Original Paper

Implications of the Iron Deficiency in Lower Tract Respiratory Acute Infections in Toddlers

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ABSTRACT: Iron deficiency anemia can result in an abnormal immune response and an increased incidence of the respiratory tract infections. In this study we analyzed statistically the association of acute lower respiratory tract infections with anemic status and associated risk factors for a number of 166 toddlers (1-3 years), using a control group of 26 cases without infectious status. The statistical analysis indicated the significant association of the infectious status with the anemic status of the patients as well as with the rural living areas, non-natural nutrition, prematurity and respiratory history. At the same time, we found a statistically significant association of anemic status with rural living areas and non-natural diet. The results obtained can be used to stratify patients for standardized treatment to regulate the iron metabolism and implicitly to combat the infectious disease.

KEYWORDS: *Iron deficiency anemia, respiratory infection, toddlers*

Introduction

Iron is an essential element for cellular respiration, oxygen transport, being involved in the metabolism of numerous proteins and enzymes that play a role in DNA synthesis, cell growth and immune defense [1-3]. Iron deficiency is considered a health problem worldwide, mainly due to widespread persistence, despite improved nutrition and access to substitution treatments [3]. At the same time, anemia is one of the most common diseases in pediatric practice, having in most cases as trigger pathogenic factor the deficiency of iron [4,5].

The iron deficiency perspective is controversial, and recent literature data has provided evidence of its effects. The involvement of iron in the development and harmonious growth of children supports its participation in the etiopathogenic mechanisms of various pathologies [6,7]. Thus, the respiratory tract infections appear to be directly related to insufficient or inefficient use of iron, and an altered immune response, issues that are the subject of nutritional immunology research [8,9]. The relation between acute lower respiratory tract infections and iron deficiency are supported by mechanisms in which mediators of inflammation such as TNFα (Tumor necrosis factor), IFNγ (Interferon), IL-1β (Interleukin) and IL-6, which play a role in the activation of monocytes and neutrophils, can induce the synthesis of proteins associated with iron metabolism (hepcidin, siderocalin, haptoglobin, hemopexin), some with a blocking effect on the duodenal iron absorption, but also inhibiting the liver and spleen iron recycling resulting in iron deficiency anemia [6,10-12].

On the other hand, other studies explain the frequency of iron deficiency in the population by superiority to the survival of this phenotype following the exposure to infection and selection throughout the human biological evolution [3]. It has been suggested that the protective effect of moderate iron deficiency against infections is supported by the low availability of iron for pathogens [3,13].

Iron deficiency is frequently identified during the 6 months to 3 years on the one hand due to the loss of the iron stock taken from the mother during the last trimester of pregnancy and on the other hand to the lack of iron intake due to the food diversification and exploration period [7]. At the same time this age coincides with the recording of most episodes for lower respiratory tract infections [14].

In this study we analyzed the risk factors and clinio-epidemiological aspects of the iron deficiency anemia in the context of acute lower tract respiratory disorders in toddlers.

Material and Methods

In this retrospective study, 192 toddlers (1-3 years old) were included, of which 166 with acute lower respiratory tract infection (study group with infectious status) and 26 cases without respiratory infectious status (control group without infectious status). The patients were hospitalized and treated between 2016-2017 in the Pediatric Clinic I of the

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Craiova County Emergency Clinical Hospital, for the control group selection being excluded the pathology associated with iron deficiency anemia at the admission.

The patients with malformations, malnutrition, systemic illness, respiratory pathology in the past 6 months, immunocompromised patients, or those who have been treated with antibiotics or iron supplements over the past three months have also been excluded. The diagnosis of iron deficiency anemia was supported by criteria elaborated and updated by World Health Organization working groups [15,16]. The infectious disease was established based on anamnesis, clinical, paraclinical and imaging investigations, all cases in the study group presenting the onset of symptoms.

The analysis was done integrated, the clinical and epidemiological data (gender, living area, anemic status) and risk factors for anemia (prematurity, diet, respiratory history) being statistically analyzed by the chi square comparison test ($\chi 2$). The analysis was performed in the SPSS10 (Statistical Package for Social Sciences) software, values of $p<0.05$ being considered statistically significant. In this study, the ethical standards in research have been respected and the written informed consent was obtained from all the patients.

