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Ferrotherapy Mistakes in Toddlers in Primary Health Care

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Rationale. *According to the World Health Organization, 20-30% of the world population have iron-deficiency anemia. Despite the availability of diagnostic and therapeutic capabilities, the real medical practice in the sphere of iron-deficiency anemia remains on the low level. As a result, the situation with iron-deficiency anemia in infants has not been significantly improving for 20 years.* ***Study objectives:*** *assessment of the current tactics of managing infants with anemia and identification of the possible ambulatory ferrotherapy mistakes.* ***Methods.*** *The authors conducted a retrospective analysis of management of 135 3-year-old children with anemia in primary healthcare. Inclusion criteria: previous two or more clinical blood analyses demonstrating an age-low hemoglobin level (according to the WHO).* ***Results.*** *A follow-up clinical blood analysis in the event of anemia was prescribed within 6 months to 100 (70.4%) patients; however, it was conducted by the optimal deadline in ¼ of the patients only; other children did not have documented previous ferrotherapy. Notices of treatment onset after the first episode of hemoglobin reduction were included in medical records of 26 (19.3%) children; 40 (29.6%) children underwent treatment with an adequately dosed iron preparation, 16 (11.9 ± 2.8%) – with a low-dose (below the recommended level) iron preparation. The second anemia episodes were observed in 41 (30.4 ± 4.0%) children; multiple anemia episodes were observed in several children. The average duration of iron-deficiency anemia within the first three years of life in children was 6.4 years.* ***Conclusion.*** *Most infants with iron-deficiency anemia receive treatment late. Lack of adequate hemoglobin level control is the most significant issue.*
Keywords: *iron-deficiency anemia, anemia, primary healthcare, iron preparations, ferrotherapy, children, infancy.*
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RATIONALE

According to the World Health Organization, 20 to 30 percent of the global population suffer iron deficiency anemia (IDA), which is more than 1.6 billion people; iron deficiency is one of the most frequent alimentary-dependent conditions in the world [1]. This pathology is most frequent in pregnant women (42%), non-pregnant women of reproductive age (30%), and toddlers (47%) [1, 2].
According to Russian researchers, IDA remains a serious healthcare and social issue in Russia and is frequent at 17 to 47%, which overall coincides with global frequency values [3]. At the same time, data point out extremely strong prevalence of this pathology in some regions of

Russia. Thus, its frequency reaches 50 to 60 percent in Northern Russia, Eastern Siberia, and Northern Caucasus [4, 5].

The main issue about IDA is its potential effects on the physical and psychomotor development of children. Iron deficiency anemia is associated with reduced weight and height, sexual development delays, immunity disorders, increased morbidity of acute respiratory infections, intestinal infections, prolonged and complicated course of bacteria-induced diseases [6–8]. Almost all the scientists that study IDA recognize its effects on children's psychomotor development [9, 10], but there is no common stance on the intensity and duration of such effects.

At the same time, the today's primary care physicians have all the tools for quality diagnostics (clinical blood tests, iron metabolism values) and treatment of IDA (peroral and parenteral drugs based on organic and non-organic iron compounds in the form of mixed drugs). If a physician has methodological manuals and tools to diagnose and treat this condition properly, then IDA in children should be identified and dealt with as quickly as possible and should not have any consequences. Unfortunately, the real world clinical setting is not that efficient, neither in Russia nor globally.

IDA therapy quality control and efficiency recording remain problematic [11]. P.G. Biondich et al. have found out that only in 18.3% of cases where anemia was identified by blood testing, a follow-up control check-up was prescribed within 6 post-diagnosis months, and only in 11.6% of such cases hematoglobulin level normalization was registered [12].

Treatment strategy selection is also far from perfect in real-world clinical setting [13, 14]. C. Daniel et al. have analyzed IDA treatment of children at primary healthcare institutions [13]. More than half of patients received improper iron dosage; after being checked-up at a specialized clinic, poor compliance was noted for a third of those children. The list of reasons why physician-recommended treatment was abandoned included drug intolerance (19%), dyspepsia (11%), and misunderstood recommendations of the physician (14%); but in most cases, the patient and/or their parents thought the prescribed dose was excessive and reduced it on their own (41%).

