Febrile Seizures in Thalassemic Patients in Babylon Teaching Hospital for Maternity and Children

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Abstract

Febrile seizures are the most common seizures in children. Their incidence is (2-5 %). To date, the pathophysiology of febrile seizures is unknown. But several hypotheses have been supposed that it may relate with plasma iron level. Such low risk in thalassemic patients whose plasma iron level is high could give some clues to this hypothesis.

Aim of the Study: Determine the risk of febrile seizure in thalassemic patients in comparism with the corresponding control group.

Patients and Methods: This case –control study was conducted on one hundred fifty patients with thalassemia major between six month and six years of age who were visit Babylon center for inherited blood diseases in the Teaching hospital for maternity and children from April 2019 to January 2020. All medical records of thalassemic patients were thoroughly reviewed and the occurrence of febrile seizures are interviewed and compared with the control group .The children in the control group are neither thalassemic nor has iron deficiency anemia.

Results: Febrile seizure was detected in one case of the thalassemic group (0.66%) versus six cases (4%) of the control group. The risk of febrile seizure in the control group was 6 times more than that in the thalassemia group, which was statistically significant (P =0.036).

Conclusion: The risk of febrile seizures in thalassemic patients was (0.16) that of the general children population. Thus, iron overload may be a major factor involving the brain metabolism that prevents febrile seizures.

Keywords: *Patients, Children, Maternity, Thalassemic , Febrile Seizures*

Introduction

Febrile seizures are seizures that occur between the age of 6 and 60 mo with a temperature of (38oC) or higher, that are not the result of central nervous system infection or any metabolic imbalance, and that occur in the absence of a history of prior afebrile seizures [(1)]. Febrile seizures are the most common cause of convulsions in children and a frequent cause of emergency hospital admissions (2) Between 2% and 5% of neurologically healthy infants and children experience at least one, usually simple febrile convulsion [(1)]. Febrile seizures are typically divided into two types: 'simple' and 'complex.' A simple FS is a generalized seizure (without focal features) which lasts less than [(15)] minutes and occurs only once during a 24-hour period of fever in a neurologically normal child[(3)]. The pathophysiology of febrile seizures remains unclear. It is generally believed that FS is an age-dependent response of the immature brain to fever[(4)].This postulation is supported by the fact that most (80-85%) of febrile seizures occur between (6) months and (3) years of age, with the peak incidence at

(18) months(7,8). A positive family history for febrile seizures can be elicited in(25-40)% of children with febrile seizures. Familial clustering studies indicate a doubling of risk in children when both parents, rather than one parent, had febrile seizures [5]. Studies show a higher concordance rate in monozygotic as compared to dizygotic twins. Although there is clear evidence for a genetic basis, the precise mode of inheritance is unclear. Most studies suggest that the mode of inheritance of susceptibility to febrile seizures is mostly polygenic and rarely autosomal dominant [6]. Certain ion channels in the brain are temperature sensitive and may generate fever-associated synchronized neuronal activity [7]. There is also evidence to suggest that hyperthermia-induced hyperventilation and alkalosis may play a role [8]. Children with febrile seizures have been reported to have significantly low levels of plasma ferritin, suggesting a possible role of iron insufficiency[9].Also low ferritin level or low serum iron, was associated with increased risk of febrile seizures [10]. Iron also plays specific roles in the central nervous system (CNS). It is involved in myelin formation , as well as in the production of several neurotransmitters such as dopamine , norepinephrine and serotonin , and generation of GABA activity . In addition, iron overload is implicated as a cause of neuronal death [11]. The incidence of febrile seizures in thalassemic children is significantly lower, and iron overload may be a major factor that prevents their occurrence[12] [13]

Aim of the Study

To determine the risk factors of febrile seizure in thalassemic patients in comparison with the corresponding control group, to prove that high iron storage is a protective factor against febrile seizure.

