Mild form of iron deficiency anemia and a latent iron deficiency as a border – line state in infants aged under 2 years

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Abstract. The mentioned forms of iron deficiency in infants aged 6 mos - 2 yrs were found to be wide – spread, almost blurred clinically, and of high spontaneous reversity. Therefore, failing to affect the children's growth, physical development and the morbidity rate these disorders could be considered as a border–line stete.

1 Introduction

Iron deficiency anemia (IDA) is an unusually widespread condition, affecting 20% of the world's population. Therefore, research on the epidemiology of IDA and its effect on the body is very important [1-5]. Numerous publications rather unambiguously emphasize the adverse effects of anemia on the physical and mental development of the child, the functional and morphological state of the gastrointestinal tract and immunity indicators, and most importantly, the connection between the increased susceptibility of young children to infection and the frequency of IDA. If these disorders are indeed induced by IDA, then they should be found in at least 60% of young children, since iron deficiency (ID) is manifested not only by anemia, but also by tissue, i.e., latent, iron deficiency (LDI). It is generally accepted that the clinical and biochemical basis of IDA and LDH is the same, although the degree of hyposiderosis is different [10-21].

The role of iron deficiency states in the genesis of these disorders artificially increases due to the fact that the development of ID itself, and even more so IDA, is considered in isolation from physiological prerequisites, as well as some social factors (unfavorable or incomplete families, poor living conditions and medical supervision). As a result, deliberately false ideas are formed about the possibility of solving some general pediatric problems (improving the health of young children, reducing the incidence of respiratory infections, etc.) with the help of Ferro therapy and especially Ferro prophylaxis [22-34].

Iron deficiency anemia in children is a type of deficiency anemia, which is based on the absolute or relative deficiency of iron in the body. The prevalence of iron deficiency anemia among children of the first 3 years of life is 40%; among teenagers - 30%; among women of reproductive age - 44%. Without exaggeration, we can state that iron deficiency

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anemia is the most common form that specialists in the field of pediatrics, obstetrics and gynecology, therapy, and hematology have to deal with. According to experts from the World Health Organization, iron deficiency ranks first among the 38 most common human diseases [5, 16, 17, 18, 30]. It has been established that with a frequency of iron deficiency anemia of 20% in the population, LAD is present in 50% of the population [6, 20, 33]. Children, especially the first 2 years of life, adolescent girls, women of reproductive age are the groups at the highest risk for developing iron deficiency due to their physiological characteristics and high need for this element [7–13]. On average in the world, up to 50% of preschool children, up to 50% of pregnant women and 30% of non-pregnant women of childbearing age have anemia [6, 11, 12].

During fetal development, iron enters the baby's body from the mother through the placenta. The most enhanced transplacental transport of iron occurs in the period from 28 to 32 weeks of pregnancy. By the time of birth, the body of a full-term baby contains 300-400 mg of iron, a premature baby - only 100-200 mg. In a newborn, neonatal iron is consumed for the synthesis of Hb, enzymes, myoglobin, regeneration of the skin and mucous membranes, compensation for physiological losses with sweat, urine, feces, etc. The rapid growth and development of young children cause an increased need for iron in the body. Meanwhile, the increased consumption of iron from the depot leads to a rapid depletion of its reserves: in full-term children by the 5–6th month of life, in premature infants - by the 3rd month [14, 23].

For normal development, the daily diet of a newborn should contain 1,5 mg of iron, and the diet of a child 1-3 years old should contain at least 10 mg. If the loss and expenditure of iron prevail over its intake and absorption, the child develops iron deficiency anemia. Iron deficiency and iron deficiency anemia in children contribute to hypoxia of organs and tissues, reduced immunity, an increase in infectious morbidity, and impaired neuropsychic development of the child [35, 36].

2 Materials and research methods

This article presents the results of many years of research on the epidemiology of IDA and LVAD, their age-related evolution and impact on the development and incidence of children. In order to study their prevalence, we examined 2566 children aged from 1 month to 16 years, selected by non-repeated random selection.

As is known, with the help of this method, representative data can be obtained to estimate the prevalence of the disease in the entire population. So, In our work, the marginal error of a random sample was 2% with an allowable 5%. Representativeness was preserved in determining the sample size not only in general, but also in individual age groups.