Such an approach to diagnosing and treating IDA explains why the global achievements in IDA frequency reduction are so poor. An analysis of dynamics for the last two decades reveals that IDA prevalence in children has decreased the least (compared to that in reproductive age women and pregnant women) [15].

It is extremely important not only to study the real-world clinical setting in terms of IDA, but also to look for and eliminate possible reasons of non-compliance with methodological manuals.

The aim of this study is to research the level of anemia-affected pediatric patient diagnostics and management under outpatient conditions.

METHODS

Research Design. We have analyzed retrospectively the strategy of anemia-affected toddlers management at the primary healthcare institutions

Fitting Criteria. Inclusion criteria were as follows. A child should be no older than three at the start of the research, and have at least two consecutive blood tests taken while monitored at the outpatient facility, indicating a hematoglobulin level under age-appropriate levels. We assumed age-appropriate hematoglobulin levels as recommended by the WHO, i.e. 110g+/l for 6-to-59-month-old children, 115g+/l for 5-to-11-year-old children, 120g+/l for 12-to-14-year-old children [16]. The severity of anemia was determined by the level of hematoglobulin. If lowered to 90g/l, it was considered mild anemia; 89-70g/l was anemia of moderate severity; 69g/l or less indicated severe anemia [17]. The exclusion criterion was an age above three and the presence of only one clinical blood test indicating a hematoglobulin level under age-appropriate levels.

Physical development of children was assessed by the standard deviations method, as recommended by the WHO [18]. The social level of families was assessed by the parents' job at the time of their child's birth: top manager, specialist, middle-ranking specialist, unskilled labor,

student, temporarily unemployed (for men), householder (for women), and private entrepreneur (where the job qualifications cannot be identified). If parents' qualifications differed within a single couple, the higher qualification was taken. Single parenting was considered an indirect indicator of low socio-economic status of such a family. Maternal health was assessed by protocols of prenatal home nursing carried out by local nurses and pediatricians, as well as by means of prenatal records.

Research Conditions. The research was carried out at five random pediatric outpatient units of Samara (43 pediatric districts).

Research Duration. Children's development histories were sampled from July 1st, 2013 till October 1st, 2014.

MEDICAL INTERVENTION

Research Events. For this research, the main event was hematoglobulin level normalization, recurrent anemia (post-treatment re-occurence of hematoglobulin level reduction to below age-appropriate levels according to the above criteria), anemia and relapse duration. The latter terms refers to the number of days since the first test indicating low hematoglobulin level, where the case begins, until the first test indicating age-appropriate hematoglobulin levels, where the case ends. Control clinical blood testing within six months since hematoglobulin level reduction was registered, as well as treatment with iron-based drugs were considered additional research events.

Event Registration Method. Anemia and relapse case beginnings and endings, as well as the duration thereof, were registered on the basis of the outpatient blood test results found in children's development histories (112/y-forms).

Ethical Expertise. Bioethics Committee of Samara State University of Medicine, protocol no. 155 dd. February 4th, 2015. E.A. Balashova's study Health Conditions of Children Suffering Iron Deficiency Anemia in the Samara Region is compliant with ethical norms.

Statistical Analysis. Sample size was not pre-calculated, we registered all the cases that passed the inclusion criteria. Statistical analysis was performed using Microsoft Office Excel 2007.

RESULTS

Study Enrollment

In accordance with the inclusion criteria, we have selected 155 children (155 outpatient cards). 20 children were excluded from further analysis, 2 of whom were excluded due to perinatal HIV contacts, as prophylactic antiretroviral therapy and the virus itself can affect hematopoiesis; the rest were excluded because their hematoglobulin levels had not been normalized according to outpatient card data. Since the retrospective research design does not allow to identify the reason why anemia persisted (improper treatment or no treatment at all, lack of subsequent laboratory control, incorrect diagnosis, or another causative factor of anemia which had not been eliminated), we excluded those children who did not have at least one post-case clinical blood test indicating appropriate hematoglobulin level. As a result, 135 children were analyzed after all, 60.7% of whom were boys.

