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RRI Children: Preventive Vaccination Issues

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ABSTRACT

Based on the years of experience of immunization against infectious diseases, it is stated that preventive vaccinations should only be given to healthy children. Children with altered reactivity should be vaccinated only if certain conditions are met. However, the vaccination schedule can not be stable. The effectiveness of immunoprophylaxis largely depends on the correct age for primary immunization and optimal intervals between vaccinations taking into account their state of health to exclude disturbances in the course of the vaccination process. The issue of contraindications to the provision of preventive vaccinations is urgent and complex in the problem of preventing infectious diseases. There is a category of children for whom the full immunization schedule provided for healthy children is an unbearable burden. Contraindications to the conduct of a vaccine is determined not only on the basis of the anamnesis, but also on the clinical examination. The ability to react or not to react to any particular antigen, as well as the height of the immune response, are genetically encoded. One of the most important factors that significantly affect the development of children is their morbidity, especially during the first three years of life. Active immunization depends on this factor. About 10% of children do not get vaccinated due to temporary medical contraindications. Although there are only two reasons for withdrawing from vaccinations: hypogammaglobulinemia and a high probability of a severe outcome as a result of vaccination. Difficulties in solving a problem of clinical safety force pediatricians to exclude from immunization most children with the problems in the anamnesis. It prevents the formation of collective immunity among children and creates the danger of a more frequent occurrence of a severe course of infectious diseases (measles, whooping cough) in children with the problems in the anamnesis.

Keywords: Vaccination specific immunological prophylaxis, Disimmunoglobulinemia, RRI children, immunoglobulins, immune deficiency, preventive vaccinations.

INTRODUCTION

Based on the many-year experience of contagious disease immunological prophylaxis, it is found that only healthy children should be subject to preventive vaccination. Children with changed reactivity should be vaccinated only when specific requirements are met. Moreover, vaccination calendar cannot be stable[1]. The effectiveness of immunological prophylaxis largely depends on well-chosen age for preimmunization and optimum time between vaccinations. The issue of contra-indications of preventive vaccination is relevant and difficult. There's a category of children for whom the complete schedule of immunization provided for healthy children is intolerable[2]. Contra-indication

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of some or other vaccination is defined not only based on medical case history data but also on the clinical research. The ability to respond or ignore any particular antigen, as well as the height of immune response, are genetically coded[3]. One of the most important factors, which have a significant impact on the children development, is their morbidity, especially during first three years of their life. Implementing extensive immunization depends on this factor. About 10% of children aren't timely vaccinated because of temporary medical contra-indications[4].

A group of sick children sent from the suburban area and city children's hospitals with different pathologies was examined in the city centre of infantile infection immunological prophylaxis of Nizhni Tagil of the Sverdlovsk Region to solve the problem of carrying out preventive vaccination and making the individual schedule of specific immunological prophylaxis[5]. Among them, a group of children who suffered the laboratory confirmed condition of the depression of the secretion of immunoglobulins of the humoral component of immunity conditionally defined as immunoglobulins syndrome was distinguished. The antiinfective profile of sick children was studied to determine what an effect preventive vaccinations have on the immune system of the children of early age with disimmunoglobulinemia syndrome, to elaborate recommendations on implementing preventive vaccinations and possibilities of using them in case of "absolute" contra-indications involving assessing the level of specific immunity tension against some vaccine-preventable infections (diphtheria, tetanus, measles)[6].

MATERIALS AND METHODS

1127 children aged from 8 months to 5 years with a clinical syndrome of antiinfective protection violation in the form of recurrent diseases of viral and bacterial etiology, in whom the decrease in one or several isotypes of immunoglobulins in the serum had been found, were observed. Among them, a group with disimmunoglobulinemia syndrome of 280 patients was distinguished. This group was chosen for a deeper and more detailed examination.

A special method developed by Altukhov Y.P. and Kurbatova O.L. based on the children distribution by weight and body length to give proper characteristics of the latter group of children was used[7] . Each child, depending on his indicators at birth, was subsequently assigned to one of 9 groups, i.e. with average, low and high characteristic values, with low and high values of body weight at an average length, with low and high values of body length at an average mass, as well as with a low body length at a large mass and with a low mass at a large body length. The average conditional " was determined. The method enabled the analysis of compared groups by the number of children included in different areas, the analysis of the structure of their morbidity and providing corresponding characteristics[8].

