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QUANTITATIVE CHANGES IN THE IMMUNOGLOBULINS OF YOUNG CHILDREN DURING RESPIRATORY VIRAL INFECTION AND PNEUMONIA

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Block	Italic	Transliteration	Block	Italic	Transliteration
А а	*А а*	A, a	Р р	*Р р*	R, r
Б б	*Б б*	B, b	С с	*С с*	S, s
В в	*В в*	V, v	Т т	*Т т*	T, t
Г г	*Г г*	G, g	У у	*У у*	U, u
Д д	*Д д*	D, d	Ф ф	*Ф ф*	F, f
Е е	*Е е*	Ye, ye; E, e*	Х х	*Х х*	Kh, kh
Ж ж	*Ж ж*	Zh, zh	Ц ц	*Ц ц*	Ts, ts
З з	*З з*	Z, z	Ч ч	*Ч ч*	Ch, ch
И и	*И и*	I, i	Ш ш	*Ш ш*	Sh, sh
Й й	*Й й*	Y, y	Щ щ	*Щ щ*	Shch, shch
К к	*К к*	K, k	Ъ ъ	*Ъ ъ*	"
Л л	*Л л*	L, l	Ы ы	*Ы ы*	Y, y
М м	*М м*	M, m	Ь ь	*Ь ь*	'
Н н	*Н н*	N, n	Э э	*Э э*	E, e
О о	*О о*	O, o	Ю ю	*Ю ю*	Yu, yu
П п	*П п*	P, p	Я я	*Я я*	Ya, ya

*ye initially, after vowels, and after ъ, ь; e elsewhere. When written as ё in Russian, transliterate as yë or ë. The use of diacritical marks is preferred, but such marks may be omitted when expediency dictates.

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GRAPHICS DISCLAIMER

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RUSSIAN AND ENGLISH TRIGONOMETRIC FUNCTIONS

Russian	English
sin	sin
cos	cos
tg	tan
ctg	cot
sec	sec
cosec	csc
sh	sinh
ch	cosh
th	tanh
cth	coth
sch	sech
csch	csch
arc sin	$\sin^{-1}$
arc cos	$\cos^{-1}$
arc tg	$\tan^{-1}$
arc ctg	$\cot^{-1}$
arc sec	$\sec^{-1}$
arc cosec	$\csc^{-1}$
arc sh	$\sinh^{-1}$
arc ch	$\cosh^{-1}$
arc th	$\tanh^{-1}$
arc cth	$\coth^{-1}$
arc sch	sech^{-1}
arc csch	csch^{-1}
rot	curl
lg	log

GREEK ALPHABET

Alpha	A	α	ϰ		Nu	N	ν	
Beta	B	β			Xi	Ξ	ξ	
Gamma	Γ	γ			Omicron	O	ο	
Delta	Δ	δ			Pi	Π	π	
Epsilon	E	ε	∈		Rho	P	ρ	ϱ
Zeta	Z	ζ			Sigma	Σ	σ	ς
Eta	H	η			Tau	T	τ	
Theta	Θ	θ	ϑ		Upsilon	T	υ	
Iota	I	ι			Phi	Φ	φ	ϕ
Kappa	K	κ	ϰ		Chi	X	χ	
Lambda	Λ	λ			Psi	Ψ	ψ	
Mu	M	μ			Omega	Ω	ω	

QUANTITATIVE CHANGES IN THE IMMUNOGLOBULINS OF YOUNG CHILDREN DURING RESPIRATORY VIRAL INFECTION AND PNEUMONIA

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The study of the cellular and humoral factors which are important in the formation of the resistance of a child's body is becoming of increasingly greater interest in pediatrics.

The body's ability to produce an antibody in response to the stimulation caused by antigens lies at the basis of the phenomena of humoral immunity. Antibodies are proteins in biochemical structure and are detected in β- and γ-globulin fractions of blood serum. In recent years the molecular unhomogeneity of antibodies, which served as the basis for isolating the 5 classes of immune globulins (IgG, IgA, IgM, IgE, IgD) which are distinguished by functional, immunologic and biological properties has been comparatively well studied. All of the classes of immunoglobulins

have identical light chains but are distinguished by the structure of the heavy chains which determine the biological activity of the antibodies.

