Research Article

J Ped. Nephrology 2015;3(2):67-70
http://journals.sbmu.ac.ir/jpn

The Relationship Between Iron Deficiency Anemia and Reflux-Related Renal Injury in Infant and Children

How to Cite This Article: Yousefichaijan P, Eghbali A, Taherahmadi H, Rafiei M, Naziri M. The Relationship Between Iron Deficiency Anemia and Reflux-Related Renal Injury in Infant and Children. J Ped. Nephrology 2015;3(2):67-70.

Parsa Yousefichaijan,[1]
Aziz Eghbali,[2]
Hassan Taherahmadi,[3]
Mohammad Rafiei,[4]
Mahdyieh Naziri[5*]

1 Associate Professor of Pediatric Nephrology.
2 Assistant Professor of Pediatric Oncology- Hematology.
3 Assistant Professor of Pediatrics.
4 Associate Professor of Biostatistics.
5 MSc in Statistics.

*** Corresponding Author**
Mahdyieh Naziri
Deptartment of Basic Science, Clinical Research Office of Amir al Momenin Hospital, Arak University of Medical Sciences. Arak**,** Iran.
E-mail: nazirimahdyieh@yahoo.com

Received: Jan-2015
Revised: Feb-2015
Accepted: Feb -2015

Introduction: Anemia may be defined either quantitatively or physiologically. A diagnosis of anemia is determined by comparison of the patient's hemoglobin level with age-specific and sex-specific normal values. The easiest quantitative definition of anemia is any hemoglobin or hematocrit value that is 2 standard deviations (SDs) (95% confidence limits) below the mean for age and gender. The aim of this study was to evaluate the relationship between anemia and reflux nephropathy in patients with vesicoureteral reflux.
Material and Methods: This case-control study included 260 children aged from 6 months to 2 years. They were divided into two groups of 130 children: the case group suffered from VUR with reflux nephropathy and the control group had VUR without reflux nephropathy.
Results: The results of our study showed that the prevalence of anemia in the reflux nephropathy group was not considerably different than that of the control group.
Conclusions: We conclude that there is no direct correlation between anemia and reflux nephropathy in patients with vesicoureteral reflux.

Keywords: Anemia, Iron-Deficiency; Vesico-Ureteral Reflux; Child.

Running Title: Iron Deficiency Anemia and Reflux-Related Renal Injury

Introduction

Iron deficiency anemia (IDA) is the most widespread and common nutritional disorder in the world. It is estimated that 30% of the global population suffer from iron-deficiency anemia, and most of them live in developing countries [1-3]. The incidence of iron-deficiency is related to basic aspects of iron metabolism and nutrition. The body of a full-term newborn infant contains about 0.5 g of iron, compared to 5 g of iron in adults. This change in the quantity of iron from birth to adulthood means that an average of 0.8 mg of iron must be absorbed each day during the first 15 years of life [4].

Vesicoureteral reflux refers to the retrograde flow of urine from the bladder to the ureter and kidney. The ureteral attachment to the bladder is normally oblique, between the bladder mucosa and detrusor muscle, creating a flap-valve mechanism that prevents reflux [4]. Reflux occurs when the sub mucosal tunnel between the mucosa and detrusor muscle is short or absent. Reflux is usually congenital, occurs in families, and affects approximately 1% of children. Reflux predisposes the person to kidney infection (pyelonephritis) by facilitating the transport of bacteria from the

bladder to the upper urinary tract [2]. The inflammatory reaction caused by a pyelonephritic infection can result in renal injury or scarring, also termed reflux-related renal injury or reflux nephropathy (RN). In children with a febrile urinary tract infection (UTI), those with reflux are 3 times more likely to develop renal injury compared to those without reflux. Extensive renal scarring impairs renal function and can result in renin-mediated hypertension, renal insufficiency or end-stage renal disease, impaired somatic growth, and morbidity during pregnancy [1, 5]. Regarding the prevalence of iron deficiency anemia and RN in children and the importance of the relationship between IDA and infections or chronic diseases in childhood [3,5], the aim of this study was to investigate IDA in children with RN and compare it with VUR patients without RN.