Patient statistics was as follows. 54.1% were born in a first pregnancy; 36.3% were born in a second or third pregnancy, and 9.6% were born in a fourth or later pregnancy. Beside children born in a 4th or later pregnancy, pediatric patients at risk of IDA include children of young girls, elderly women, and women affected with somatic pathology; the group also includes children born in a multifetation, in a high-risk pregnancy, or into a family of low socio-economic status. 2.2 percent of children were born by young girls, 3.0% were born by elderly primiparas (35 years or older). 1.5% of children were born in twin pairs; 6.7% were born into single-parent families.

Most children (46.7%) belonged to families of high socio-economic status, i.e. where at least one parent was a specialist or a top manager, see. Fig. 1. 16.3% of children belonged to families of low socio-economic status, i.e. where both parents were unskilled workers or unemployed.

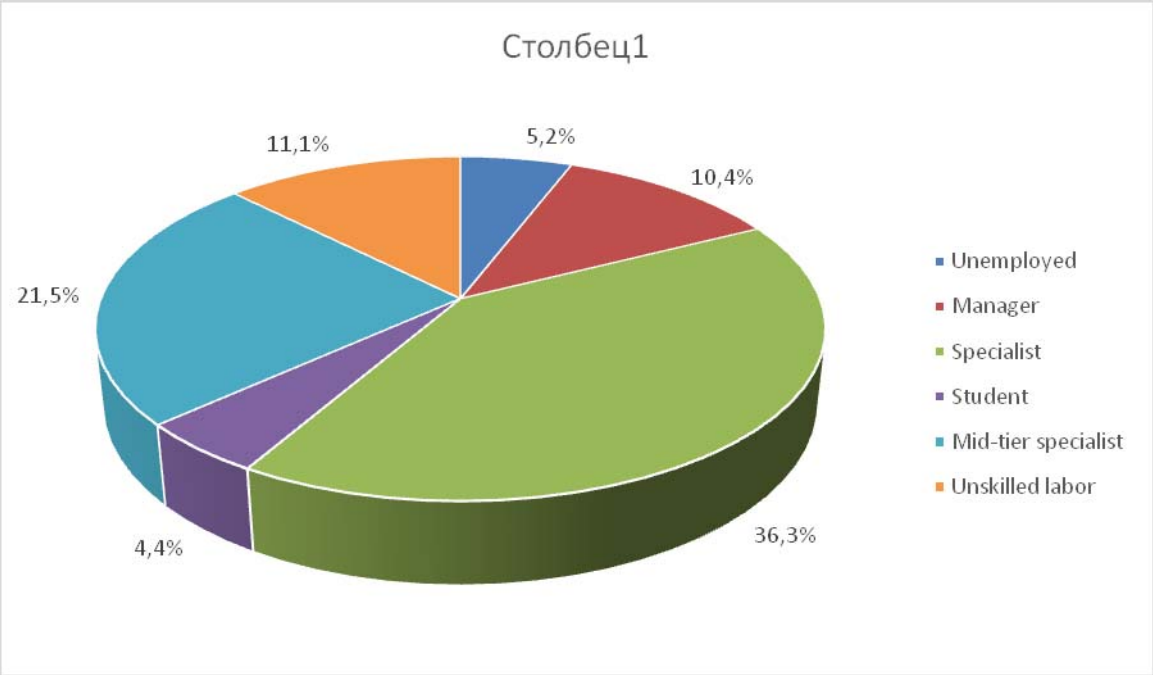

Fig. 1. Socio-economic status of anemia-affected children

The most frequent pregnancy pathologies were chronic placental insufficiency (28.1%), gestosis (26.7%), chronic intrauterine hypoxia (20.7%), and threatened miscarriage (20.0%). 7.4% of children were born prematurely. 38.5% of women had gestational anemia; 3.0% of women were not monitored while pregnant.

Most children (74.0%) were of average birth weight (Fig. 2). 3.7% of children were of too low birth weight (-2σ to-3σ and below-3σ for 2.2% and 1.5%, respectively). Delayed intrauterine development diagnosed in 15.6% of children. 17.0% of children were below average weight at the age of 12 months.