Results

In the study, the group with patients with infectious status represented 86.5% (166 cases), while the control group constituted 13.5% (26 cases).

The analysis of clinical and epidemiological data indicated for the whole analyzed group the slight predominance of the male patients (50.5%), who came from the rural area (52.1%). While female patients (52.4%) from rural areas (56.6%) predominated in the case of patients with infectious status, in control the group, males (47.6%) and the urban area (43.4%) were more common (Table 1).

Anemia status was identified for the entire group analyzed in 104 cases, which accounted for 54.2% of cases. While for the study group with infectious status, anemia status was present in 98 cases (59%), in the control group without infectious status, it was present in only 6 cases (23%) (Table 1).

Patient history indicated inappropriate prophylaxis or absence of prophylaxis for anemia for 67 cases (34.9%). The most common signs associated with anemic and infectious status were the pale and dyspnea.

Table 1. Cases distribution depending on analyzed parameters and statistical significance

p value (χ2 test)	Parameter	Study group (infectious status)	Control group (noninfectious status)	
0.186	**Gender**	Male	79	16
		Female	87	10
0.001	**Living area**	Rural	94	6
		Urban	72	20
0.001	**Anemia status**	Present	98	6
		Absent	68	20
0.036	**Prematurity**	Present	106	11
		Absent	60	15
<0.001	**Diet**	Breast milk	24	13
		Powder milk	79	7
		Cow-milk	26	4
		Mixed	37	2
<0.001	**Respiratory history**	Present	108	3
		Absent	58	23

The analysis of the risk factors for anemic status indicated some differences between the study and control examined groups. Thus, prematurity was recorded for 117 patients in the analyzed group (60.9%), the cases being more frequent in the study group with infectious status compared to the noninfectious control group, respectively 106 (63.8%) and 11 (42.3%) cases (Table 1).

Regarding the nutrition (diet), we found that for the whole group the use of powdered-milk and mixed diet was present in 44.8% and 20.3%, followed by the use of breast milk and cow’s milk, present in 19.3% and 15.6%.

In the study group with infectious status, the use of breast-milk was present in only 24 cases (14.5%), while for the control group with noninfectious status the natural nutrition (breast-milk) was identified in only 13 cases (50%) (Table 1). Thus, for the study group with infectious status, we found that 80.7% of the toddlers included in the study were fed from the first months of life with the formula of powdered milk or milk of animal origin.

Respiratory history was present for the whole group in 111 cases (57.8%). Within the study group with respiratory infectious status, the respiratory history was identified in 108 cases (93.1%), compared to the control group without infectious status, which was identified in only 3 cases (11.5%).

The statistical analysis of case distribution for the two groups analyzed in relation to the clinical and epidemiological and risk factors revealed significant differences, respectively the association of the patients group with inferior respiratory tract infection with the rural living area (p=0.001, χ2 test), the presence of anemic status (p=0.001, χ2 test), presence of prematurity (p=0.036, χ2 test), non-natural diet (p<.0.001, χ2 test) and presence of the respiratory history (p<.0.001, χ2 test) (Table 1, Fig.1A-E).