Materials and Methods

This case-control study included 260 children aged from 6 months to 2 years. They were divided into two groups of 130 children: the case group suffered from VUR with reflux nephropathy and the control group had VUR without reflux nephropathy. Patients with grade 2, 3, 4 and 5 CKD, neurologic bladder and other chronic diseases were excluded from the study. At the outpatient clinic, the children underwent careful physical examinations by the assistants and emergency personnel of the pediatric ward, especially with respect to symptoms of iron deficiency anemia. After a diagnosis of UTI and doing imaging studies with renal ultrasonography, voiding cystoureterography (VCUG) and Dimercaptosuccinic acid scan (DMSA), in order to find cases of iron deficiency anemia, 5 ml blood sample was taken from each child for a complete blood count (CBC) and to measure the levels of serum iron, plasma ferritin, and TIBC (total iron binding capacity). Anemia is diagnosed when the hemoglobin level falls more than two standard deviations below the normal level of the related age and sex group. If the hemoglobin level of the child (taking the age of the child into consideration) is lower than the normal range for the related age group, the child is considered to be anemic. To separate iron deficiency anemia from other common causes of this condition, we used the CBC test and the levels of serum iron, plasma ferritin, and total iron-binding capacity. In iron deficiency, serum ferritin and plasma ferritin decline but TIBC rises. Serum iron concentrations of less than 40 mg/dl in children less than 1 year of age and lower than 50 mg/dl in children over one year of age, ferritin levels of less than 7 mg/l, and TIBC values higher than 430 µg/dl confirm iron deficiency. Under these conditions, CBC will also show a fall in red blood cell indices (the number and the volume of the red blood cells and the mean hemoglobin concentration) and iron deficiency anemia develops. Children with anemia resulting from other causes (hemolysis, bleeding, thalassemia, etc.) were excluded from the study. The Ethics Council of Arak Medical Sciences University approved this study. All the parents or guardians of the sick children provided their written consent to the participation of their children in the study; they could withdraw from the study anytime they desired. The researchers in this study were committed to the Helsinki Declaration at all stages of the study. Results of the experiments concerning the case and control groups were separately entered into the SPSS-19.

Results

In the case and control groups, the ratios of the number of boys (45%) to girls (55%) in the two groups were similar with no significant differences. The means RBC count (p value=0.63), Hb (P value=0.6), Hct (P value=0.81), MCV (P value=0.67), MCH (P value=0.6), and MCHC (P value=0.7) was not significantly different between the reflux nephropathy group and the control group. The mean Fe, TIBC, and ferritin was higher in the control group than those in the case group but the difference was not significant. The mean RBC in the control group was higher than that of the control group, but this difference was not significant either. The WBC, neutrophil and platelet count was significantly higher in the reflux nephropathy group than the control group (P-value =0.003). Thirty-nine patients in the reflux nephropathy group and 37 patients in the control group suffered from iron deficiency anemia with significant difference (P-value=0.1).

Discussion

Given the effects of anemia, and especially those of iron deficiency anemia that is the most common type, it is possible that anemia influences the occurrence of reflux nephropathy in patients with VUR. The habits and diets of the children play an important role in the absorption and storage of iron and in preventing iron deficiency anemia. There were no significant differences in the economic conditions of the families of the two groups of children. The patients who participated

in this study were all breast-fed or received formula until they were 6 months old, and received solid food such as cereals, beans, carrot and vegetables soup, egg yolk, and fruit juice after this age. Most children naturally adapted themselves to the program of three meals a day by the time they were 2 years old. Moreover, the differences between the two groups regarding iron supplements were not significant. The results of our study showed that the prevalence of anemia was not considerably different between the RN and the control group. Subramanian G concluded that iron deficiency was not just anemia as it could be responsible for a long list of other manifestations. This topic is of great importance, especially in infancy and early childhood, for a variety of reasons. First, the iron need is maximum in this period. Second, diet in infancy is usually deficient in iron. Third and most importantly, iron deficiency at this age can result in neurodevelopmental and cognitive deficits, which may not be reversible. Hypochromia and microcytosis in a complete blood count (CBC) make iron deficiency anemia (IDA) the most likely diagnosis [3]. The absence of response to iron may indicate other differential diagnoses like β thalassemia trait and anemia of chronic disease. Celiac disease is the most important cause of true IDA not responding to oral iron therapy. While oral ferrous sulphate is the cheapest and most effective therapy for IDA, no pharmacological and pharmacological measure can go a long way in prevention of iron deficiency [3]. Power GM reported that the approach to the diagnosis and treatment of IDA in childhood was widely variable among responding ASPHO (the American Society of Pediatric Hematology/Oncology) members. Given the lack of an evidence-based protocol to guide clinical decision making, further research investigating IDA management is required [2]. AL Ghwass M concluded that the high frequency of IDA was a severe public health problem in developing countries like Egypt, especially in children from rural areas, those from low social class, and those of low maternal educational level. Iron-rich foods should be advised by health care providers. Prophylactic iron supplements should be given to all infants from 6 to 23 months [6]. Nasiri SJ showed that fibroblast growth factor 2 (FGF2) was a potent mitogenic factor of cortical fibroblasts and induced kidney fibrosis. They hypothesized that serum levels of FGF2 had an association with the severity of vesicoureteral reflux (VUR) and renal parenchymal scar. Between 2007 and 2009, a total of 28 children with VUR were enrolled in this study and were compared with 52 healthy children. All children with VUR underwent technetium Tc 99m dimercaptosuccinic acid renal scintigraphy. Fibroblast growth factor 2 was measured in both groups. The mean level of FGF2 was 65.0 ± 19.0 pg/mL in the VUR group and 62.5 ± 15.3 pg /mL in the control group (P> 0.05). There was no correlation between serum levels of FGF2 and sex, age, or the grade of VUR. Of the 28 children with VUR, 19 had renal parenchymal scar on dimercaptosuccinic acid renal scintigraphy. The mean serum level of FGF2 was not significantly different between the children with and without renal parenchymal scar. This study showed no correlation between serum FGF2 and renal parenchymal scar or grade of VUR [5]. Soliman NA evaluated one hundred and seven children with congenital anomalies of the kidneys and urinary tract (CAKUT). Familial clustering was identified in 14% of the cohort and syndromic CAKUT accounted for 31.8% of cases. Different anomaly entities were identified with posterior urethral valve (PUV) being the commonest detected abnormality (36.4%). Of note, 9.3% of the cohort patients had ESRD at presentation, of whom 60% had PUV as their primary renal disease. Obstructive cases were noted to present significantly earlier and attain advanced CKD stages rather than non-obstructive ones. CAKUT is a clinically heterogeneous group of diseases with diverse clinical phenotypes. The authors suggested that more efforts should be aimed at improving antenatal detection as well as classification with comprehensive reference to the clinical, genetic and molecular features of the diseases. The high frequency of familial and syndromic CAKUT among the patients was seemingly a convincing reason to pursue the underlying genetic defect in future studies [7]. We evaluated several factors in patients with reflux and reflux nephropathy in the past and determined the correlation between these conditions and the grade of reflux or reflux nephropathy [8-13], but the relationship between iron deficiency anemia and reflux nephropathy was not evaluated before in our studies and the other investigations.