According to the WHO recommendations, the criteria for LDJ were considered to be the level of serum iron (SF) below 12 mmol/l, the total iron-binding capacity of serum (TIBC) more than 69 mmol/l, the transferrin saturation coefficient (CNT) less than 17% with a hemoglobin content of at least 110 g/l l in children under 6 years of age and 120 g / l in children over 6 years of age. If the conducted indicators of serum iron metabolism were combined with lower hemoglobin values, IDA was diagnosed [2].

3 Results of the study and their discussion

The maximum frequency of IDA was observed in children of the first 2 years of life (24,7%) with a peak in the 2nd half of the year (39,5%). In children older than 3 years, the frequency of IDA sharply and steadily decreased; 8.2% - in children 3-6 years old, 6% - 7-

11 years old, 5% - 12-13 years old and 3-4% - 14-16 years old. Similar rates of IDA frequency and its decrease with age have been established in children in Europe and the USA [17, 22, 23, 25]. However, most domestic authors [3, 7, 13, 14, 24, 25], noting a decrease in the frequency of IDA with age, cite incomparably higher rates of its prevalence in children in various regions of Russia (54-77%). The reasons for this discrepancy, as we pointed out in previous publications, lie in the insufficient scale of the ongoing studies (relatively small contingents of children and low representativeness of the results), the inadequacy of the set of methods included in the screening program, and the use of non-standardized (mainly calorimetric) methods for determining the level of hemoglobin. The latter circumstance is also associated with the high frequency of moderate forms of anemia (14,7-16,5%), given in the domestic literature [3, 13, 14, 26, 27]. According to foreign authors [22, 28], hemoglibin levels of 90 g/l and below are detected only in 1,3–2% of children in the general population. According to our data, in unorganized and organized children under the age of 2 years, the severe form of IDA does not occur at all, and the moderate form (hemoglobin level 70–90 g/l) is observed in 0,8–1,4%. Therefore, the increased infectious morbidity in IDA can be associated (if such a relationship exists) only with a mild form of anemia.

The frequency of LVH in infants was 39,7%, 3-6 years old 22,4%, 7-11 years old - 20% and 12-14 years old 17,5% [2, 8, 29]. By the way, our data on the decrease in the frequency of LDH with age do not coincide with the latest studies by A.V. Papayan [7], who revealed sideropenia in 78% of schoolchildren with a hemoglobin level of 126-130 g/l. These discrepancies are fundamental, since the clinic and pathogenesis of iron deficiency states are associated with tissue ID and, to a lesser extent, with anemia [4, 11, 21, 31, 32].

Thus, in total, ID is detected at the age of up to 3 years in 64,4% of children, 3-6 years in 30,6%, 7-11 years in 26%, 12-13 years in 22,3% and 14-16 years at 19,4%. Meanwhile, in children. 6-18 months the development of ID, detected in 73,3% of cases, is almost inevitable, and the probability of its transformation into anemia is very high. The instability of iron homeostasis and the pattern of development of its tissue deficiency at this age are predetermined by a number of reasons, the main of which are a decrease in antenatal iron reserves from 70-75 to 35-40 mg/kg per year, an increase in the child's body weight by 3-4 times and the lack of necessary amounts iron (no more than 5 mg with a need of 8-10 mg / day) in a dairy-vegetarian diet, its worst absorption due to the transient immaturity of enterocyte enzyme systems, selectively adapted to iron absorption mainly from breast milk. As a result, children of the first 1.5 years of life are not able to significantly increase the absorption of alimentary iron, even with deep hyposiderosis.

A spontaneous decrease in the frequency and severity of ID also indicates its conditional physiology (borderliness) for children aged 6-18 months. Thus, we observed a spontaneous increase in hemoglobin level with age in IDA (from 93,3±1,6 to 103,2±2,3 g/l) and in children of the control group (from 116,2±1,4 to 131, 2±0,6 g/l).

The concept of the almost complete inevitability of the development of ID, at least in the 2nd - 3rd half of life, is also supported by the results of studying the exchange of SF and desferal siderouria. For example, it was found that at an early age, the indicators of TIBC, taking into account ±1o, go far beyond the diagnostic limits, not only in IDA and LVH (66,4±14,8 and 60,0±12,5 mmol/l, respectively), but also in children of the control group (63,3±10,7 mmol/l). With age, the indicators of TIBC decrease in LVH and in children of the control group, which indicates a decrease in the intensity of iron metabolism. By the way, in the diagnosis of ID, we recently prefer to focus primarily on the level of TIBC (more than 75 mmol/l in children under 2 years of age and more than 70 mmol/l in children over 2 years of age), which, according to the principle of feedback (compensatory activation), increases with any genesis of hyposiderosis and adequately reflects the developing stress in iron metabolism. According to a number of authors [18, 20], the

indicators of TIBC correlate with the level of serum ferritin and approach it in terms of their information content. N.I. Stuklov provides a retrospective meta-analysis of 30 studies on the use of Totem®, including 1077 patients, and gives a high assessment of its effectiveness and good tolerability [7, 8].