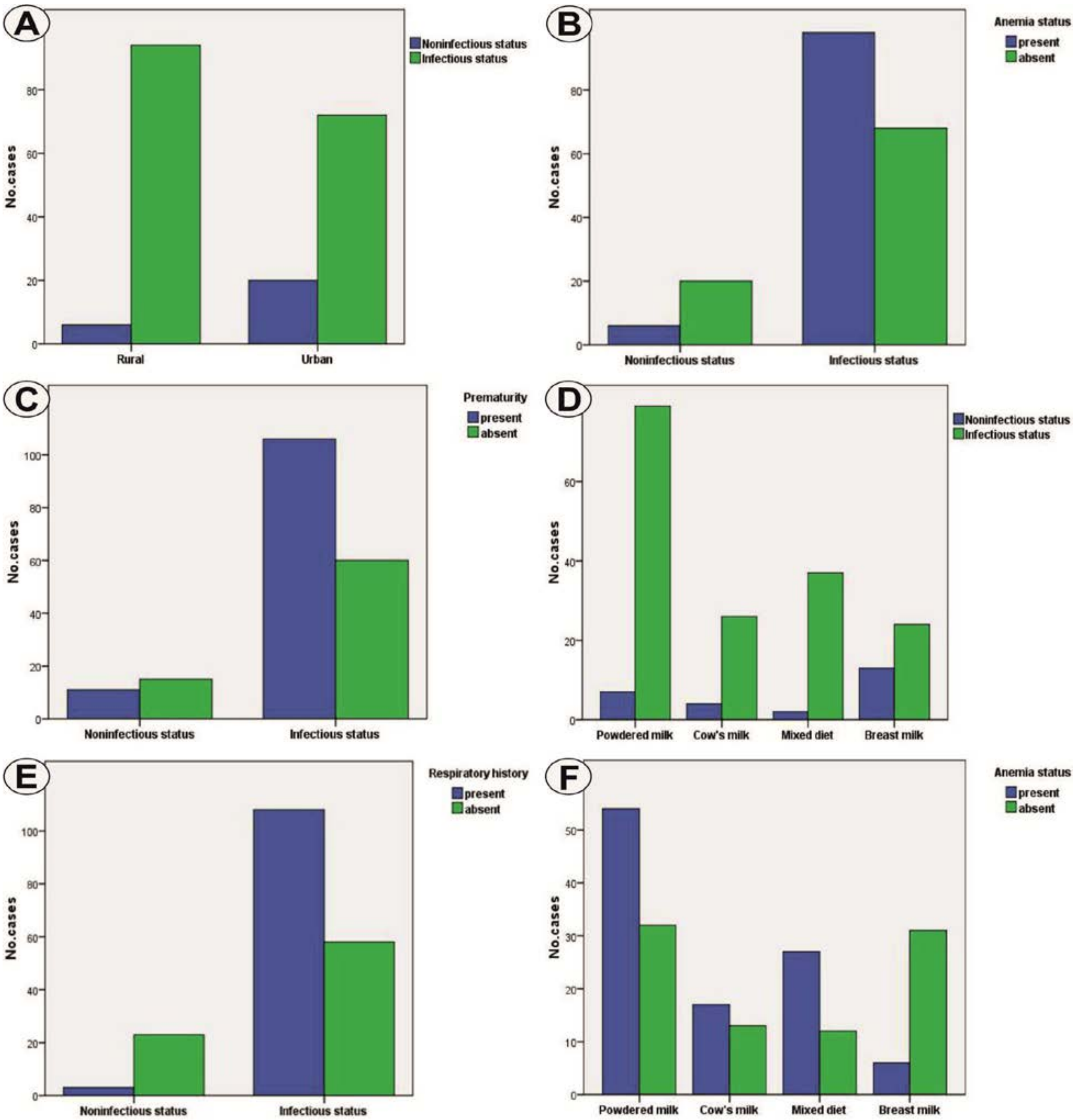

Fig.1. Cases distribution in relation with infectious status and environment (A), anemia status (B), prematurity (C), diet (D), respiratory history (E); Cases distribution in relation with anemia status and diet (F)

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Also, in this study, the positive anemic status was more common in rural patients (69.6%) (p=0,023, $\chi2$ test), as well as in patients with non-natural diet (51%) (p<.0.001, $\chi2$ test) the aspects being statistically significant (Fig.1F).

Although the positive anemic status was more frequent in the case of prematurity and respiratory history, the aspects were statistically insignificant (p>.0.05, $\chi2$ test).

Discussions

Lower respiratory tract infection includes all diseases of the respiratory system below the larynx, being responsible in the acute form for approximately 20% of all deaths in children less than 5 years of age [12,17-19].

The increased incidence of lower respiratory tract infections in toddlers is attributable to the loss of acquired immunity and the fragility of the defense system in the context of contouring and consolidation of the immune status but also of the contact with the environment [9,17].

There are numerous studies that examined the relation of iron deficiency with the incidence of lower respiratory tract infections, the impact that iron deficiency has on immunity and implicitly on favoring infections being controversial [1,4,6-8,20,21]. In our study, we found a statistically significant association of the infectious status with the patient's anemic status.

Data from the literature indicates that iron deficiency can induce neutrophil and bactericidal activity, but also reduce the number and activity of natural killer lymphocytes [9]. Some studies have demonstrated statistically, through the use of inflammatory markers or for anemia, the association of iron deficiency with infection for different pediatric age categories [1,12,17].