The "disimmunoglobulinemia syndrome" condition was identified if the immunoassay of children aged from 8 months to 5 years revealed a recurrent decrease in one or several isotypes of immunoglobulins in the serum: Ig G less than 5 g/l, Ig less than 0,2 g/l, Ig " less than 0,4 g/l coupled with a low or high concentration of cortisol (less than 100 nmol/l or more than 500 nmol/l). We have already established the close correlation relationship between the low levels of immunoglobulins and serum cortisol in the previous researches; which indicates the role of the stress-induced depression of the level of secretion of immunoglobulins of immunity humoral component[7].

To obtain consistent results we determined generalized dispersion B^2, generalized variation coefficient ($!_v$ and $!_v'$), generalized bonding strength @, generalized factor impact r_w and factor impact isotropy indicator r_I, population couples' resemblance indexes r[9].

Registration documents "registration cards" and "child's disease diaries" were specially developed. They feature data from the case history of both mother and father, delivery data, gestation course, the features of the neonatal period, morbidity, infant feeding pattern, examination data, immunization history[10]. The following indicators were analyzed: sex ratio, mass and height indicators of children at birth, the level of , " and G serum immunoglobulins content, sub-populations of

T-lymphocytes, ACTH and pituitary-hypothalamic area, determining sensitivity in vitro to immune response modifiers, the activity of transferases, the condition of antidiphtheritic antitoxic immunity, titers of anti-measles antibodies and antibodies to the poliomyelitis virus of 3 types with due account for case history and morbidity. The control group consisted of 426 relatively healthy children selected by the method of defining the "adaptive norm" of this city population[11].

All patients were examined at different stages of inflammatory process activity: acute stage, the period of early convalescence, the stage of late convalescence, the period of non-stable remission, the period of stable remission of the main pathological process. None of the patients experienced the persistent low-intense process[12]. The absence of the clinical manifestation of diseases for more than one year, as well as the complex of laboratory, including immunologic parameters indicating the absence of pathological process activity, were criteria determining the remission persistence[13].

The analysis of antidiphtheritic immunity based on the data of antidiphtheritic antitoxic immunity in passive hemagglutination test (PHT) according to Persistent Erythrocytic Diagnostic Preparations Usage Manual approved by the USSR Ministry of Healthcare 23.06.81 was carried out[14]. Hungarian-made microtitrator *Takachi* was used for PHT. Persistent erythrocytic diphtherial diagnostic preparations produced by Mechnikov Moscow Research Institute of Vaccinations and Sera were used as antigens. To determine the sensitivity of diagnostic preparations the test was carried out in each set of tests with standard antitoxic antidiphtheric serum containing 10ME in 1 ml produced by State Control Institute Medical Biological Preparations. The last dilutions of standard sera with positive results were considered the sensitivity index, which was used to translate hemagglutination units into antitoxic ones. The tests of the serum in PHT were carried out by macromethod in 10 dilutions, titers 1:160 were considered reliable, 1:20 – 1:80 – conditionally protective, 1:10 and antibody-negative – non-protective[15-20].

Anti-measles antibodies' titers in hemagglutination-inhibition test (HAIT) with sera treatment with kaolin and erythrocytes to get rid of spontaneous haemagglutinins were detected; to obtain more active haemagglutinin the culture was treated according to the Nornby method. The titer of hemagglutinating antigen was identified with a 0,5% monkey erythrocyte suspension at room temperature. Detecting the fourfold and greater rising of antibody titer in the second serum had a diagnostic significance[21].

The content of ACTH in the serum (cortisol) was determined by immunoenzyme method using *Biorad* assay kits, USA. The following values were considered standard: cortisol in 8-10 hours – 185-500 nmol/l or 50-230 ng/ml.

Each fifth child was randomly taken from the control group of healthy children for antiinfective profile examination. Each hundredth child was randomly taken from the group of sick children whose immune deficiency state wasn't confirmed.

RESULTS AND DISCUSSION

Children from community-based policlinics (80% of children) or hospitals (20%) with the following clinical implications were requested to see pediatrician-immunologist: recurrent frequent ARVI (40%), recurrent otopyoses (12%), thymomegaly (24%), recurrent bronchitis (8%), recurrent furunculosis (8%), digestive dysbacteriosis (4%), lymphohypoplastic diathesis (4%). Thymomegaly was identified by X-ray when examining with obstructive bronchitis and persistent low-grade fever diagnosis. Thus, the signs of inadequate infectious morbidity were the actual cause of primary immunoassay in all observed children. It should be noted that infective disease overfrequency was registered in children who had satisfactory social and living conditions and stayed at home. A part of observed children was vaccinated according to the place of their residence before the examination and treatment by pediatrician-immunologist. Vaccinations aggravated main pathological processes against the background of the organism weakened by infections causing their need to consult pediatrician-immunologist[22].