Patients and Method

This case-control study was conducted on one hundred fifty patients with thalassemia major between six months to six years of age, who were attending the center for inherited blood diseases in Babylon Teaching hospital for maternity and children from the first of April 2019 to the end of January 2020. To avoid bias, just one child from each family was selected & interviewed about. All medical records of thalassemic patients were thoroughly reviewed. The children who were diagnosed as thalassemic patients on the basis of clinical manifestations, complete blood count and hemoglobin electrophoresis were studied. We summarized data regarding percentage of hemoglobin, MCV, MCH, MCHC, RDW, type of thalassemia, and serum ferritin level . The control group consisted of one hundred fifty non-thalassemic patients selected at the same hospital with similar sex and age distribution as the cases. Exclusion criteria for both groups were history of any brain lesion, mental retardation, cerebral palsy, , family history of epilepsy and history of afebrile seizure. Another exclusion for control group if there CBCs and blood films show a hypochromic microcytic anemia with a high RDW, and reduced RBC it means they have a presumptive diagnosis of iron deficiency anemia .

This exclusion made because of many researches that found iron deficiency anemia is a risk factor for febrile seizure to guarantee better comparism. Questionnaires containing demographic data and past history of febrile seizure, onset of febrile seizure, hospitalization, number of episodes, family history of febrile seizure , history of afebrile seizure and its etiology were included. More information to differentiate febrile seizure from shivering, temper tantrums, breath holding spells, and other types of seizures has been taken if parents reports history of seizure like activity . We exclude (38) controls from the study because they have a presumptive diagnosis of iron deficiency anemia , two others have family history of epilepsy and one case has history of afebrile seizure.

Data Analysis

Statistical analysis was carried out using SPSS version 18. Categorial variable were presented as frequency and percentages. The Pearsons, Chi-square test (X2) test was used to determine the

associations between two groups . A P-value of <0.05 was considered as statistically significant. Logistic regression analysis was also done for the analysis by using Fishers exact test.

Results

One Hundred fifty thalassemic patients range from six months to six years old , and one Hundred fifty non thalassemic children as a control group were evaluated in this study. Table (1) shows seventy eight thalassemic patients (52%) were male, and seventy two (48%) were female, the sex distribution was comparable with control group in which eighty one (54%) were males and sixty nine (46%) were females and the small differences are statistically not significant.

Table (1): distribution of thalassemic and control groups by sex .

Sex	Cases		Controls	
	Number	%	Number	%
Male	78	52	81	54
Female	72	48	69	46
Total	150	100	150	100

P-value = 0.729

Table (2) shows The age distributions are nearly similar between the two groups and the little differences are statistically insignificant .

Table (2) distribution of thalassemic and control groups by age

Age	Cases		Controls	
	Number	%	Number	%
6 months-2 years	38	25.33	40	26.66
2 years -4 years >	52	34.66	49	32.66
4 years - 6 years >	60	40	61	40.66
Total	150	100	150	100

P-value = 0.928

Eighty one cases were from rural areas (54%) versus seventy two controls (48%).The residence distribution among two groups shown in table (3)

Table (3) : Distribution of of thalassemic and control groups by residence.

Residence	Cases		Controls	
	Number	%	Number	%
Rural	81	54	72	48
Urban	69	46	78	52
Total	150	100	150	100

P-value = 0.729

Febrile seizure was detected in (1) case (0.66%) and (6) cases (4%) in the thalassemic and control groups respectively. FS in the control group was (6) times more than that in the thalassemic group , which was statistically significant (P = 0.036) as in table (4).

Table (4) : comparison between FS in the thalassemic and control groups.

Risk	Cases	Controls
Febrile seizure	1	6
No febrile seizure	149	142
Total	150	150

P-value = 0.036

The data of patient with thalassemia and FS with history of admition to our hospital have been reviewed. The information are shown in table (5).

Table (5): Details of the case with thalassemia and FS .