Additional evidence of the intensity of iron metabolism, in particular, its low tissue reserves in children aged 3-4 years, are the indicators of daily excretion of iron in the urine after the administration of desferal. It was in this age group that its level was the lowest (0,41±0,03 mg/day). By the age of 12-14, the indicators of desferal siderouria almost doubled (0,73±0,7 mg/day), but did not reach its level in adults (1,03±0,04 mg/day) [2].

Thus, the totality of all the above indicates that hyposiderosis in children of the first 2 years of life is a physiological state to a certain extent, reflecting the age-related instability of iron homeostasis and the difficulty of its adaptation to changed growth rates in conditions of unbalanced nutrition. In this sense, it is legitimate to compare LDH with such transient states as physiological hyperbilirubinemia, hypocoagulation shifts, hypoimmunoglobulinemia, and transient inadequacy of the immune response in the first months of life. As you know, these conditions, being compensatory-adaptive, do not manifest as a disease, undergo spontaneous regression and are not subject to treatment. In our opinion, the vast majority of children with LDH also do not need treatment.

Why is LDJ, which we refer to the physiological state of the 1st-2nd year of life, so often aggravates and transforms into IDA? According to our research, the leading causes of this evolution are malnutrition (in 86,5% of children) and accelerated growth rates (in 13,5%), as well as a combination of both factors (in 22,3%) or one of them with nasal and (or) uterine bleeding (12%).

We detected iron deficiency states 1.5 times more often in premature babies and twins only during their examination at the 1-2nd year of life. In children older than 2 years old, born prematurely and from multiple pregnancies, LVH and IDA were registered no more often (in 22,8 and 8,6%) than in the general population [8. 26]. These data do not support the widely held view that insufficient antenatal iron storage, which is common in preterm infants, increases the likelihood of developing ID in older children and adults [3, 6]. We were unable to note an increase in the frequency of LDH and its transition to IDA in children born from repeated pregnancies accompanied by toxicosis and (or) hyposiderosis. So, in mothers of three groups (IDA, LDJ and healthy), we equally often observed children with both forms of hyposiderosis and normal hemoglobin, TIBC and CNT.

Unlike other authors [5, 15, 16], we did not observe a decrease in the frequency of ID in children whose mothers received ferropreparations during pregnancy for therapeutic or prophylactic purposes. Thus, among children born from 223 women with (IDA and LJD), 153 of whom were prescribed Ferroplex or Ferrum-lek during pregnancy, and 70 did not take ferropreparations, a mild form of anemia developed in 17% of cases and latent sideropenia - in 31% (in the control 13 and 31%, respectively).

Thus, the really significant reasons for the development of ID in children of the first 2 years of life are poor nutrition and the rapid growth rates characteristic of this age. The first reason is the main, controlled and managed. No less important is the fact that both of these causes, as the child grows (after 3-5 years), lose their dominant role in the etiology of ID. At preschool and school age, latent blood loss and impaired iron absorption begin to predominate among the causes of LDH and especially IDA, which in themselves are not very characteristic of children. Moreover, intestinal absorption of iron at this age is easily activated under the influence of various factors (hypoxia, etc.), even in children on a ferrodeficient diet. Obviously, the main purpose of enterocyte apoferritin is not to activate, but to inhibit the absorption of iron (within 1 mg / day, i.e. 8-15% of the content in the diet), since its excess intake into the body is incomparably more dangerous than hyposiderosis.

According to our data, overt clinical symptoms of sideropenic genesis are an extremely rare occurrence in mild IDA of LV in children, especially in the first 2 years of life. In essence, of the reliable sideropenic symptoms at this age, only taste perversion is observed (smell is almost possible to assess), noted in 14% of children with IDA and 10% with LDH.