In the process of ontogenesis the formation of the classes of immunoglobulins occurs in a determined sequence. First the synthesis of IgM begins, in the 2nd week - IgA and the formation IgG occurs only after 2 months of extrauterine life, which subsequently determines a large part of the immunoglobulins. This class includes the bulk of the antibodies which appear during infection and vaccination. In the opinion of the majority of researchers, precisely this class of immune globulins is especially important for the body, since it together with the complement carries out many protective phenomena. IgG has biological activity which is expressed in the phenomena of precipitation, the immobilization of bacteria, the neutralization of viruses, the antitoxic properties, and the bonding of the complement (Isliker et al.). But this same class of immunoglobulins conditions anaphylactic type allergic reactions (Coher and Milstein; Gitlin et al.).

About 50% of class G free immune globulin is concentrated in the blood stream and about 5% is catabolized daily. γG antibodies are stable to increases in temperature and pass through the placenta easily.

IgM has special importance for a child's body, appearing during the early periods after the introduction of an antigen and being almost wholly located in blood stream. Its destructive metabolism is 3 times higher than IgG. γM antibodies are more sensitive to increases in temperature and are less specific in comparison to γG. These antibodies do not pass through the placenta. In the process of the mature immunologic response the M-antibodies are replaced by γG antibodies. IgM's include antibodies against typhus O, paratyphoid B, isohemagglutins, and the rheumatoid factor. Thus, like IgG's, IgM's are capable of fixing or activating the complement.

Unlike IgM's class A immune globulins are not capable of bonding the complement, but possess agglutinating properties (Tomasi and Thomas). There are data on the protective role of the antibodies that are of composition IgA during viral infections. Since it is the main immunoglobulin being secreted, IgA is contained in large quantities in the tracheobronchial secretion, the salvia, the intestinal juice, bile, etc. and, apparently, plays a role in the protection from intestinal and respiratory infections. The class A immunoglobulins are catabolized with the same intensity as IgM.

Thus, immunoglobulins are the basis of the protective functions of the body; therefore their deficiency in any combination causes the danger of the increased predisposition to infections.

The information obtained about structure and function of immune globulins served as the basis for their study in the development of the immune process during different diseases. A number of authors showed a change in the content of immunoglobulins of one or several classes with different pathology (Yamadzaki Dziro; Vacek et al., Pearlman; Buckley; Rebecca et al.; Tanaka Mutsuo et al., etc.).

The goal of this work was the study of the quantitative changes in the immunoglobulins of classes A, M and G in young children during respiratory viral infection and pneumonia.

Material and Methods

Immunoglobulins were studied in the blood of children with a phlogistic process in the respiratory tracts during an influenza epidemic and also an outbreak of adenoviral and para-influenzal infection (December 1969-April 1970). Forty children aged from 1 to 3 months inclusively, hospitalized in the Infants Department of Hospital No. 9 imeni F. E. Dzerzhinskiy were under our observation.

On the 1st day of illness six children were hospitalized, on the 2nd day - nine, on the 3rd - eleven; the remaining children were admitted from the 4th to the 10th day from the onset of the illness. All of the children were admitted with the diagnosis of acute respiratory illness, since from the 1st day of illness apathy, restlessness, loss of appetite, a subfebrile temperature and catarrhal phenomena in the form of rhinitis, tussiculation, conjunctivitis, and hyperemia of the pharynx were noted. Taking into account the epidemiological circumstances, the contact of the majority of the children with parents ill with a respiratory infection and also the positive (in 28 children) result of the cytologic immunofluorescent analysis with influenzal and parainfluenzal serum (D. V. Sergeyev), we could draw the conclusion of the viral etiology of the beginning of the illness with great reliability. In the clinical picture we could not isolate the symptoms that would make it possible to narrow down the nature of the viral causative agent, since the general symptoms of intoxication predominated and the local symptoms and cyclicity of the disease were imprecisely expressed.

