, cTnI was elevated in 15 athletes (56%) and the mean value for the entire co-hort increased (0.17 vs 0.49microg/L, p<0.01). BNP rose in every athlete and the mean increased significantly (12.2 vs 42.5 etag/L, p<0.001). Left ventricular ejection fraction (LVEF) was unchanged (60.4 vs 57.5%, p=0.09), but integrated systolic strain decreased (16.9% vs 15.1%, p<0.01). New regional wall motion abnor-malities developed in 7 athletes (27%) and LVEF was reduced in this sub-group (57.8% vs 45.9%, p<0.001). RV function was reduced in the entire cohort with decreases in fractional area change (0.47 vs 0.39, p<0.01) and tricuspid annular plane systolic excursion (21.7 vs 19.1mm, p<0.01). At follow-up, all parameters returned to baseline except for one athlete with persisting RV dysfunction. Conclusion was made, that myocardial dam-age occurs during intense ultra-endurance exercise and, in particular, there is a significant reduction in RV func-tion. Almost all abnormalities resolve within 1 week.

There are also other points of view. For example, the article "Effects of a long-distance run on cardiac markers in healthy athletes" by M. Leers et al. suggests that the increase could be partially attributed to cardiac stress. The transient increases in BNP, NT-pro-BNP and troponin T are more likely to reflect myocardial stunning than cardiomyocyte damage. They also write, that the magnitude of the increase in BNP could serve as a marker of the biological age of the myocardium.

In their study 25 male and 2 female runners (age 34-64 years) who were running the Visй-Maastricht-Visй marathon. Blood samples were drawn just before and immediately after finishing the marathon. An additional blood sample was collected 24 h later. As a result, running the marathon led to a significant increase in cortisol. This returned to baseline values 24 h after the marathon. There was a slight increase in brain natriuretic peptide (BNP); however, this was not statistically significant. On the contrary, the N-terminal fragment of BNP (NT-pro-BNP) was significantly increased immediately after the run and was normalized 24 h later in 26 out of 27 runners (96%). The magnitude of the transient elevations in BNP and NT-pro-BNP increased with the age of the athletes. Furthermore, in 9 out of 27 runners there was a significant increase in troponin T. However, in all these runners this increase was transient and troponin-T levels returned to baseline values 24 h after the marathon.

It is possible the elevation represents hypertrophic cardiomyopathy, as suggested by article "Athlete's heart or hypertrophic cardiomyopathy: Usefulness of N-Terminal pro-Brain Natriuretic Peptide" by P. Godon, V. Griffet et al.

In Godon's study, NT-proBNP levels were measured at rest and after effort in trained athletes referred for sus-pectedly abnormal (≥ 13 mm) left ventricular hypertrophy. Seventeen patients were included, 10 of whom were diagnosed with hypertrophic cardiomyopathy (group I) while the other 7 presented typical signs of athlete's heart (group II).

NT-proBNP levels did not significantly differ between groups, whether at rest or after effort. NT-proBNP levels were, however, significantly elevated in 3 subjects in group I, while being consistently nor-mal in group II.

Authors conclude, that in active athletes presenting with ambiguous left ventricular hypertrophy, abnormal NT-proBNP levels indicate hypertrophic cardiomyopathy, whereas normal values are inconclusive. The article makes it obvious that the NT-proBNP test is extremely useful in differentiation of athletes heart from hypertro-phic cardiomyopathy.

The article "Hypertrophic Cardiomyopathy vs. Athletes Heart" by T. Cheng. also puts NT-proBNP test as one of the most important tools for the two conditions differentiation.

A Greek/Swiss research based article "Growth-differentiation factor-15, endoglin and N-terminal pro-brain natriuretic peptide induction in athletes participating in an ultramarathon foot race" by I. Tchou, A. Margeli, M. Tsironi, Katerina Skenderi, I. Papassotiriou et al. states that elevated circulating GDF-15, endoglin and NT-pro-BNP levels reflect a transient endothelial dysfunction in these athletes who participated in a foot race con-sisting of continuous, prolonged and brisk exercise. Here is a short abstract data of their research, which repre-sents the base for the conclusion made: "The actions of growth-differentiation factor (GDF)-15, endoglin and N-terminal pro-brain natriuretic peptide (NT-pro-BNP) was investigated in 15 male athletes who participated in the ultradistance foot race of the 246 km 'Sparthathlon'. Measurements were performed before (phase I), at the end of the race (phase II) and 48 h post-race (phase III). GDF-15 and endoglin serum concentrations were de-termined with enzyme-linked immunosorbent assay and NT-pro-BNP plasma levels by electrochemilumines-cence. GDF-15 levels were increased from phase I (563.9 ± 57.1 pg ml−1) to phase II (2311.1 ± 462.3 pg ml−1) and decreased at phase III (862.0 ± 158.0 pg ml−1) ($p < 0.0002$). NT-pro-BNP levels followed a similar pattern to that of GDF-15 from 38.1 ± 4.8 pg ml−1 at phase I to 1280.6 ± 259.0 pg ml−1 at phase II and 89.8 ± 13.6 pg ml−1 at phase III ($p < 0.0001$) and at the same time points, endoglin levels were 4.7 ± 0.2 ng ml−1 at phase I, 5.8 ± 0.2 ng ml−1 at phase II and 4.3 ± 0.2 ng ml−1 at phase III ($p < 0.002$)."

Koning and co-workers wrote (article: "Myocardial Stress after Competitive Exercise in Professional Road Cy-clists", also discussed earlier) that, strenuous endurance exercise in professional road cyclists does not result in structural myocardial damage. The rise in BNP in older athletes may reflect a reversible, mainly diastolic left ventricular dysfunction. This needs to be confirmed by larger trials including different intensities, sports, and age groups. They examined 11 highly trained male professional road cyclists (age 27 ± 4 yr; VO2peak 67 ± 5 mL•kg-1•min-1; training workload 34,000 ± 2,500 km•yr-1). None of the athletes showed pathological findings in the cardiac examination. CK ($P < 0.01$), CKMB ($P < 0.05$), and Myo ($P < 0.01$) were increased after the race. Normal postexercise cTnT levels indicate that the increase in CK, CKMB, and Myo was of noncardiac origin. In contrast, BNP rose significantly from 47.5 ± 37.5 to 75.3 ± 55.3 pg•mL-1 ($P < 0.01$). Pre- and postexercise values of BNP as well as the individual exercise-induced increase in BNP were significantly correlated with age.