Conclusion

Based on the current study, there were no differences in prevalence of iron deficiency anemia between children with and without reflux nephropathy. However, due to the importance of

the relationships between different types of anemia and reflux-related renal nephropathy and the lack of adequate evidence concerning the relationship between IDA and different stages of VUR in children, further studies in this field are recommended.

Acknowledgement
This paper was the result of a student thesis. We would like to express our gratitude to all the people who supported and assisted us.

Conflict of Interest
Authors have no conflict of interest to declare.

Financial Support
None declared.

References
1. Norma B, Lerner and Richard Skills, Iron-deficiency anemia. Kliegman, Stanton, St.Geme, Schor, Behrman. Nelson Text Book of Pediatric. 19th edition, Philadelphia, Elsevier Saunders 2011, Chapter 499, p:1655-1657.
2. Powers JM, McCavit TL, Buchanan GR. Management of iron deficiency anemia: A survey of pediatric hematology/oncology specialists. Pediatric Blood Cancer 2015;Feb 7.
3. Subramanian G, Girish M. Iron Deficiency Anemia in Children. Indian J Pediatric 2015;Feb 1.
4. Jack S.Elder, Vesicoureteral Reflux .Kliegman, Stanton, St.Geme, Schor, Behrman. Nelson Textbook of Pediatric, 19th edition, Elsevier Saunders, 2011, chapter 533, P 1834-46.
5. Nasiri SJ, Hooman N, Mehrazma M, Movahed M. Correlation between serum level of fibroblast growth factor 2 and severity of reflux nephropathy. Iran J Kidney Dis 2015;9(1):46-9.
6. Al Ghwass MM, Halawa EF1, Sabry SM, Ahmed D. Iron deficiency anemia in an Egyptian pediatric population: a cross-sectional study. Ann Afr Med 2015;14(1):25-31.
7. Soliman NA, Ali RI, Ghobrial EE, Habib EI, Ziada AM. Pattern of Clinical Presentation of Congenital Anomalies of the Kidney and Urinary Tract among Infants and Children. Nephrology (Carlton) 2015;Feb 3.
8. Yousefichaijan P, Rafiei M, Eghbali A, Sharafkhah M, Taherahmadi H, Naziri M, and Khalighi S. Mean Platelet Volume: A useful marker ln reflux nephropathy. J Ped. Nephrology 2014;2(4):137-139.
9. Yousefichaijan P, Eghbali A, Rafiei M, Sharafkhah M, Zolfi M, Firouzifar M. The relationship between iron deficiency anemia and simple febrile convolution in children. Journal of pediatric neurosciences 2014;9(2):110-114.
10. Yousefichaijan P, Dorreh F, Rafiei M, NouriKopaei S, Naziri M. Effective factors in growth and development in children and infants with vesicoureteral reflux (VUR). Medical journal of Mashhad University of medical sciences 2014; 57(5):690-696.
11. Yousefichaijan P, Cyrus A, Dorreh F, Rafiei M, Sharafkhah M, Safi F, Naziri M, Taherahmadi H. Correlation of sacral ratio and reflux – related renal injury in children with and without nephropathy. J Ped. Nephrology 2014;2(3):116-118.
12. Yousefichaijan P, Cyrus A, Dorreh F, Ahmadi Mohtasham M. Comparing the sacral ratio in children with various degree of Vesicoureteral reflux with children without reflux.AMUJ 2005;10(3):94-99.
13. Yousefichaijan P, et al. Sacrum index in children suffering from different grades of VUR. Pakistan journal of biological sciences 2013;16(11):545-547.