"Epithelial" symptoms in the form of pallor and dryness of the skin, hair and nail trophic disorders, angular stomatitis and smoothness of the papillae of the tongue were observed in 12-17 children, mostly older than 4-5 years. Perversion of taste and smell at this age was detected extremely rarely (in 6 and 3,6% of children). Almost all symptoms were found in IDA and LDH equally often, probably due to the ease of anemia (hemoglobin level of at least 90 g/l). It is important to emphasize that many clinical deviations, traditionally associated deviations traditionally associated with ID (taste perversion, skin pallor, dyspeptic and asthenovegetative disorders, weight loss, dental caries, etc.), were recorded with the lowest frequency in children with normal hemoglobin and SF exchange. In particular, we did not find in children with both forms of ID the delay in physical development, which many authors write about [3, 27]. 75% of children with IDA and LDH had predominantly average physical development (in the control 76,4%) and normal body weight (its deviations were found in 13,5% of children, in the control - in 10,8%).

We paid much attention to the study of immunity. The latter was examined in every 3rd child with an as yet unknown level of hemoglobin. All children did not have severe background pathology and during the previous month did not suffer from infectious diseases and were not subjected to immunization. Our studies did not reveal any immunological abnormalities, which, according to a number of authors [7, 19], are characteristic of IDA. In particular, the phagocytic activity of neutrophils, the level of intraleukocyte iron-containing enzymes, and the hemolytic activity of complement turned out to be unchanged [8]. The relative and absolute number of the main subpopulations of lymphocytes, as well as the functional activity of T-lymphocytes, assessed by RBTL on PHA, did not differ in children with IDA and healthy children. No significant differences were found in the concentrations of IgM and Igg. A slight decrease in the content of IgA in children with anemia at the age of 1,5 years was not accompanied by any clinical manifestations and was leveled by 2 years. The titers of staphylococcal antitoxin, iso- and heterohemagglutinins, reflecting the state of background antitoxic and antibacterial immunity, did not differ in children of the compared groups [9, 10, 15].

We paid special attention to the immune response, according to which it is possible to integrally evaluate the final result of various immune effector systems. At the same time, no differences were found in the frequency and level of response seroconversion to respiratory viral and intestinal infusions in children with mild IDA and healthy children. The indicators of seroconversion in children of the compared groups were the same and when they were immunized with staphylococcal toxoid [10]. These data allow us to recommend that children with mild anemia be vaccinated on a calendar basis.

Having found no abnormalities in immunity in children with mild IDA, we considered it necessary to test the established concept of their increased incidence of infections. We did not find any differences in the frequency of pneumonia, viral and intestinal infections in children with IDA, LDH and healthy children. This position is proved by our prospective observations in the form of weekly examinations of 103 children for 9-12 months and analyzes of the developmental histories of 213 children. The concept of increased susceptibility of children with IDA to infection, on the contrary, is usually justified retrospectively, on the basis of anamnesis data, without taking into account the sequence of their occurrence. Meanwhile, repeated infections in young children often develop not against the background of IDA, but precede its appearance. Thus, according to our data, the incidence of the entire group of patients with pneumonia and 47% of patients with intestinal

infections, as well as 75% of frequently ill children, is formed due to diseases transferred before the age of 6 months, i.e. before the development of anemia. Therefore, it can be assumed that the development of IDA itself is to some extent associated with recurrent infections, under the influence of which the intensity of iron metabolism increases (its redistribution and less intake with food due to a decrease in appetite and absorption in the intestine). Based on this, it is inappropriate to study the metabolism of the SF and prescribe ferropreparations at the height of the infection and in its early reparative period.

The absence of a protective effect in 84 patients from the administration of ferrum-lek in a course dose of 200-300 mg also does not agree with the idea of an increased susceptibility of children with IDA to infection. Thus, among treated and untreated children, frequently ill children with repeated acute respiratory viral infections (up to 4 times or more) and pneumonia were equally common [10]. Resistance to ARVI did not increase in patients with bronchial asthma either, although iron is absorbed and utilized more fully in them even with an unbalanced diet, and an elevated hemoglobin level (162,3±8,3 g/l) with CNT 26,3±4,7% rule out hyposiderosis. Therefore, the statement of a number of authors [3, 6, 7, 24] that using the methods of ferrotherapy and ferroprophylaxis can reduce the incidence of viral infections in young children seems untenable.