In 37 patients pneumonia developed during different periods (on the 2-12th day) from the onset of the illness: acinose in 24, predominantly interstitial in three, confluent in six, focal in four. The onset of pneumonia was accompanied by the deterioration in condition, a raised temperature (not in all), the development of toxicosis (in eight patients), the quickening of respiration, and the onset of cyanosis; the cough was intensified, bubbling rales and the rigid respiratory tone were heard in the lungs, more rarely - the reduction of sound during percussion. The diagnosis of pneumonia was verified by X-ray examination. In 12 children the pneumonia took the severe recurrent course. Relapses (their number for the time the child was retained in the department - one, less often - two) were accompanied by a deterioration of condition, the arisal of catarrhal phenomena and phlogistic changes in the lungs. The severe nature of the inflammation was explained by an unfavorable background (congenital developmental

defects, hypotrophy, exudative diathesis, premature birth) and by corresponding diseases (otitis, pyoderma, infection of the urinary tracts). One of the causes for the relapse of a catarrh of the respiratory tracts and pneumonia, apparently, was viral reinfection, which is confirmed by the features of the clinical picture and in a number of cases by the repeated positive result of the immunofluorescent analysis with different sera; this conclusion corresponds to the data of Professor M. Ye. Sukhareva and Professor Ye. S. Ketiladze concerning the value of the crossed viral infection in departments for young children.

The course of the viral infection and pneumonia in 28 children was complicated by an accompanying bacterial process of different localization: by pyoderma, stomatitis, infection of the urinary tracts, suppurative conjunctivitis, abscess, and enteritis. During the inoculation of the contents of the pustule, sputum and feces the growth of pathogenic staphylococcus was found in twelve children. The direct dependence of the degree of toxicosis, the severity of the condition and the duration of the pheumonia during the respiratory infection on the manifestation of the local corresponding bacterial process was noted. The average length of illness was 22 days.

Thus, in the young children (the first 3 months of life) we observed the respiratory viral infection had an effaced course, did not have a pronounced phasal nature, was complicated early by pneumonia and frequently was combined with other diseases of bacterial etiology. The plan for the immunologic studies has considerable interest in studying the nature of the immune response to the viral invasion and the invasion of bacterial nature. But we could only state the clinical picture of the viral infection without complication (before the development of pneumonia) at the beginning of the acute period in twelve children. Basically, the results presented of the study of immunoglobulins characterize the immune response of the young child's body to the complex multi-antigenic, virus-bacterial action during the complicated respiratory-viral infection.

For the quantitative determination of immunoglobulins in the children the method of simple radial immunodiffusion was used according to Mancini Carbonara and Heremans.

For this purpose a 2% solution of agar was prepared by dissolution in a boiling water bath of the corresponding quantity of Difco agar in a Michaelis buffer of pH 8.6 (a 14.8 mℓ 0.1 solution of HCl was added to a 100 mℓ 0.1 m sodium diethyl barbiturate solution). Merthiolate (1 mℓ in the dilution 1:100 in a 100 mℓ agar solution) was used as the substance for preserving the agar. The hot agar solution was poured into 3 test tubes in 9.5 mℓ amounts and cooled to 50° whereupon it was mixed with antiserum (2 mℓ) preheated to the same temperature with regard to one class of immunoglobulins. The mixture was transferred to a heated Petri dish 9.5 cm in diameter. Upon careful shaking the even distribution of agar formed a layer about 1.5 mm thick. After a short period of time at room temperature the agar congealed and openings 2 mm in diameter were pressed into it using a polished injection needle. About 36 of these openings were inserted into each dish.

Using a microsyringe the test sera were introduced into the pressed-out openings in an amount that would ensure the disappearance of the reflex from the surface of the introduced liquid. For determining IgA and IgM whole sera were taken, for determining IgG the sera were diluted by a physiological solution in a 1:10 relationship.