Data	Variable
Age , sex	(3) years ,male
Onset of seizure	(1) year old
Hospitalization ,period of it	Yes, (2)days
CSF exam	Negative
Biochemistry (serum calcium and blood sugar)	Normal
Temperature	39 C^{O}
Recurrence, number of episodes	Yes, once
Age of recurrence	(2)years and (4) months
Prophylaxis	No

Three controls with FS were males and three were females. Four controls with FS have family history of FS while two have no family history of FS.

More informations about the controls with FS are shown in table (6).

Table (6): Details of the children with FS in the control group.

Variable	Case I	Case II	Case III	Case IV	Case V	Case VI
Sex	**Female**	**Female**	**Female**	**Male**	**Male**	**Male**
Age (months)	24	30	48	14	12	20
Number of attack(s)	1	3	1	2	1	1
Time of seizure(s) (months)	24	18, 24&27	48	10&13	12	20
Family history of FS	Yes	No	No	No	Yes	No
Hospitalization	Yes	Yes in the 1st (2) attacks	Yes	Yes in both attacks	Yes	Yes
Prophylaxis	____	no	____	no	____	____

Discussion

In accordance with the present study, the risk of febrile seizures in thalassemic patients is lower than that of control group.

The results of this study are consistent with the results of a previous study performed by Auvicha in Thailand[13]. They reviewed (430) patients with β-thalassemia. Three of them had febrile seizure and the rate of febrile seizure was 4.4 times less than the normal population.

In another study by Dauod, (Department of Pediatrics, Jordan University of Science and Technology) it was shown that serum ferritin was significantly lower in cases with febrile seizure compared to individuals in the control group[14],but in another study, Hartfiel (Department of Pediatrics, University of Alberta, Canada) showed that the rate of Iron deficiency anemia in patients with febrile seizure was two times less than its rate in febrile patients without seizure[15].

The explanations to support the conclusion that said " high iron storage might probably act as a protective factor against febrile seizure" illustrated below.

It has been known that the complex balance between glutamate-GABA systems plays a crucial role in controlling convulsions. Hyperthermia was reported to reduce the activity of the GABA system while increasing the activity of glutamate via the decrease in glutamate reuptake and therefore inducing the up-regulation of glutamate receptor and resulting in a convulsion.

Iron has been reported to correlate with various functions of the nervous system especially neurons for a long time[16,17].Iron deficiency was also reported to reduce the GABA metabolism via the alteration of glutamate decarboxylase and GABA transaminase enzymes [18,19].

Therefore, the effect of iron on febrile seizures could possibly be due to iron overload increasing the activity of GABA system which is the main inhibitory neurotransmitters in the brain. This system is particularly important in suppressing seizures . In the case of febrile seizure in the thalassemic group , there were no data on the serum ferritin level at the time of febrile seizure but the nearer levels of serum ferritin before and after the event are (1420) nanogram/ml and (1575) nanogram/ml respectively . Taking into account the prevalence of iron deficiency anemia in children and the relationship between febrile seizure and the serum ferritin level, as shown in the present and similar previously study, it could be suggested that iron supplement and treatment of iron deficiency anemia could reduce the corresponding risk of febrile seizure.[1,10]

Conclusions

1. The risk of febrile seizures in thalassemic patients was less than that of the controls.

2. Iron overload may be a factor involving the brain metabolism that prevents febrile seizures.

Recommendation:

1. Further similar studies are recommended, better to be a multicenter studies which will include larger sample size about the risk of febrile seizure in thalassemic patients and the effect of iron overload in prevention of febrile seizure.

2. Therapy for those with iron deficiency anemia could decrease the risk of seizure recurrence and will prevent other sequelae of iron deficiency in the young children.

3. Special attention for thalassemic patients presented with fever and convulsion to exclude CNS infection and other potential causes as the frequency of FS are very low in those patients.

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Conflict of Interest: None to declare.

Ethical Clearance: "All experimental protocols were approved under the faculty of medicine and carried out in accordance with approved guidelines".

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