It was supposed that the increased BNP and cTnT levels represent cardiac fatigue and not myocardial damage ("Effect of competitive marathon cycling on plasma N-terminal pro-brain natriuretic peptide and cardiac troponin T in healthy recreational cyclists", Neumayr et al.). Neumayr and his measured BNP and cTnT in recreational cyclists ($n = 29$) during the Otztal Radmarathon 2004. In all subjects, NT-pro-BNP significantly in-creased from 28 +/- 21 to 278 +/- 152 ng/L immediately after the race ($p < 0.001$), decreased again on the fol-lowing day, and returned to baseline values 1 week later. The mean percentage increase in NT-pro-BNP was 1,128 +/- 803%. CTnT, negative in all subjects before the race, increased transiently in 13 athletes (45%), with levels ranging from 0.043 to 0.224 mug/L in 8 of them (28%). One day after competition, cTnT had normalized in all athletes.

It becomes quite clear that the BNP and NT-proBNP tests can be very useful in athletes heart assessment, but a lot of further research is needed, as suggested by Scharhag, Koning Kupricka, Almeida, Serrano-Ostariz, Legas-Arrese and others in their articles.

Nounopoulos and others, recommend a routine check-up of plasma NT-proBNP before and after exercise as a screening test, and state that elevated levels warrant further evaluation.

Pagourelias also suggests that, BNP might be useful as a pre-participation screening test in athletes, in his and his co-authors recently published article "Brain natriuretic peptide and the athlete's heart: a pilot study"

The group of Greek scientists used an integrated M mode, two-dimensional B mode and Doppler echocardio-graphical study and plasma BNP levels test to examine 25 strength athletes, 25 patients with established hyper-trophic cardiomyopathy (HCM) and 25 healthy volunteers. Among athletes, BNP levels correlated negatively with the total training time ($r = -0.79$, $p = 0.002$) and positively with ejection fraction ($r = 0.58$, $p = 0.049$) and fractional shortening ($r = 0.57$, $p = 0.049$). A BNP cut-off value of 11.8 pg/ml had 88% specificity and 74% negative predictive value for the exclusion of HCM.

As already mentioned, exercise-induced BNP increase was shown to be significantly correlated with athletes' age. Some of the articles, such as the one by Leers et al. suggest that NT-pro BNP can be used as a marker for biological age of myocardium. At the same time some others, as Krupicka's article "Effect of short-term maxi-mal exercise on BNP plasma levels in healthy individuals" did not find any such correlation, putting this possible usefulness under question and need of further research.

Reports of BNP response to exercise in healthy control individuals are also controversial and different mecha-nisms of BNP elevation where suggested (Krupicka et al., Scharhag et al.)

CONCLUSION: Having made a general overview of the present problem and related literature, we consider that the topic is quite important and it is necessary to conduct further investigations. Of course not all related articles are discussed in this text. You can find some of those not discussed but considered in our article in the literature list. Sports medicine, particularly cardiology problems and a new possibility of using BNP and NT-proBNP tests to assess athletes heart made us decide to start our own original research program which is now being managed. We propose a project of

some stages, with possible developments according to results got in our original pilot study, which considers testing 10 experienced rowers of the Georgian national rowing team, before and after exercise, as well as control group of healthy individuals. We decided to make BNP tests and not NT-proBNP as both are shown to be elevated in the below mentioned articles, and in our conditions it would be more suitable to test BNP and not NT-proBNP. Further studies may consider different sports activi-ties, age and exercise duration, as well as comparing the results with echocardiography and electrocardiography data, as well as clinical histories, general examination, capillaroscopy and possibly other assessment methods.

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MITRAL VALVE PROLAPS

ROSTOM AMIREJIBI
Resident

Mitral valve prolapse syndrome has been given many names, including the systolic click murmur syndrome, Barlow syndrome, billowing mitral cusp syndrome, myxomatous mitral valve, floppy valve syndrome, and redundant cusp syndrome. It is a common but variable clinical syndrome that results from a diverse pathologenic mechanisms of one or more portions of the mitral apparatus, the valve leaflets, chordea tendineae, papillary muscle, and valve annulus. MVP usually associated with myxomatous degenaretion, affect up to 2-3% of adults in industrialized countries, with a 2:1 female predominance.

The condition was first described by John Breleton Barlow in 1966, and was subsequently termed mitral valve prolapse by J. Michael Criley.

MVP has been observed in all ages.

Most frequenty non-classic mitral valve prolapse occurs as a primary condition unassociated with other diseases. Patients present with a mid-systolic click or clicks, mild billowing of non-thickened mitral valve leaflet, the mitral valve leaflet coaptation point on the ventricle side of the mitral annulus and no or minimal mitral regurgitation.

However, classic mitral valve prolapse has been reported to be associated with many condition. It is characterized by increased redundancy or thickening (myxomatous changes) of varying portions of the mitral valve leaflets. There is surface fibrosis of the mitral valve leaflets, mitral annular dilatation, chordal redundancy and lengthening and fibrin deposits. MVP occurs quite commonly inheritable disorders of connective tissue that increase the size of the mitral leaflets and apparatus, including the Marfan syndrome, Ehlers-Danlos syndrome, osteogenesis imperfects, Ebstein's anomaly, atrial septal defect and the Holt-Oram syndrome. Classic mitral valve prolapse may be familial, non-familial. There appears to be a high incidence of MVP in patients with asthenic habitus and a variety of congenital thoracic deformities, including a straight back, a pectus excavatum and a shallow chest.

Secondary mitral valve prolapse can appear in coronary artery disease due to a relative displacement of the ischemic papillary muscle.

Functional mitral valve prolapse results from a disproportion of the mitral valve leaflets and chordate in relation to the internal left ventricle dimension. A reduction or alteration in left ventricular cavity size or shape may cause normal mitral valve leaflets to move past the mitral valve annulus during ventricular systole.