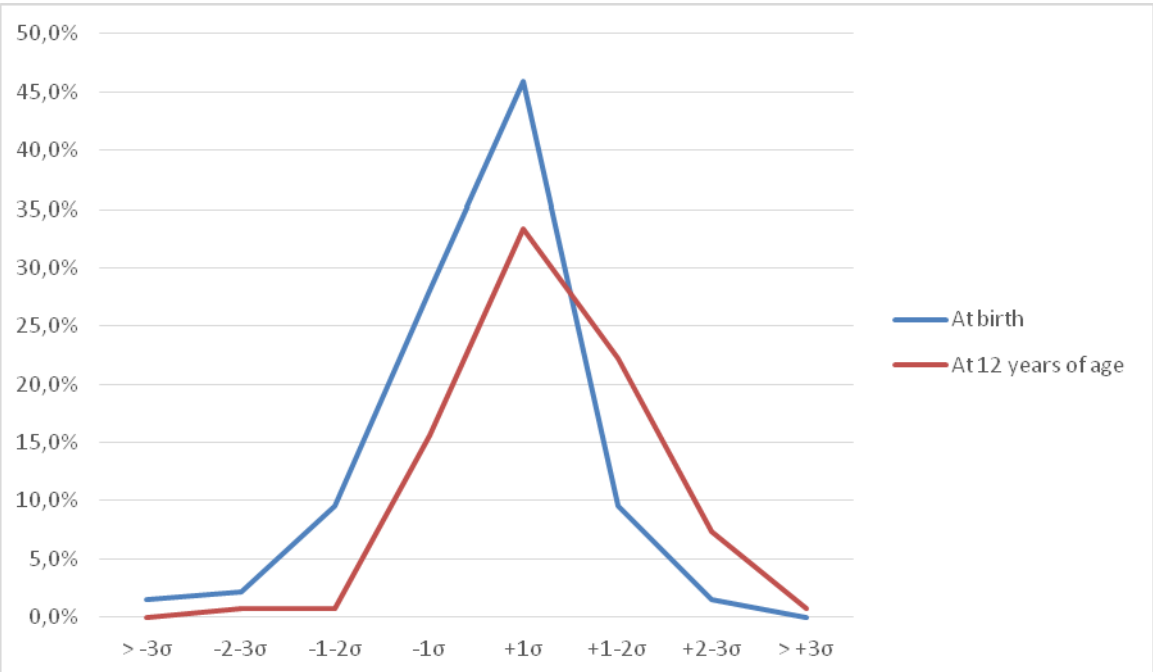

Fig. 2. Body weight of anemia-affected children upon birth and age of 12 months

Birth body length of these children was well above average (Fig. 3). 26.7% of children had more than 3σ longer bodies as compared to average body length values.