For constructing the calibration curve stabilized standard human serum for the immunologic determination of plasma proteins of the Behring* firm was used, whose immunoglobulin content was γA 130 mg/100 mℓ, γM 55 mg/100 mℓ, γG 740 mg/100 mℓ. The serum

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*Translator's Note. The spelling was not confirmed. The original cyrillic is Беринг; possible variations in spelling are Bering and Boering.

was introduced in three different dilutions in order to obtain three values of the standard by which the curve was then plotted.

The Petri dishes were placed in a humid chamber for 48 hours at room temperature, after which the measurement of the diameters of the annuli of the precipitation was made with an accuracy within 0.1 mm. The evaluation of the results was conducted using a graph; along the x axis the values of the immunoglobulin content in milligrams per 100 ml in the standard dilutions were plotted, and along the y axis - the squares of the radii of the precipitate of the corresponding dilutions of the standard serum. A curve was plotted along the three points obtained. The content of immunoglobulins in the studied sera was calculated from the value of the diameters of the precipitate by the consecutive projection of the point obtained from the y axis of the standard curve, and then for the x axis.

Results

The determination of immunoglobulins was produced repeatedly during the different periods of illness in the majority of patients. In the analysis of the findings the clinical features of the disease (the character of pneumonia, the presence toxicosis and the septic component, the duration of the illness, treatment) were considered besides the period of illness. One hundred and sixteen determinations of the immunoglobulins in the blood serum were made in all.

For comparison in the process of adopting a procedure we studied the sera of the essentially healthy children of different age groups from a children's home. The data we obtained (Table 1) agree with the data of other researchers (Johansson and Berg; Stoop et al.; Buckley et al.). We used one group 1-3 months in age from this group of children as the control for our studies.

Table 1. The content of the individual classes of immunoglobulins (in mg %) in the children of different age groups (M±σ).

Age period	Number of children	A	M	G
Umbilical blood.....	2	0±0.0	2.0±2.4	647.5±10.5
1-10 days.....	5	0±0.0	7.1±3.1	652.0±78.6
10 days-1 month.....	7	1.0±1.7	33.5±30.9	301.4±226.3
1-3 months.....	18	11.9±7.1	43.5±23.9	345.8±180.8
3-6 months.....	11	29.2±14.9	59.8±23.4	501.0±370.0
6-10 months.....	4	53.7±14.8	65.1±19.4	600.0±140.0
10 months-1½ years.....	17	58.2±17.4	58.0±24.3	642±117.0

During the acute period of respiratory-viral infection, before the onset of pneumonia, twelve children were examined who had not been ill earlier. The characteristics of the clinical picture: the condition of the children was not severe, they had subfebrile temperature, restlessness, the disturbance of sleep, the loss of appetite, catarrhal phenomena (rhinitis, conjunctivitis, light cough), and a number of the children had a loose stool. There were not actually any changes in the level of immunoglobulins in the children during this period of illness in comparison with the same in the control (Table 2).

Table 2. The content of the individual classes of immunoglobulins (in mg %) in the children with respiratory-viral infection and pneumonia (M±σ)

Period of study	Number of studies	A	M	G
Control group.....	18	11.9±7.1	43.5±23.9	345.8±180.8
Initial symptoms of the acute period of illness.	12	10.9±13.3	42.7±27.4	342.7±137.0
Acute phase, the addition of pneumonia, flush.....	52	17.3±24.9	80.6±54.2	417.0±198.2
Protracted pneumonia, septic component.....	34	27.0±23.4	99.0±40.8	422.0±143.9
Convalescence period.....	18	30.4±18.5	66.2±17.9	557.8±242.6

A statistically reliable increase in fraction M of immunoglobulins corresponded to the onset of pneumonia, the deterioration in the overall condition, the arisal of symptoms of hypoxemia

and hypoxia, and toxicosis. Separate observations show that an especially rapid and significant increase in fraction M during the acute period of pneumonia occurs in children with the corresponding local septic process (prolonged failure of the umbilicus* to heal, emphalitis, pyoderma), and also in the children in whose anamnesis similar illnesses were noted. It is possible that one should consider a rapid increase in fraction M of these sensitized patients in the period of deterioration of condition (a new antigenic stimulus) as the secondary response reaction.