The myxomatous appearance of the leaflets in MVP is due to a loss or dissolution of the normal dense collagen fibers (fibrosa), with replacement and invasion of a less sturdy type of connective tissue (spongiosa). The leaflets, chordae tendineae, and annulus all may be affected by myxomatous proliferation. The leaflets are thickened and redundant, and the chordae tendineae become elongated. Both mitral leaflets can be affected in MVP, but the posterior leaflet is more commonly involved.

Myxomatous proliferation, although most commonly affecting the mitral valve, is not limited to this valve but has been described in the tricuspid, aortic, and pulmonic valves, particularly in patients with Marfan syndrome, and may lead to regurgitation of these valves.

Prolapse represents abnormal superior systolic displacement of the mitral

valve leaflets; one or both of the leaflets extend beyond the normal systolic coaptation point, allowing MR to occur. During systole, individual scallops or an entire leaflet may billow excessively into the left atrium. For severe MR to be present, both leaflets must be affected or one leaflet may be flail, such as in the case of a ruptured chordae tendinea. The stress on the ballooning leaflets during ejection may result in additional stretching of the valve tissue and chordae. Thus, prolapse may be get greater prolapse.

Mitral valve prolapse is often diagnosed from the physical examination, when the classic auscultatory finding of a mid-to-late systolic click and/or murmur is appreciated. Alternatively, it may be incidentally diagnosed during routine echocardiography or discovered when complications of MVP manifest.

Most patients are asymptomatic. Symptomatic patients with MVP are separated into 3 categories: (1) those with symptoms related to autonomic dysfunction; (2) those with symptoms related to the progression of mitral regurgitation; and (3) those with symptoms that occur as a result of an associated complication (ie, stroke, endocarditis, or arrhythmia).

- Symptoms related to autonomic dysfunction are usually associated with genetically inherited MVP and include the following:
  - o Anxiety
  - o Panic attacks
  - o Arrhythmias
  - o Exercise intolerance
  - o Palpitations
  - o Atypical chest pain
  - o Fatigue
  - o Orthostasis
  - o Syncope or presyncope
  - o Neuropsychiatric symptoms
- Symptoms related to progression of mitral regurgitation include the following:
  - o Fatigue
  - o Dyspnea
  - o Exercise intolerance
  - o Orthopnea
  - o Paroxysmal nocturnal dyspnea (PND)
  - o Progressive signs of congestive heart failure (CHF)
- ECG usually is normal, but can show nonspecific ST-segment and T wave abnormalities especially in leads II, III, aVF.
- MVP is also commonly seen in patients with inheritable connective tissue disorders.

Clinical characteristics are typically benign in young women, whereas men older than 50 years tend to have serious consequence of mitral regurgitation.

- Common general physical features associated with MVP include the following:
  - o Asthenic body habitus
  - o Low body weight or body mass index (BMI)
  - o Straight-back syndrome
  - o Scoliosis or kyphosis
  - o Pectus excavatum
  - o Hypermobility of the joints
  - o Arm span greater than height (which may be indicative of Marfan syndrome)
- The classic auscultatory finding is a mid-to-late systolic click, which is present due to the leaflets prolapsing into the left atrium resulting in tensing of the mitral valve apparatus. It may or may not be followed by a high-pitched, mid-to-late systolic murmur at the cardiac apex.
  - o The midsystolic click can vary in intensity and timing, primarily depending on left ventricular volume.
  - o End-diastolic volume can be reduced by performing a Valsalva maneuver or by having the patient stand. These maneuvers result in an early click, which is close to the first heart sound, and a prolonged murmur. In the supine position, especially with the legs raised for increased venous return, left ventricular diastolic volume is increased, resulting in a click later in systole and a shortened murmur.
- Patients with MVP most frequently have symptoms of autonomic dysfunction, including easy fatigability, dizziness, and atypical chest pain. This pain is perhaps related to papillary muscle strain (ie, excessive pulling on the left ventricular wall with prolapsed leaflets in the left atrium).

Differential Diagnoses – Mitral regurgitation

WORKUP

- Echocardiography
  - o Findings
- Classic MVP: The parasternal long-axis view shows > 2 mm superior displacement of the mitral leaflets into the left atrium during systole, with a leaflet thickness of at least 5 mm.
- Nonclassic MVP: Displacement is > 2 mm, with a maximal leaflet thickness of < 5 mm.
- Other: Other echocardiographic findings that should be considered as criteria are leaflet thickening, redundancy, annular dilatation, and chordal elongation.
- Contrast ventriculography: This study can also help in defining MVP with or without mitral regurgitation. However, with the advent of echocardiography, contrast ventriculography is rarely necessary.
- Chest radiography: Radiographs may demonstrate the progression from asymptomatic to chronic, severe mitral regurgitation with the development of cardiomegaly secondary to left atrial and left ventricular dilatation and evidence of heart failure.

TREATMENT

- Asymptomatic patients with minimal disease
  - o These patients should be strongly reassured of their benign prognosis.
  - o They should undergo initial echocardiography for risk stratification. If no clinically significant mitral regurgitation and thin leaflets are observed, clinical examinations and echocardiographic studies can be scheduled every 3-5 years.
  - o These patients are encouraged to pursue a normal, unrestricted lifestyle, including vigorous exercise.
- Patients with symptoms of autonomic dysfunction
  - o A trial of beta-blockers for symptomatic relief can be recommended.
  - o Abstinence from stimulants such as caffeine, alcohol, and cigarettes is also recommended. An ambulatory 24-hour monitor may be useful to detect supraventricular and/or ventricular arrhythmias.
- Patients with evidence of or progression to severe mitral regurgitation
  - o Close follow-up and referral for surgical repair are indicated early, before left ventricular dilatation and systolic dysfunction develop.
  - o Asymptomatic patients with moderate-to-severe mitral regurgitation and left ventricular enlargement, especially those with atrial fibrillation and/or pulmonary hypertension, should undergo surgery before left ventricular function deteriorates.
  - o If the physician is unsure if the patient is asymptomatic, a treadmill stress

test for exercise tolerance can be performed. That is, have the patient demonstrate that he or she can walk vigorously without symptoms.