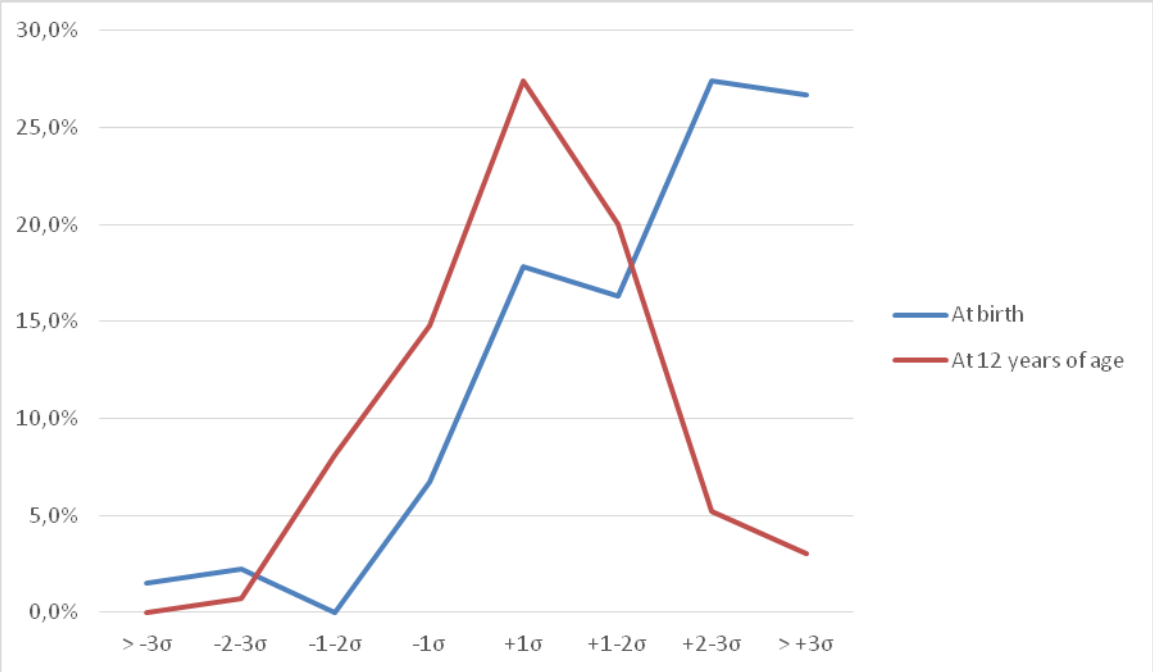

Fig. 3. Birth body length of anemia-affected children upon birth and at age of 12 months

25.2% of children were breast-fed for no more than three months; 18.5% were breast-fed for 12 months.

The examined children had some common assident pathologies, namely innate maldevelopments (12.6%), nutritional failure (2.2%), and excess body weight (3.0%). Both infectious and non-infectious gastrointestinal pathologies were frequent in those children, with functional disorders accounting for 22.2% and acute intestinal infection accounting for 28.9%. Helminthosis was identified in 3.7% of children.

Primary Research Results

Most children (80.7%) had mild anemia, 18.5% suffered moderate severity anemia, and 0.7% had severe anemia.

On average, the duration of anemia in those children was 6.4±4.1 months over the first three years of life. We found out that recurrent anemia was very frequent. 41 children, or 30.4%, had a single relapse, 9 children (6.7%) had it twice, and one child (0.7%) had three anemia relapses over the first three years of life. On average, the duration of anemia relapses was 5.4±2.8 months.

Additional Research Results

Indeed, the efficiency of pathogenetic IDA treatment, due to the available variety of drugs, depends first of all on how quickly and consistently primary care physicians act. Despite the growing numbers of people opposing this method [12, 19], clinical blood tests remain the primary indicator of hematoglobulin levels in blood. Over the first year of life, children were screened for IDA 3.5±2.5 times on average.

We have found out that most children (70.4%) were tested within six months since hematoglobulin level reduction. At the same time, only for 21 (15.6%) children was this type of control exercised within an optimal time period, which is the period from the expected

hematoglobulin level elevation till the end of the treatment course. This optimal period usually spans over the second fortnight since hematoglobulin level reduction.
We did not manage to find recorded data on iron-based drug treatment in 76 (56.3%) outpatient cards. 26 (19.3%) children started to receive treatment after lowered hematoglobulin levels were first identified by means of blood testing. 12 (8.9%) children started to receive treatment after two consecutive tests, 7 (5.2%) received treatment after three tests, and 3 (2.2%) children were only treated after four or more tests had been taken. In case of IDA relapses, treatment delays were not that significant, which was probably due to apprehensive attitude on the part of primary healthcare physicians.
IDA was mostly treated with iron(III)-hydroxide polymaltose complex (43 children, or 32%), as well as iron salts, i.e. iron chloride and iron sulphate (27 children, 20%), or iron protein succinylate (2 children, 1.5%). In 6 (4.4 ± 1.8%) cases, a drug that should not be applied to children under 12 was used; it was Fenules, iron sulphate combined with polyvitamins. It should be noted that in 16 (11.9%) cases, the iron-based drug was replaced unreasonably; in 3 (2.2%) cases, this was done multiple times.
Only 40 (29.6%) patients were prescribed appropriate iron-based drug dosage.
In most cases, therapy duration was appropriate; only in 7 (5.2 ± 1.9%) cases, iron-based drugs were prescribed for a fortnight-or-shorter period.
In 25 (18.5%) children, anemia was treated with other therapeutic means beside iron-based drugs. These included multivitamins (12 children; 8.9 ± 2.5%); drugs affecting the gastrointestinal tract, i.e. prebiotics and probiotics as well as enzymes (11 children, 8.1%); vitamin B_{12} and folic acid drugs (2 children, 1.5%).
In 6 (4.4%) cases, children were checked-up by hematologists, who did not change the diagnosis. In one case, poor compliance was detected; in another case, the child was admitted to the hematology unit due to an extremely low hematoglobulin level of 65 g per liter.