In our opinion, GI itself and the background pathology that often accompanies it (rickets, malnutrition), as well as repeated acute respiratory viral infections, are a consequence of the low socio-cultural level of parents and poor medical care. Therefore, the treatment and prevention of ID should be based on the organization of the physiological regimen and nutrition (with artificial feeding, adapted mixtures enriched with iron; timely and versatile complementary foods using meat products) [1]. However, it is unphysiological and unjustified to introduce early juices, yolk, complementary foods and meat in order to prevent ID, since its prevention with the help of a rational diet alone in children at risk is hardly possible (fast-growing, premature, twins). A number of these products contain little iron (in 50 ml of any juice 0,1-0,3 mg with a need of at least 0,7 mg / kg / day) or, being presented in a non-heme form, it is poorly utilized (liver, yolk). Meanwhile, the early introduction of these products can lead to the development of allergic or histamine-liberating reactions, as well as to a decrease in the absorption of food medicated iron (pulp juices, eggs).

Treatment of IDA with ferropreparations is absolutely necessary. For any of its forms, oral iron preparations (ferrocal, ferroplex, conferon, feramid) are used, prescribed at the rate of 1,5-2,5 microns / kg / day for the first 3-5 days and then with good tolerance at 3-5 mg / kg / day for 2 months. By the way, the administration of ferropreparations at a dose of less than 6 mg/kg/day of elemental iron guarantees their good tolerability. However, the treatment of severe forms of IDA is justified to begin with the intramuscular injection of ferrum-lek (no more than 2-3 injections), under the influence of which the well-being and condition of the child quickly improve. It is permissible to resort to a longer and even more course use of parenteral ferropreparations extremely rarely (intolerance to oral drugs, hyposocial family, occult and obvious gastrointestinal bleeding with an unknown source).

A study of peripheral blood after 2-3 weeks from the start of treatment makes it possible to make sure that it is indicated and whether the diagnosis is accurate (according to the increase in hemoglibin and reticulocyte crisis), and after the end of ferrotherapy, to evaluate its final effect.

Recommended by many authors [3, 7, 13, 14] the use of half-dose ferropreparations for 3-6 months after the normalization of hemoglobin levels or their appointment for a longer period with a prophylactic purpose (premature infants from 2 months to the end of the 1st year of life , full-term from the risk group for 3-6 months), in our opinion, are unjustified and unrealistic. As the physiological growth rate decreases and the diet expands due to non-dairy products, the tension of the iron balance decreases and the LDH spontaneously

disappears, and such a long-term administration of ferropreparations to a practically healthy child is hardly possible. Therefore, we use ferropreparations for prophylactic purposes according to the treatment program (3-5 mg / kg / day for 2 months) and only in children at risk at the age of 4-6 months.

All other drugs (vitamins, hormones, microelement cocktails) recommended by many authors [15, 16] for the prevention and treatment of ID are never used. Special controlled trials have shown that the combination of ferropreparations with ascorbic acid, injections of vitamins B1, B6, B12 and the intake of folic acid and copper sulfate will not accelerate the increase in hemoglobin and SF levels, and will not shorten the duration of treatment with iron preparations [1-9]. We do not consider justified therapy according to a special program (iron preparations in combination with nerobol and prednisolone) and atypical forms of IDA isolated in children with chronic focal infection and organic lesions of the central nervous system, as well as with malabsorption syndrome and deep dystrophy [3]. Treatment of anemia in these patients is not an independent task, and normalization of hemoglobin and SF levels does not improve their condition. The elimination of anemia and sideropenia in these patients is possible only with successful treatment of the underlying disease, in the reparative period of which the appointment of ferropreparations without hormones and vitamins is quite sufficient, as evidenced by our experience.

4 Conclusion

In children of any age, LD and mild IDA are the dominant forms of iron deficiency. At the age of 6 months to 2 years, these forms of ID are especially widespread, almost do not manifest clinically, are characterized by high spontaneous reversibility and do not affect the growth, physical development and morbidity of children, i.e., they can be considered as a borderline condition. Treatment is subject to IDA of any severity, LDH in girls of puberty and in all children with advanced sideropenic symptoms (at least 3-4 signs). For premature, rapidly growing children and twins, ferropreparations are prescribed prophylactically at the age of 4-6 months. At the same time, ferropreparations for therapeutic and prophylactic purposes are used according to a single scheme (3-5 mg / kg / day for 2 months) and, in the absence of special indications, are not combined with vitamins and microelements. Active immunization of children with a mild form of IDA and LDH is carried out on a calendar basis.

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