- Patients with MVP and neurologic findings

o After atrial fibrillation and left atrial thrombus are excluded, these patients should be given daily aspirin therapy at a dosage of 80-325 mg/d.

o Cessation of smoking and oral contraceptive use to prevent a hypercoagulable state should be recommended.

o Warfarin should be used when patients older than 65 years have atrial fibrillation, especially if they have associated risk factors of a previous stroke or TIA, clinically significant valvular heart disease, hypertension, diabetes, left atrial enlargement, or a history and/or findings of heart failure.

- Patients with a mid-systolic click and late-systolic mitral regurgitation murmur

o Consider antibiotic prophylaxis in these patients, including those with increased leaflet thickening or redundancy.

o Antibiotic prophylaxis is not recommended for the patient with an isolated mid-to-late systolic click without a murmur, unless the echocardiogram demonstrates significant leaflet redundancy and/or thickness.

Mitral valve prolapse associated with severe mitral regurgitation can be treated with repair or surgical replacement of the mitral valve. Repair of the mitral valve is always preferable to replacement and should be performed by surgeons that are skilled in the procedure. Current ACC/AHA guidelines suggest that early repair of mitral valve, performed in centers of surgical excellence, should be considered even in patients without symptoms of heart failure. Symptomatic patients, those with evidence of diminished left ventricular function or left ventricular dilatation need urgent attention.

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"CARDIOVASCULAR SYSTEM IN THE SPORTS - CHILDREN HOLDING PREVENTION ARRANGEMENTS AGAINST WEEK RINGS"

G. CHAKHUNASHVILI, N. JOBAVA, D. PRUIDZE, D. TABUTSADZE, V. KANDELAKI, M. CHKHAIDZE

Pediatric clinic of State Medical University Tbilisi, Georgia

Profilactic Center for Mother and Child Tbilisi, Georgia

Topicality (urgency) of the problem. Today a number of people who goes in for sports in order to improve their health grows steadily as well as a number of professional sportsmen. These persons, as a rule, go in for sports since the childhood. Proceeding from this, the attention of pediatrics should be attracted namely to this period. According to this, the functional indices of junior-sportsmen should be studied under various conditions of their training (N.M. Amosov, Ya.A. Bendet, 1984; A.G. Dembo, E. Zemtsovski, 1989). The investigation was carried out taking into account different methodological positions. At a single glance, a proper approach to this as if banal but really complicated problem will answer to many questions facing both pediatrics and the children who wish to get perfect physical development. The topicality of the problem is doubtless. By means of the newest achievements in pediatrics the absolutely new prerequisites have been created in order to establish interrelations between functional and structural possibilities of the organism. This makes it possible to avoid a number of clinical errors which regarding to the physical training is connected to the formation of the child.

Goal of the investigation was a detailed study of the dynamics of clinical-instrumental and laboratory indices in junior-sportsmen during their training in various kinds of sport.

The tasks of the investigation were: 1) clinical-instrumental study of the juniors engaged in for sports taking into account various methods of their training; 2) determination of structural indices of blood cells which are the dynamic data, pointing to general state of the growing organism before and after the training; 3) determination of general dynamic criteria of clinical and laboratory data (structural indices of blood cells); 4) inclusion of specialized Georgian licensed preparations and food supplements in the treatment of the junior-sportsmen and determination of the criteria of their effectiveness using already existing clinical-laboratory methods.

Scientific novelty:

- sport indices of juvenile wrestlers were determined;
- ECG indices in fifteen recordings were determined before and after the physical loading;
- functional changes on cardiovascular system in sportsmen were revealed under conditions of prolonged adaptation to physical loading;
- action of apivit, apikor, apihebat, apipulmo and kartan intake was studied in juvenile wrestlers for the improvement of adaptive mechanisms;
- morphology of blood cells in juvenile wrestlers were studied under conditions of adaptation to physical loading.

MATERIAL AND METHODS OF INVESTIGATION

Total of 150 children (juvenile sportsmen) at the age of 12-15 were under the examination. They were divided into three groups (50 sportsmen in each group). These sportsmen were engaged in classical wrestling, judo and free-style wrestling. Each above-mentioned group was divided into two subgroups. One group used to take kartan+apivit+apikor according to the developed scheme, while the second group did not take the medicine.

The clinical data of all children (juvenile sportsmen) have been studied. At the same time the blood of those children who were not engaged in for sports (20 children) was studied. The blood of examined persons was taken from the finger. In order to study the clinical data of each juvenile sportsmen, the following methods of investigation were used: detailed anamnestic material of the sportsmen was collected, ECG inves- tigation was carried out on 5-channel polyphysiograph Biocomb-5 (Hungary). The state of left auricle was determined according to the criteria of E. Frohlich, while hypertrophy of right ventricle – according to Sokolov-Leon criteria. ECG investigation was carried on in the dynamics. For the determination of bioelectrical activity of the myocardium the method of planimetric analysis was used. Depolarization and repolarization of left ventricle area were determined as well as its intensity, velocity, ratio of depolarization and repolarization intensity, etc.

The central and intracardiac hemodynamics was studied by means of the method of one- and two-dimensional echocardioscopy on the apparatus "Aloka" SSD 280 LS (Japan). Diastolic function of left ventricle was estimated by the method of impulsive dopplerography using UGR-23 doppler-block.

The following parameters were determined: main systolic and diastolic sizes, volumes of left ventricle, thickness of left ventricle posterior wall and interventricular septum in systole and diastole, ejection fraction, fractional contraction, rate of circular contraction of myocardial fibers; stroke volume, minute and second volumes, cardiac index, myocardial mass of the left ventricle was calculated as well as average hemodynamic pressure, general and specific peripheral resistance of the vessels, energy and power of the left ventricle, an initial rate of left ventricle pressure increase, etc.

The dopplerography of arterial vessels has also been carried out on the apparatus "Vasoscan" (England) and the ultrasound angiography – on the dopplerograph "Appeton Floscan Plus" (England) by means of which a degree of damage in the vessels was determined in case of its presence.

A complete laboratory examination was carried on in all juniors: blood test, urine analysis, coagulogram, lipid metabolism, as well as morphological investigation of blood cells was carried out.

The study of lipid metabolism was done on the apparatus "Refletron" (Germany). The level of overall cholesterol, triglicerides and lipoproteins and their dynamics in the process of training were determined. For the determination of hyperlipidemia the classification approved by the World Health Organization was used, which was based on Fredricson's investigations.

