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Original research article/Artykuł oryginalny

Thalassemia major may decrease the frequency of febrile convulsions in children

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ARTICLE INFO

Article history:
Received: 02.09.2013
Accepted: 21.10.2013
Available online: 28.10.2013

Keywords:
- Febrile convulsion
- Thalassemia
- Children

ABSTRACT

Aim: We aimed to determine the relative frequency of febrile convulsion in children with major thalassemia to theorize that higher serum iron levels could reduce the incidence of febrile convulsion. **Background:** Febrile convulsion is the most common type of seizure in childhood that its causes are not fully understood. However, some risk factors have been cited such as the serum iron level. **Materials and methods:** Three hundred and fifty-nine children aged more than 5 years with major thalassemia who were receiving blood were enrolled as the case group. The control group consisted of 357 children without thalassemia aged 4–7 years (151 boys, 206 girls) who were referred to healthcare centers for routine health monitoring. Included data were the history of febrile convulsion, age of onset and type and the frequency of convulsions. **Results:** Children in control group significantly experienced more febrile convulsions than thalassemic children [4/359 (1.1%) in the thalassemic children and 14/357 (3.9%) in the control group had experienced febrile convulsions ($P = 0.017$)]. **Conclusion:** The frequency of febrile convulsion in children with major thalassemia is less than that of normal children. Children with thalassemia major may have higher serum levels of iron and such high serum iron levels might have a protective role in the children who have a vulnerability for febrile convulsions.

Introduction

Febrile convulsion is the most common type of seizure during childhood and has a prevalence of 2–4% in different societies. Febrile convulsion usually occurs in 9 month to 10-year-old children, reaching its peak incidence at 14–18 months of age [1–3]. Although its mortality and morbidity rates are low, but many parents are concerned about the recurrence of seizures [1–3].

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http://dx.doi.org/10.1016/j.pepo.2013.10.002

The cause and pathophysiology of febrile convulsions are not fully understood. Genetic studies have shown a relation between the genes on chromosomes 8 and 19 and susceptibility to this entity [2]. Some studies have assessed the effect of microelements deficiency, and recently a few studies such as one performed in Iran have focused on iron deficiency, and have recommended the use of iron supplements [4–6]. Two recent studies in Iran and Thailand mentioned a lower frequency of febrile convulsions in patients with major thalassemia [7, 8].

In patients who have thalassemia major, iron is accumulated in the body as a result of ineffective erythropoiesis and frequent blood transfusions. A few studies had reported lower incidence of febrile seizures in children with major thalassemia; therefore, iron accumulation might have a protective or preventive role in the occurrence of febrile convulsions in patients with major thalassemia [7].

In one study in Thailand on 430 patients with thalassemia aged 6 months to 10 years, the researchers found that the frequency of febrile convulsion was 4.4 times lower in children with thalassemia compared with the general population. In the mentioned study, the annual incidence of febrile convulsion was 1.1/1000 individuals in patients with thalassemia, compared with 4.8 in the normal population [7].

In a study performed in Iran comparing patients with febrile convulsion and febrile patients without convulsion, no significant association was found between anemia and the incidence of febrile convulsions [9].

Major thalassemia is more frequent in southwest of Iran (Khouzestan) than that of the other provinces because of the more frequency of thalassemia genes in the general population and consanguineous marriages in this area of Iran. To the best of our knowledge, no study has been performed to measure the frequency of febrile convulsions in patients with major thalassemia in Khouzestan, southwest Iran. We aimed to assess the relative frequency of febrile convulsion in children with major thalassemia comparing to a group of healthy children to theorize that higher serum levels of Iron in children with major thalassemia might have a protective role against febrile convulsions in these children.

Patients and methods

This cross sectional study was performed in Jundishapur University of Medical Sciences, Ahvaz, southwest Iran from April 2010 to April 2011.