The particularities of the immunization history of observed children are as follows: 28% of children are vaccinated according to their age without complications, 8% experienced minor vaccine-induced responses (temperature rise to subfebrile values, allergic rashes), 64% of children aren't vaccinated: among them 28% because of frequent infective diseases, 36% because of other related conditions (neurological deviations, digestive dysbacteriosis, thymomegaly).

All observed children passed a complex of clinical-laboratory tests, the methods of functional diagnostics, which enable describing the state of different body functional systems (central nervous system, peripheral nervous system, endocrine, immune, skin, digestive, respiratory ones, etc.) and defining patients' clinical diagnosis, were used. An emphasis was put on abnormal development and dysembryogenesis stigmas. Anamnestic data paid a lot of attention to perinatal period flow, the parents' health status before the child conceiving, during pregnancy, delivery course, the neonatal period. The features of developing clinical implications of pathological processes were defined: disease onset, frequency and flow pattern, the appearance of clinical symptoms of disease, intensity and their pathomorphism[23].

The diagnosis – disimmunoglobulinemia syndrome – was made if during immunoassay of children from 6 months to 5 years a decrease of one or several isotypes of immunoglobulins was recurrently found: Ig G less than 5 g/l, Ig less than 0,2 g/l, Ig " less than 0,4 g/l. Laboratory characteristics of children aged from one year to three years with disimmunoglobulinemia syndrome are given in Table 1.

The predominant deficit of Ig was observed in 45 children, Ig G – in 180, combined decrease in Ig and Ig G – in 55 children; there were no children

Table 1: Laboratory characteristics of children aged from one year to three years with disimmunoglobulinemia syndrome

Index	Units of measurement	Correlation diagram area			
		M0	M+	M-	Mpd
Ig A	g/l	0,40	0,30*	1,6	0,66
Ig M	g/l	0,95	0,75	0,41	1,26
Ig G	g/l	4,0	4,0	3,6*	3,58*
CD 3	%	48,0	56,0	68,0	60,0
CD 4	%	15,0	18,0	48,0	29,0
CD 8	%	36,0	26,0	12,0	27,5
0	%	34,0	30,0	32,0	31,5
Circulating immune complexes	UNITS	60	34	70	43,8
Cortisol	nmol/l	175,0	990,0	145,0	963,5
Lactogenic hormone	<"/l	253,0	230,4	443,5	498,5
Testosterone	nmol/l	0,9	0,0*	0,1*	0,6
Alanine aminotransferase	nmol/l	1,8	0,25	0,8	0,96
AAT	nmol/l	4,2	2,2	2,2	0,9
Crude protein	g/l	6,8	7,2	7,0	6,98
Thymol test	UNITS	2,4	1,2	2,2	2,38
Exercise tolerance test					
with thymalin	Index	1,0	1,0	1,0	1,0
with tymogen	Index	1,0	1,0	1,0	1,0
with levamisole	Index	1,0	1,0	1,0	1,0
Total children	280	60	49	39	132

Note: * – data are statistically valid

Table 2: The rate of antibody-negative children vaccinated against vaccination-preventable infections in the groups of children with disimmunoglobulinemia syndrome (per 100 children of this group)

Vaccination	Children suffering disimmunoglobulinemia syndrome with a low level of Ig and cortisol				with a low level of Ig and a high level of cortisol				Control group of healthy children	
	vaccinated before treatment		vaccinated after treatment		vaccinated before treatment		vaccinated after treatment			
	n	p	n	p	n	p	n	p	n	p
Diphtheria vaccination 1st	23	62,16*	29	46,77	40	63,49*	57	48,31	37	43,53
Diphtheria vaccination 2nd	7	18,92*	6	9,68	12	19,05*	13	11,02	9	10,59
Diphtheria revaccination	3	8,12*	0	0,0	5	7,94*	0	0,0	0	0,0
Tetanus vaccination 1st	14	37,84*	13	20,97	23	36,51*	23	19,49	13	15,29
Tetanus vaccination 2nd	3	8,12	5	8,06	5	7,94	9	7,63	6	7,06
Tetanus revaccination	2	5,41*	0	0,0	4	6,35*	0	0,0	0	0,0
Measles vaccination	14	37,84*	13	20,97*	22	34,92*	25	21,19*	9	10,59
Total children	37		62		63		118		85	

Note: n – actual frequency
p – relative frequency
* – the difference of data with the control group of healthy children is statistically valid

with a low content of Ig ". The average age of children when admitted for observation was 1,6±1,2 years. The hypogammaglobulimenia condition was first registered at the age of to 1 year in 22 children, from 1 year to 2 years – in 123 children, from 2 to 3 years – in 67, from 3 to 4 – in 56, from 4 to 5 years – in 12.