At the same time together with the clinical investigations the blood cells of young sportsmen were studied. The blood was taken from the finger, the smears were prepared which were fixed in neutral fixative holder. Then these blood smears were studied by means of light microscope. Photomicroscope-III of the firm "Opton" (Germany) was used.

One part of clinical material has been studied by using of electron microscope method. The blood cells, in particular, erythrocytes, neutrophiles, lymphocytes and thrombocytes have been studied. The observations were carried on in all three groups. The subgroups were taken into account before the inclusion of Georgian food supplement "Apivit" into food allowance of the sportsmen and after the cessation of its intake during the physical loading.

The substructural organization of the erythrocytes (its membrane) has been studied. The nucleus, cytoplasm, membranous and non-membranous structures were studied in the neutrophile. As to lymphocytes, there the nucleus and cytoplasm, its membranous and non-membnrabous structures were also studied. In thrombocytes a character of granules (α - and dense granules), a size of processes, adhesion, spreading of glycogen granules have been studied by means of BS-500 type electron microscope (firm "Tesla", Czech Republic).

By the use of interference-polarization microscope the physical parameters of the erythrocytes (normocytes) were determined, in particular: optical path difference / ψ /, gradient of optical path difference /dt/dx/, amount of dry matters per surface unit / m 1 /, amount of dry matters in the cell /m/, concentration of dry matters /C/, thickness of the cell /t/, its density / δ /, cell volume /v/, cell area /S/, coefficient of light refraction /$P_{w1} - P_{w2}$ /, phasic deflection of light wave /W/.

The selection and processing of the material were carried on according to the principles of affirmative medicine.

All above-said indices were calculated per 100 cells for light and electron microscopes, while for interference-polarization microscope – per 25 cells. The digital indices were processed by means of variation-statistical method using a special computer program "Start-2". Mean arithmetical (M) and mean quadratic deflection ($G=+V\Sigma d^2 / (n-1)$) have been determined as well as mean arithmetical error (m), the indices "t" and "P" (possibility of the error). A correlation analysis was done by using the coefficients of correlation matrix.

From structural-cytochemical point of view, the stereotype cases had the same character. So, description of the cases for all groups were given totally. The estimation of reliability of quantitative indices was made by the use of Student's criterion (t), while the same in regard the qualitative indices – by the use of χ^2 criterion. The comparison between the groups was made by Pearson. The difference was considered to be reliable, if $t>1,96$; $<0,05$ and $\chi^2 >3,84$;

P<0,05 (R. Fletcher, S. Fletcer, 1998; G. Gaiatt, D. Renny, 2003; O. Rebrova, 2003). Mathematical provision was made by the use of program package SPSS 11-5.

All junior sportsmen were examined before and after their training by the use of clinicallaboratory method. As it has been noted above, according to the developed scheme, a part of training sportsmen took kartan+apivit+apikor+api hepat+apipulmo.

For fully estimation of the action of mentioned medications during the analysis of the data obtained, the cases were considered to be negative when there occurred the deterioration of hemodynamic indices during the fulfillment of 3 or more indices and functional tests of cardiovascular system. Then the evaluation of the treatment was made proceeding from the principles of affirmative medicine.

As it is shown in the Table No 1, the deterioration of functional and physical indices significantly decreases in the group of sportsmen who have taken medications.

The relative risk of the negative result during medication intake and control groups is presented in the Table No 2.

In the group of medication intake the decrease of relative and absolute risk was observed. The amount of those sportsmen the training of which was necessary in the given period for receiving of one positive result equaled to 2.

So, in the group of classical wrestling the decrease of relative and absolute risk of main indices of dysadaptation is noted, what makes it possible to consider that the use of these medications and food supplements is possible both for improvement of adaptation to the loading and for the prevention of dysadaptation.

There were no drastic changes (reliable increase) in anthropometric indices for the group without medications intake, especially during judo and classical wrestling. The frequency of respiration and pulsation increased only after the training.

The changes in amplitude parameters of cardiac cycle in the wrestlers before the medication intake before and after the training point to a low ability of adaptation of cardiovascular system, as compared to physical loading.

After the complex intake of medications (according to the developed scheme) the anthropometric indices of the stlers improved.

After the complex intake of medications the following physical and functional indices of the wrestlers, especially of the judoists and free style wrestlers were improved: indices of breath holding, average arterial pressure, systolic and minute volumes of blood circulation, coef cient of endurance.

According to electrocardiographic data, the energetic maintenance of the myocardium and indices of its blood supply have been improved.

The complex use of the medications (kartan+apivit+ap ikor+apipulmo+apihepat) improves the capacity for work of the sportsmen, enlarges adaptive mechanisms to training and contest conditions, increases rehabilitation processes after the intensive physical loading.

In the group of the sportsmen engaged in free style wrestling the decrease of relative and absolute risk of main indices of dysadaptation was observed: COR=67,9% (95%, CI:43-72%; CAR=50,5% (95%, CI:31,1-69,9%), as well as amount of the sportsmen, the treatment of which is necessary for receiving one positive result in the mentioned group (NNT=2).

So, according to initial characteristics of the overstrain and dysadaptation were observed expressed in the decreased pulse and increased average pressure, a high index of Ru e and coef cient of endurance, low Lilienstrad and Tsander indices, tests of Genche and Shtange.

The initial characteristics of amplitude parameters of the cardiac cycle in the wrestlers (low P wave and depressed T wave, decreased ST segment against the background of tachycardia) point to the loading of cardiovascular system and comparative low ability of adaptation.

The use of complex method of physical training (physical training + complex of medications according to the developed scheme: kartan+apivit+apipulmo+apihepat+apikor) intensi es the functional possibilities of the organism expressed in changes in euchromatin area, the amount of adhesive cells, the area of mitochondria, as well as in the growth of endoplasmic reticulum and lysosoma (see Figs 1 and 2). At the same time the decrease of relative and absolute risk of main parameters of dysadaptation has been noted: COR=67,9% (95%, CI:43-72%; CAR=50,5% (95%, CI:31,1-69,9%).

The different types of physical training have a heterogeneous in uence on the development of the organism.