It so indicated a 2-5.7 fold increase in the incidence of acute lower respiratory tract infections in patients with iron deficiency anemia [4,6-8,19,21].

On the contrary, other studies have indicated the absence of a relation between iron deficiency and lower respiratory tract infections. Such results were obtained by Broor S et al., the study being conducted on a group of patients with different ages and diets [22]. Similar results were obtained by Murray MJ et al. in a study conducted on African nomadic populations [9,23]. Furthermore, some authors indicate that a mild/moderate iron deficiency may have a protective effect on respiratory infections, aspect related to adaptive evolutionary theory [1].

The variable results obtained so far can indicate the heterogeneity of the analyzed groups, exposure to risk factors or infection/anemia protectors that have not been analyzed. At the same time, some authors have used lots of different ages and diets [12,22], and some data indicate that iron status should be evaluated by several parameters (hemoglobin concentration, serum ferritin, reticulocyte hemoglobin, receptor 1 transferrin) to increase sensitivity and specificity [18]. Also, some studies indicate the difficulty of diagnosing iron deficiency anemia in case of concomitant infection, which may require multiple exclusion markers [8]. In this study, the WHO criteria for iron deficiency anemia have been respected, and for the group homogeneity, the patients included in the study presented the infectious disease at onset.

In our study, we considered a number of risk and clinical and epidemiological factors that literature describes as possible causes for iron deficiency. Thus, we found a statistically significant association of the lower respiratory tract infection rate with the rural living area, non-natural nutrition, prematurity and respiratory history. At the same time, we found a statistically significant association of anemic status with rural area and non-natural nutrition, as well as a higher frequency of association of anemic and infectious status to male gender.

Males seem more likely to develop anemia and respiratory infections [19,21], but rural provenance can raise some problems. Most patients included in the study were identified as coming from rural areas, which involved multiple issues such as poor living conditions, lack of education, poor access to growth and optimal development of children. Some studies have shown the association of iron deficiency and respiratory infections with a low educational and social level of mothers [12]. Although iron deficiency anemia is a nutritional problems affecting all areas and ages regardless of socioeconomic status, over time it could demonstrate that developing countries and rural areas are more frequently associated with this pathology [7,17]

The frequency of iron deficiency anemia is higher for toddlers compared to other age groups, one of the causes being inadequate supplementation or completion of the natural nutrition [6]. In our study, only 19.3% of patients have breast-milk diet, in 80.7% of cases being used cow's milk, powdered milk or mixed diet, which may be the premise of a future iron deficiency [24]. In the case of toddlers, the iron-rich foods appear to be more effective for regulating iron metabolism than artificial supplements, which may have some adverse effects that decrease patient compliance [18].

In our study, prematurity was identified for 60.9% of patients in the study group. Over time, data have been published that indicated prematurity as having an increased risk of developing various pathologies based on immunological deficiencies or deficiencies of different elements [25,26].

The iron deficiency anemia prophylaxis is done in term-born babies from the age of 6 months when breast milk is banned from this oligo element. In our study, prophylaxis was inadequate or absent in 34.9% of cases. In the premature baby who did not receive the mother's iron reserves by failing to finish the last trimester of pregnancy, prophylaxis of anemia is done earlier from 3-4 months, in order to ensure optimal iron status [9].

In our study, respiratory history was present in 57.8% of the analyzed cases. The recurrence of respiratory episodes appears to be related to the disruption of iron metabolism, inappropriate administration of it as a supplement or food, or interference with other pathologies [9].

At present, there are studies that support the need for iron status screening at the age of 9 months-1 year that could also identify the associated risk factors [8,18].

Future studies are needed which along with risk factors for anemia and inflammation, to consider the degree of iron deficiency, the severity and type of acute inflammation, which may improve the therapeutic measures to establish an effective balance of iron metabolism. The aspect is important because some studies indicate the hypothesis that inappropriate iron treatment may be a risk factor for the appearance and persistence of an infectious disease [8,27].

Conclusions

The study indicated the significant association of acute lower respiratory tract infections in toddlers with iron deficiency and associated risk factors such as rural living area, prematurity and non-natural diet. Identifying the factors that are involved and potentiating the relation between anemia and infection can lead to stratification of patients for a standardized therapeutic management for different ages that regulates iron metabolism to combat infectious disease.

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