Data were collected using related questionnaires. We enrolled 363 patients with major thalassemia over the age of 5 who referred to the thalassemia clinics of Shafa, Abuzar, and Naft Hospitals in Ahvaz as the case group. The patients were confirmed as having major thalassemia based on their history, medical records, blood tests, and hemoglobin electrophoresis. In the control group, 363 healthy children with an age range of 4–7 years who had referred to healthcare centers in Ahvaz for growth monitoring and vaccination were also selected after informing their parents about the aims of the study.

A trained nurse interviewed the participants regarding their demographic information, history of febrile convulsion, age of the initial onset of convulsion, number of recurrent febrile convulsions, history of febrile convulsions in first degree relatives, familial history of epilepsy, developmental condition, history of related hospital admission, type of febrile convulsion, history of anti-convulsant intake, and history of hypoparathyroidism. A precise history regarding the patients' febrile convulsion and their medical records was taken.

In order to prevent bias, the control group was selected from healthy children who had only referred to the healthcare centers for routine growth assessment.

If the patients were admitted to the hospitals, their medical records were used to diagnose febrile convulsion. If the medical records were unavailable, febrile convulsion was confirmed based on a previous diagnosis made by a pediatrician or family physician.

Febrile convulsion was considered if the seizures were accompanied by fever and no signs of other diseases such as meningitis, encephalitis, and colitis or history of psychomotor retardation, epilepsy, or brain tumor were present.

In the case group, we included patients with beta thalassemia major who had experienced febrile convulsion, neither have psychomotor retardation nor suffer from meningitis, encephalitis, and colitis during seizures, with the informed consent of their parents. Patients whose parents were incapable of remembering the accurate history of convulsions were excluded from our study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in *a priori* approval by the institution's human research committee.

Statistical analysis was performed using SPSS version 16.0 statistical software (SPSS, Inc., Chicago, IL). χ^2, t, and Fisher's exact tests were used when appropriate. A biostatistician who was blinded to the study groups performed the statistical analysis.

Results

We enrolled to this study, 363 children aged more than 5 years with major thalassemia (169 boys, 194 girls) who were receiving blood as the patient group and 363 children without thalassemia aged 4–7 years (154 boys, 209 girls) who had referred to healthcare centers for routine health monitoring as the control group.

Of the 363 patients with thalassemia major, 4 patients were excluded from the study because of psychomotor retardation (PMR), suspected shivering, suspected breath holding, and history of convulsion at the age of 10 months and long hospital stay. In the control group, 6 children were excluded for reasons such as having meningitis ($n = 1$), shigellosis ($n = 2$), and suspected shivering ($n = 3$).

Among the children with thalassemia major, 4/359 (1.1%) had a history of febrile convulsion as compared with 14/357 (3.9%) children in the control group ($P = 0.017$, χ^2 test). Among the four children in the case group who had a history of febrile convulsion, 3 (1.8%) were girls and 1 (0.5%) was a boy ($P = 0.25$), compared to 9 (5.8%) boys and 5 (2.4%) girls in the control group ($P = 0.09$).

In overall, 18 children had a history of febrile convulsion in both groups including 12 (66.7%) boys and 6 (33.3%) girls.

The mean (±SD) age of the initial onset of febrile convulsion in both groups was 20.26 (±9.1) months (range: 6–36 months). The mean (±SD) age of the initial onset of febrile convulsion in the case and control groups were 22.5 (±12.4) and 19.7 (±8.4) months, respectively ($P = 0.59$, t test).

Of the 4 children who had experienced febrile convulsion in the case group, 3 (75%) had experienced the simple type of febrile convulsion while 1 (25%) had experienced the complex type. In the control group, 11 (78.6%) children had had the simple febrile convulsion, while 3 (21.4%) had had the complex type ($P = 0.99$, Fisher's exact test).

Discussion

According to existing evidence, the complex balance between the activities of the glutamate-GABA systems plays an important role in controlling convulsions. Iron deficiency probably reduces the activity of GABA systems leading to the occurrence of convulsion [7]. Therefore, Iron overload may reduce the incidence of convulsion by increasing the activity of the GABA system which is an inhibitory neurotransmitter in the brain.