On the basis of the use of developed scheme, the electrocardiographic data point to the improvement of energetic maintenance of the myocardium and its blood supply.

CONCLUSION

A timely diagnostics of early symptoms and weak links of dysadaptation appears to be the first stage of pre-pathological and pathological states' prevention in the sportsmen. To carry out prophylactic measures is the second stage and the correction and individualization of train- ing process is third stage.

Table N1

Statistical estimation of the results of medication action

	Group of medications intake (%)	Control group (%)	χ^2 criterion
Meaning	**23,81**	**74,286**	**19,539**
Interval of reliability (CI)	**10,9**	**59,8**	**-**
Interval of reliability (CI+)	**36,7**	**88,8**	**-**

Table N2

Relative risk of the negative results in medication intake snd control groups

	Relative risk	Decrease of relative risk	Decrease of absolute risk	Amount of the patients the treatment of which is necessary for receiving of one positive result (NNT)
	RR	COR	CAR	NNT
Meaning	**0,321**	**0,679**	**0,505**	**1,981**
Interval of reliab-ility (CI)	**0,180**	**0,430**	**0,311**	**1,432**
Interval of reliab-ility (CI+)	**0,570**	**0,720**	**0,699**	**3,216**

INFORMATION

GEORGIAN PEDIATRICS IS 100 YEARS OLD

THE ROLE OF THE GEORGIAN PEDIATRIC CARDIOLOGY ASSOCIATION IN GEORGIAN PEDIATRICS (1992-2021)

G. CHAKHUNASHVILI,
MD. PhD. D. Sc. Professor, Academician
(CHAIRMAN GEORGIAN PEDIATRIC CARDIOLOGY ASSOCIATION)

GPCA was founded on the base of TSMU pediatric clinics in 1992 and was registered in 1999. Association was founded by five persons according to Georgian Civil Codex Regulation in 1997. Association work is not limited, has independent balance in Georgian and foreign banks. Main goals of this association is early diagnostics of diseases like – Rheumatic and None-Rheumatic Cardiovascular diseases, heart ischemic diseases, myocardial infarction, different cardiomyopathy diseases, children hypertensions, Athlete's Heart and etc. Also, one of the main goals of GPCA is to help all young people who are interested in Pediatric Cardiology. Association works include bloodless instrumental research like – ECG in 15 inclinations, PCG– during load, electric velometry, capillaroscopy, rheography, echocardiography and others, research ofimmunological and genetic markers. Members of Association can be lawyers who share the goals and main principles of work. Members of GPCA have determined rights and duties: to participate in governing of Association and various projects, use the consultations and recommendations of Association, get financial support from Association funds and leave Association. The governing system of Association is represented by general meeting of the members which is held once in a year. Each member has one vote. These charters are in action after registration. So, this association has important duties and function, which is stimulated by doctor's sensitiveness and creative work in this field.

GEORGIAN PEDIATRIC CARDIOLOGY ASSOCIATION CHARITY ACTIVITIES

From 1992 to 1998 GPCA was periodically holding humanitarian examinations. From 1998 with the help of Social Pediatrics Protection Fund started charity activities, in which Georgian pediatrists were participating. Activities included: Instrumental and laboratory research of patients in different regions of Georgia, Medical gifts, several funded emergency operations.

07.01.98 – 07.02.99 Tbilisi, - over 9200 children were examined.

23-24.01.99 East Georgia, - over 3500 children were examined.

12-13-14.02.99 Tbilisi, - over 100 children were examined and gifted medicines. Free consultations by professors were held by Mother and Child Diagnostic Centre and other hospitals once a week, consultations in leading pediatric clinics of the city once in a month. In these activities were also participating: 1. Institute of skin and vein 2.Scientific Institute of Parasitology and others.

12-13-14.03.99 expedition in Poti and Abasha (Qedisi, Marani and other), - 950 children were examined and gifted medicines.

29-30. 01-07.08.99 – 4400 children were examined and gifted medicines.

23-24-25.08.99 Khobiand Zugdidi, - Free instrumental and laboratory examinations were funded. Also medicines against louse and itch were given.

04.04.99 - Expedition in Pasanauri – over 400 children were examined.

07.05.99 – Expedition in Lanchkhuti – Free instrumental and laboratory examinations were held and medicines were gifted.

18.05.99 Rustavi, - 250 children were examined and gifted medicines.

22.06.99 Sagarejo, - 250 children were examined and gifted medicines.

13-14.08.99 Chokhatauri, - over 1500 children were examined.

15.08.99 Bakhmaro, - over 2000 children were examined.

16.08.99 Adjara high-mountain regions, - over 750 children were examined.

17.08.99 Tbilisi, – Examinations in Homeless children house.

16.10.99 Dusheti region, - over 200 children were examined and gifted medicines.

2000.

26.02.2000 Gori, - over 500 children were examined. Different medicines were given out.

23.03.2000 Axalgori, - 30 children were examined.

01.04.2000 Marneuli region (Werakvi), - General blood analysis, instrumental examinations – echoscopy, encephalography were done. Over 1500 children were examined.

15.04.2000 Gurjaani, - 1200 children were examined, medicines were given out.

29.04.2000 Rustavi, - 300 children were examined.

05.06.2000 – Children from Avchala colony were examined.

20-28.07.2000 – Children in Tskhneti Orphanage were examined.

21-22-23.07.2000 – Examinations in Abasha and Samtredia region.

7-8.08. 2000, Bakhmaro-Beshumi – 1925 children were examined.

2001.

15.03.2001. Children of employees of Rustavi Nitrogen Factory were examined.

23.06.2001. Children of employees of Rustavi Nitrogen Factory were examined.

14-15-16.09.2001 Baghdati region (Sairme, Witelkhevi, Rokhi, Ochba, Xani, Zegani,Saqraula) – over 2500 children were examined.

2002.

10.03.2002 Axalgori, - 250 children were examined.

20-04.2002 Sighnaghi, - 450 children examined.

23-24-25-26.05.2002 Khulo, - 600 children and 100 adults were examined with the help of Patriarchy.

27-28-29.06.2002 Tbilisi, - 400 children were examined in different Hospitals.

16-17-18-19.07.2002 KodorisKheoba, - 250 children were treated.