The dependence of the value of the immunoglobulin fractions on the severity of the children's condition and the duration of the acute period of illness was also revealed. Thus, in four children with neurotoxia a high content of fraction M (69-117 mg %) was noted, while fractions A and G were considerably lowered (A< <10 mg %, G within the limits of 200-300 mg %).

A statistically reliable increase in fraction M of immune globulins is also revealed during the prolonged lethargic course of pneumonia in the children with corresponding pyodermia, infection of the urine excretory tracts, and otitis, i.e. when the expressed component of bacterial inflammation is present. The repeated studies showed a steady increase in this fraction. With the aggravation of pneumonia the level of IgM was raised.

Fractions A and G are also increased with statistical reliability during the prolonged relapse process. Separate observations make it possible to assume that the considerable and prolonged reduction of these fractions with the simultaneously high level of fraction M can have unfavorable prognostic value.

In the convalescence period a statistically reliable increase in immunoglobulin A, the tendency toward a reduction in the

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*Translator's Note. The Russian term is пупочная ранка, possible misspelling for пупочная рана, umbilical wound.

fraction of M immunoglobulins and the further increase in the level of immunoglobulin G was noted.

The level of immunoglobulins and their dynamics during the acute infectious process in premature children (seven of the forty patients) did not differ substantially from that of those carried for the full time.

All the children were given antibiotics, 13 - prednisolone during the acute period of illness (1-2 mg in 1 kg weight in a 24 hour period during two weeks according to a trapezoidal plan). We were not able to note the definite dependence of the variations in the level of immunoglobulins on the introduction of antibiotics and prednisolone. It is possible that therapeutic doses of the preparations do not cause significant immunodepression.

In the analyses carried out on the 2nd-3rd days after the blood transfusion and the introduction of γ-globulin, a tendency was noted in certain children toward the increase of fraction IgG, which was not stable and therefore could not significantly influence the results of comparing the level of immunoglobulins with the periods of illness. Changes in the quantity of immunoglobulins after the plasma transfusion were not detected. Taking into account the high individual range of the variations in the quantity of immunoglobulins for short time intervals, which apparently depends basically on the function of the lymphoid system and the changed metabolism of the sick children, we consider that additional studies are necessary for explaining the action on the level of immunoglobulins of the indicated preparations.

Conclusion

During the early periods (the first four days) of respiratory viral infection without complication changes in the level of immune globulins were not noted in the children 1-3 months old who were not previously ill. During the acute phase of the

complications of the respiratory infection a statistically reliable increase in the fraction of IgM occurs. The prolonged course of the viro-bacterial infection complicated by pneumonia leads to a further increase in the fraction of IgM, and also a statistically reliable increase in immunoglobulins A and G. In the convalescence period the tendency is noted toward the reduction of IgM, the increase of IgG and simultaneously the statistically reliable increase in the level of IgA. An increase in the quantity of immunoglobulins and their dynamics in children during the first 3 months of life with viro-bacterial infection indicate the functional activity of the lymphoid cell systems that form immunity.

Considerable individual variations in the quantity of immunoglobulins are revealed; therefore the results of their determination by the indicated method during pathological conditions (eliminating expressed hypo- or dysgammaglobulinemia) can be accounted for only through repeated studies.

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Summary

The method of simple radial immunodiffusion according to Mancini, Carbonara, Heremans was used to make a quantitative determination of three classes of immunoglobulins (A, M, G) in 40 children of 1—3 months old with acute respiratory diseases complicated and not complicated by pneumonia at different periods of the disease. The increase of the IgM fraction was observed during the acute phase of respiratory infection. In protracted, complicated by pneumonia course of the viro-bacterial infection a rise in immunoglobulins of all the three fractions was noted, while during the period of reconvalescence there was seen a tendency towards a drop of IgM, further increase of IgG and IgA.