Our results show that the occurrence of convulsion was significantly lower in patients with thalassemia major (1.1% *vs.* 3.9% in the case and control groups, respectively) and this finding further suggests that children with thalassemia major may have increased serum iron levels and such increased serum iron levels may has a protective role against febrile convulsions.

Our findings are consistent with previous studies. In a similar study comparing the occurrence of febrile convulsion in children with thalassemia major and healthy controls, the researchers found that the incidence of febrile convulsion was 2.5 times more in the control group. In the mentioned study, the frequency of febrile convulsion was 0.9% and 2.3% in the case and control groups, respectively [8]. In another report, the incidence of febrile convulsion was 4.4 times higher in the normal population compared with patients with thalassemia [7].

It is hypothesized that in patients with thalassemia, iron is accumulated in the body as a result of ineffective erythropoiesis and frequent blood transfusions. Therefore, iron accumulation might have a protective and preventive role against the occurrence of febrile convulsion in patients with major thalassemia. Some researchers have demonstrated the above hypothesis by assessing serum iron and ferritin levels in patients suffering from seizures and those without a history of seizure. In one study, the researchers found that serum ferritin levels were significantly lower in 75 children with first febrile convulsion compared with age and sex matched controls suffering febrile illnesses without convulsions [4].

Vaswani and colleagues compared 50 patients aged 6 months to 6 years with first febrile convulsion and 50 age-matched febrile patients without seizure and found that the serum ferritin levels were significantly lower in patients with first febrile seizure [5].

However, Amirsalari and co-workers did not find a significant difference in serum ferritin, hemoglobin, and MCH levels between 9 months to 5-year-old patients with first seizure and the control group [10]. Moreover, in another study comparing the plasma ferritin levels in 90 children with febrile convulsion (case group) and 90 febrile children without seizure (control group), the researchers did not find a significant relation between plasma ferritin and TIBC levels between the case and control groups [11].

In addition, Momen and colleagues found a positive association between iron deficiency and the first febrile convulsion in children in a case–control study [6]. In contrast, a study comparing 100 febrile patients with 100 febrile patients without seizure showed no association between anemia and the incidence of febrile convulsion [9]. We have no definite explanation for these discrepancies between studies but different methodology of studies may explain different results.

Although our study and some other studies indicate the preventive effect of serum iron levels on the occurrence of febrile convulsion in children; other controversial reports from studies with different study design, patients' status, serum ferritin and zinc levels, and different physiological conditions have led to inconsistent findings. Therefore, further complementary studies need to be performed in order to accurately determine the role of serum iron in preventing seizures.

Our study had some limitations. The sample size was less than the desired amount because the number of patients with thalassemia major receiving blood transfusion across Ahvaz was less than the determined number in our sample size calculation. The other major limit of our study was that its design was retrospective and therefore we could not measure the serum iron level at the seizure time to demonstrate increased or decreased serum iron levels at the seizure occurrence.

Conclusion

Results of our study indicated that children with major thalassemia had a less frequency of febrile convulsions than normal children. Children with thalassemia major may have increased serum iron levels and such elevated serum iron levels may have a preventive role against the occurrence of febrile convulsions.

Authors' contributions/Wkład autorów

AAM – study concept and design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content. RAM – study concept and design, data gathering, analysis and interpretation of data, drafting of the manuscript. BKD – study concept and design, analysis and interpretation of data, critical revision of the manuscript for important intellectual content. MF – data gathering, analysis and interpretation of data, drafting of the manuscript.

Conflict of interest/Konflikt interesu

None declared.

Financial support/Finansowanie

This study was supported by research affairs of Ahvaz Jundishapur University of Medical Sciences.

Ethics/Etyka

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

Acknowledgements/Podziękowania

This study was based on the thesis of Mohsen Fathi with registration number of D/571. We would like to thank Azadeh Payami and Manizheh Chahardah Cherik who helped in data collection, and Ali Payami who helped in writing and editing this manuscript. We also thank the patients and their parents for their help and cooperation.

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