3-4-5-6.08.2000 Tusheti (Dikolo, Omalo, Shenaqo) – 200 children were treated.

2003.

05.03.2003 Samtskhe-Javakheti, - 1250 children were examined.

17.04.2003 Werovani, - 450 children were examined.

20.05.2003 Borjomi, - 870 children were examined.

25.06.2003 Mta-Tusheti, - 320 children were examined.

30.07.2003 Bakhmaro, - 630 children were examined.

20.08.2003 Zestaponi, - 210 children were examined.

07.09.2003 Racha, - 170 children were examined.

18.102003 Dmanisi, - 180 children were examined.

2004.

March, April, May – Kaspi, Gurjaani, Telavi, Akhmeta, Lagodekhi, Sighnaghi, Bodbe, Aspindza, Axaltsikhe, Borjomi, Tbilisi, Zestaponi, Kharagauli, Chiatura – over 1728 children were examined. In different regions (Zugdidi, Khulo, Khelvacharui, Qeda, Lanchkhuti, OzurgetiIngiri), SPPF held charity activities with the help of Patriarchy – over 2400 children were examined and medicines were given out.

2005.

Marneuli region – 700 children and 80 adults were examined.

18th of July, Kaspi – 450 children were examined.

8th of October, Mtskheta – 300 children were examined.

14-15-16th of October, Lentekhi – 850 children and 250 adults were examined.

2006.

18th of February –20 Painter Union families were examined.

March – over 100 refugee children were examined.

April – Charity activities were held by ambassadors in Guria.

31th of May – 450 children were examined in Rustavi.

1-2th of June - Open door day in TSMU, 400 children were examined. They were held free consultations and laboratory examinations.

9-10th of June, Kaspi - 300 children were examined.

1th of July, Ckhinvali region – 500 children of war participants were examined. In September-October – 120 children.

In November – over 200 of Journalist's families were examined.

2007.

Marneuli – Free consultations for 100 children. Childrens with Scoliosis were shown. They got espander gifts and were recommended how to treat scoliosis.

Dusheti – 250 children were examined.

Akhalsheni–85 children were held consultations.

9-10th of June, Kaspi – 300 children were examined.

1th of July, Ckhinvali region – 500 children of war participants were examined. In September-October – 120 children.

In November – over 200 of Journalist's families were examined.

2008.

1st of June – Open door day (200 children were examined).

2nd of June – Teddy bear (300 children examined).

14th of June, Akhmeta (QaQucoba) - 450 children were examined and gifted medicines. Also examinations like echoscopy of abdominal cavity and ECG were held.

27th of June – restoration of Georgian Section.

20th of August - STOP RUSSIA (meeting at Igoeti)

1st of September, Tbilisi – STOP RUSSIA (meeting of chain)

4th of October – free consultations and examinations. Painters and artists master classes were held.

6th of December – 110 children were examined in Bergman Clinics with echoscopy of abdominal cavity, ECG and other.

2009.

13.06.2009, Khashuri – 750 children were examined.

26.12.2009, Barisakho – 80 children were examined.

2010.

4th of July – Open door day for family members of war victims (50 children were examined).

10th of July, Karaleti – 200 children were examined and medicines were given out.

4th of November – St. King Tamar orphanage children were examined.

3-4th of December, Tbilisi – 400 sportsmen children were examined.

2011.

1st of June, Tbilisi – 200 children were examined.

24th of December, Tbilisi – 200 children were examined.

2012.

1st of June, Tbilisi – 350 children were examined.

22th of December, Tbilisi – 250 children were examined.

Till today over 93 727 children were examined and thousands of old people. Charity activities continue.

2013.

1-4.06.2013. Tbilisi, Batumi, Gori, Telavi – 1250 children were examined.

17-21.12.2013. Tbilisi – 350 children were examined.

2014.

1st of June, Tbilisi – 150 children were examined.

28th of December, Tbilisi – 50 children were examined.

2015.

1st of June, Tbilisi – 350 children were examined.

11.12.2015. Chkorotscu – 1300 children were examined.

2016.

3035 children were examined.

2017.

1305 children were examined.

2018.

200 children were examined.

2019.

250 children were examined.

2020.

95 children were examined.

2021.

55 children were examined.

Till today over 228 050 children were examined and thousands of old people. Charity activities continue.

SIMPOSIUMS AND CONFERENCES HELD BY GEORGIAN PEDIATRIC CARDIOLOGY ASSOCIATION:

1992. First pediatric cardiology conference – "believe the reality of better future".

01.06.1999. II conference – "Healthy child & peaceful Caucasus".

25.12.1999. III conference – "Today's economic directions in pediatric and its perspective". XXI century Pediatrics should be the start of invalid prophylaxis.

01.06.2000. IV conference – "Child must have right to be protected since embryo".

27.03.2001. Meeting in ombudsman's office – "Under aged criminals, their rights and reality".

01.06.2001. V conference dedicated to Children Protection National Day.

32.03.1999. 01.06.2000. 01.06.2001 "Child treatment in XXI century"

23.04.1999. 01.06.2000 "Child treatment in XXI century" "Orthopedic school"

17.12.1999. Mucoviszidose treatment and diagnostics.

01.06.2000. Young Pediatrists XVIII conference.

28.02.2001. Urgent questions of Therapy of respiratory diseases in pediatrics.

01.06.2001. "Child has right to be protected since embryo".

01.06.2001. "Child, adult and family violence".

13.02.2002. "Human genome project".

10.03.2002. Akhalgori, - Presentationof toner drink "Lomisi".

06.11.2002. National Conference: Medical and social problems of people who suffer from mucoviszidose and metabolism disorder.

07.11.2002. "Contemporary aspects of inborn diseases".

04.04.2003. "Urgent pediatric questions" (IX conference).

01.06.2003. Internet conference (X conference) – Social Pediatrics Protection Fund gave out journals and magazines called "Social Pediatrics" (In which is written about social, medical, pedagogic, psychological, religious and other urgent problems).

19.12.2003. Second Georgian Cardiology Congress.

22.10.2004. "Urgent Pediatric questions" dedicated to SPPF president, Victor Moroshkin.