During the first immunoassay the average level of Ig G in 235 children with Ig G deficit (isolated or combined with Ig deficit) made 4,1±0,78 g/l, but only 11 of them had the Ig G level less than 3 g/l. The average level of Ig in 101 children with Ig deficit (isolated or combined with Ig G deficit) was 0,15±0,03 g/l and varied from 0,09 g/l to 0,19 g/l.

For a comparative study of antiinfective profile with assessing the tension level of specific immunity against some vaccine-preventable diseases (diphtheria, tetanus, measles) in the groups of children with the depression of the secretion of immunoglobulins of the humoral component of immunity the sick children with disimmunoglobulinemia syndrome were divided into two large groups:

a) With a low content of immunoglobulins and cortisol in the serum;
b) With a low level of immunoglobulins and a high content of cortisol.

Each of examined groups was further divided into two groups:

a) Children vaccinated according to the place of their residence before the admission under the care of pediatrician-immunologist;
b) Children not vaccinated for some reason and requested to consult pediatrician-immunologist to address the preventive vaccination issue, as a result, these children were vaccinated after examination and treatment. The rate of antibody-negative children when vaccinated against vaccine-preventable diseases in the groups of children with disimmunoglobulinemia followed up by pediatrician-immunologist is given in Table 2.

It turned out that among the rate of antibody-negative children vaccinated with antitoxins and live vaccines before treatment was notably higher in all studied groups as compared to the control group.

Following the first diphtheria vaccination, the rate of antibody-negative children vaccinated before treatment made up 62-63%, and 43% in the control group. Following the second diphtheria vaccination, the rate of antibody-negative children in studied groups made up 18-19%, in the control group of healthy children – 10%. After diphtheria revaccination, the rate of antibody-negative children in studied groups made up 6,7%, and there were no diphtheria antibody-negative children in the control group.

Following the first tetanus vaccination, the rate of antibody-negative children in the groups vaccinated before treatment made up 36-37%, in the control group of healthy children – 15%. Following the second tetanus vaccination, the rate of antibody-negative children made up 7-8% – the same as in the control group. After tetanus revaccination, there were 5% of antibody-negative children in studied groups, and there were no such children in the control group.

Following the vaccination of children with a vaccine against measles, the rate of antibody-negative children in the groups vaccinated before treatment made up 34-36%, in the control group of healthy children – only 10.4%.

233 children were vaccinated after examination and treatment, among them 180 of children with disimmunoglobulinemia syndrome (62 children with a low content of immunoglobulins and cortisol in the serum and 118 children with a low content of immunoglobulins and a high level of cortisol).

It turned out that there were no more antibody-negative children in these groups of children after vaccination with antitoxins than in the control group of healthy children. Thus, after the first diphtheria vaccination, their rate made up 47-48%, after the second diphtheria vaccination – 9-10%, after diphtheria revaccination – 0,0%; after the first tetanus vaccination – 19-20%, after the second tetanus vaccination – 7-8%, after tetanus revaccination – 0,0%.

After live vaccination against measles in the children groups vaccinated after treatment, the rate of antibody-negative patients made up 20% among

patients with disimmunoglobulinemia syndrome, 14% – among children, whose disimmunoglobulinemia diagnosis wasn't confirmed, in the control group of healthy children – 10%.

Thus, the effectiveness of specific immunization against vaccine-preventable infections (diphtheria, tetanus, measles) in RRI children with antiinfective protection violation and the laboratory confirmed condition of disimmunoglobulinemia coupled with a high or low content of adaptive ACTH in the serum substantially increases after their treatment and normalization of clinical and laboratory indicators [24-25].

CONCLUSIONS

The findings allow us to claim that disimmunoglobulinemia syndrome in children with laboratory-confirmed hypogammaglobulimenia and dyshormonosis is not a contra-indication to preventive immunization after patient's pre-treatment. The level of specific immunity tension in children who were adequately treated in line with their pathological process was no different from those in healthy children after laboratory indicators' stabilization. RRI children with laboratory-confirmed disimmunoglobulinemia syndrome before planned immunization are, therefore, subject to pharmaceutical treatment with the provisional arrangement of comfortable nutrition and care conditions.

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