Adverse Effects

Adverse effects could not be estimated due to the retrospective research design.

DISCUSSION

The results obtained allow to state insufficient management of anemia-affected toddlers, which leads to a significant number of relapses. At the same time, the reasons why treatment strategies were inappropriate did not coincide with what is mentioned in scientific sources on this topic. According to C. Daniel et al., O.I. Pikuza et al., the main type of ferrotherapeutic errors is incorrect dosage calculation and improper treatment duration [13, 14]. In the cases we have analyzed, therapy was mostly compliant with drug manuals. The most frequent issue was delayed therapy and control blood test prescription, which we believe was due to the lack of iron metabolism parameters (serum iron and/or ferritin), which in its turn was due to physicians' desire to make diagnostics cheaper or avoid venipunctures. Besides, one cannot exclude parents' disinterestedness in additional testing. One more problem of managing anemia-affected children at primary healthcare institutions is "excess" therapy. Unreasonable replacement of iron-based drugs, often with other drugs belonging to the same group, unjustified prescription of drugs belonging to other groups, including vitamins B and folic acid, are probably due to physicians' uncertainty in the correctness of diagnostics.
There was a limitation in this study, which was our inability to confirm the iron deficiency nature of anemia due to the lack of parametric assessment of iron metabolism in the outpatient setting. We could not exclude other causative factors of anemia, where infections are of utmost importance. An acute infection can also trigger anemia which does not require immediate ferrotherapy, thus giving space for expectant management. On the other hand, Russian researchers believe IDA accounts for 70 to 90 percent of all diagnosed anemia cases in Russia

[17]. Despite the fact that clinical recommendations include iron metabolism assessment into the framework of IDA diagnostics, some therapists carry out trial treatment with peroral iron-based drugs upon identification of moderate anemia in generally healthy children [20, 21]. Besides, IDA and infection-induced anemia are not mutually exclusive. The main mechanism of inflammatory anemia formation is related to increased production of hepcidin, the protein regulating iron absorption in the intestines, and iron regulation in macrophages by means of ferroportin degradation. Iron redistribution leads to restrictive erythropoiesis, where the body's micronutrient resources are sufficient, but these micronutrients become far less accessible for erythrocyte generation [22]. However, prolonged exposure to elevated hepcidin concentrations, i.e. in a series of infectious diseases, can lead to absolute iron deficiency, especially in patients at risk of IDA.

Most Russian authors recognize the effects of iron deficiency on immune response [7, 8, 23, 24]. In the real-world setting, it is quite difficult to determine whether an infection or iron deficiency has caused anemia, if no additional tests are employed. With this in mind and considering the fact that all the children involved in our research have had their hematoglobulin levels normalized, we can suggest it was iron deficiency anemia in most cases.

The second limitation of this research was due to its retrospective design; it was our inability to retrieve lost data, like checkups and studies carried out at the parents' option outside the outpatient setting; or lost and unmarked in the 112-y form examination results; or data on prescribed treatment. Since we aimed at studying the real-world clinical setting, this limitation was inevitable.

CONCLUSION

On average, we believe the most important problem of managing IDA-affected toddlers at outpatient facilities is about insufficient hematoglobulin level monitoring. This problem can be solved by developing non-invasive hematoglobulin level evaluation techniques [25] or broad use of reticulocyte hematoglobulin [21] for pediatric diagnostics of anemia, which will allow to avoid venipuncture and increase the certainty of IDA diagnosis.

CONFLICT OF INTEREST

The authors of this article have declared absence of reportable financial support / conflict of interest.

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