01.06.2004. Second National Internet Conference.

01.06.2005. Urgent Pediatric questions.

09.09.2005. Tbilisi Marriot, - Second National Conference "Healthy child & Peaceful Caucasus".

1st of June, 2006. – SPPF conference. XXIII Congress of Young Pediatrists League.

31.05.2007. III congress of Pediatric Cardiology.

07.12.2007. SPDF XVII conference.

07.10.2008. Conference – "Section of child and adult".

20.12.2008. SPPF and ESMNS second conference.

12.06.2009. SPPF XX conference.

01.06.10. Second conference of Georgian surgeons and XXII conference of Tsalka.

03.12.2010. Conference dedicated to I. Kvachadze 85th anniversary.

01.06.2011. SPPF XXVI conference.

23-24.12.2011. SPPF XXVII conference.

01.06.2012. IV congress of Pediatric Cardiology. SPPF XXVIII conference.

21-22.12.2012. SPPF XXIX conference

1-4.06.2013. SPPF XXX conference

17-21.12.2013. SPPF XXXI conference

1-2.06.2014. SPPF XXXII conference

27-28.12.2014. SPPF XXXIII conference

1-2.06.2015. SPPF XXXIV conference

11.12.2015. SPPF XXXV conference

1.06.2016. SPPF XXXVI conference

9-10.12.2016. SPPF XXXVI conference

1.06.2017. SPPF XXXVIII conference

05.12.2017. SPPF XXXIX conference

01.06.2018. SPPF XXXVIII conference

07.12.2018. SPPF XLI conference

01.06.2019. SPPF XLII conference

14.12.2019. SPPF XLIII conference

31.05.2020. SPPF XLIV conference

20.12.2020. SPPF XLV conference

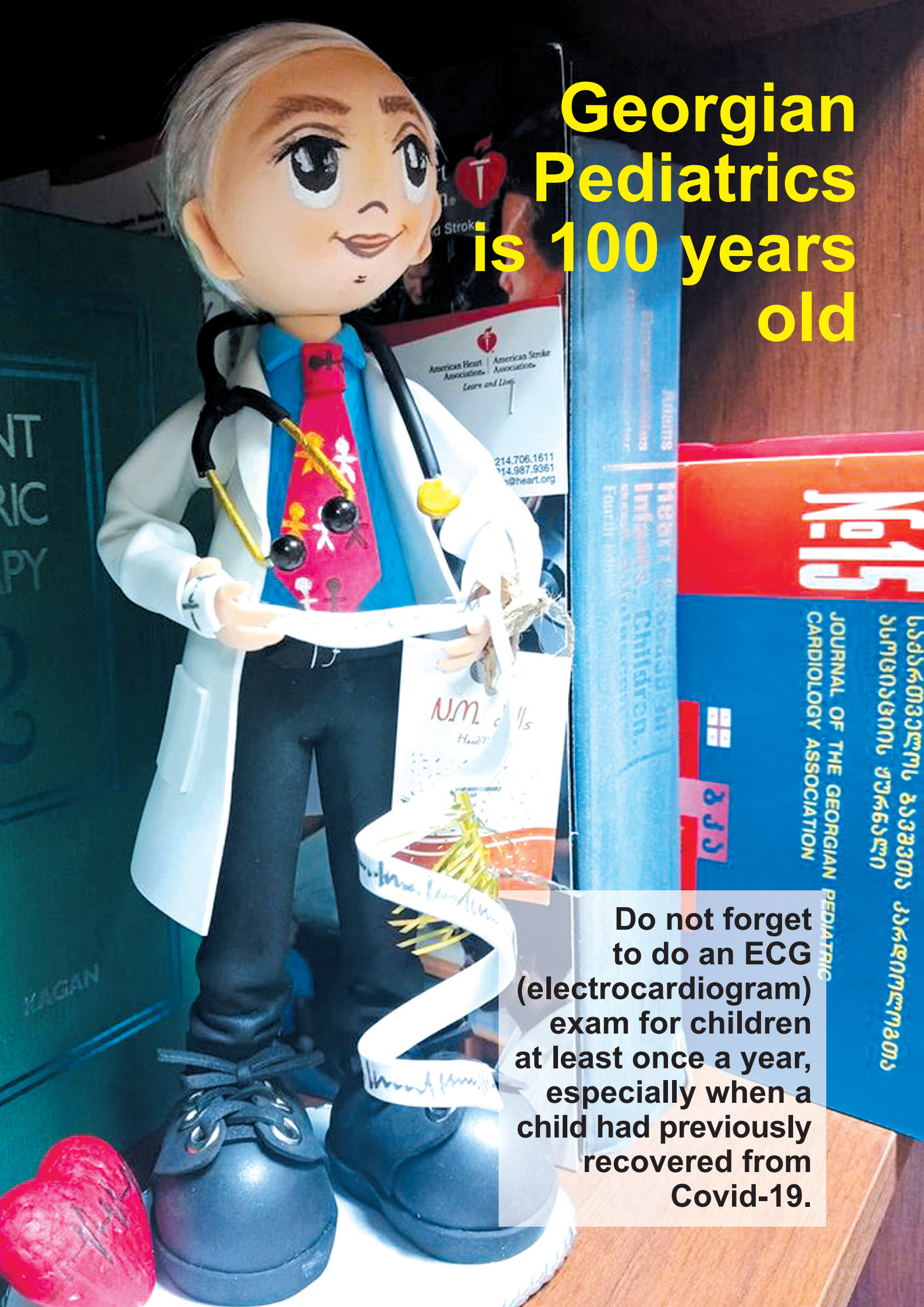
01.06.2021. SPPF XLVI conference

18.12.2021. SPPF XLV conference

In 2007, the GEORGIAN PEDIATRIC CARDIOLOGY association published a magazine „PEDIATRIC CARDIOLOGY". The magazine is still printed.


European Asian African medical summit - discussion of pediatric clinical cases
欧亚非医学高峰论坛—儿科临床病例讨论


欧亚非儿科
会议2019.4
西安


Georgian Pediatrics is 100 years old
Do not forget to do an ECG (electrocardiogram) exam for children at least once a year, especially when a child had previously recovered from Covid-19.
JOURNAL OF THE GEORGIAN PEDIATRIC COOPERATIVE
CARDIOLOGY ASSOCIATION