Incidence of Febrile Seizures in Thalassemic Patients

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Background : *Febrile seizures are the most common seizures in children. Their incidence is 2-5 % or 4.8/1000 person-years. To date, the pathophysiology of febrile seizures is unknown. But several hypotheses have been purposed that it may relate with plasma iron level. Such low incidence in thalassemic patients whose plasma iron level is high could give some clues to this hypothesis.*
Patients and Method : *Four hundred and thirty thalassemic patients from the hematology clinic at two hospitals in Northeastern Thailand were consecutively enrolled between Febuary 2003 and January2004. The authors reviewed all the medical records of the patients and interviewed their parents for occurrence of febrile seizures.*
Results : *The patients included 208 males and 222 females with an age ranged of 6 months to 10 years (mean = 6.36 years). Twenty patients (4.7%) had siblings who had febrile seizures. There were 3 episodes out of 2,734 person-years. The incidence was 1.10 per 1,000 person-years (95% CI: 0.23 to 3.20). This was statistically lower than that of the general population (p-value = 0.002). Therefore, the rate in thalassemic patients was 4.4 times less than that of the general population (95% confidence interval: 1.4 to 22.6).*
Conclusions : *The incidence of febrile seizures in thalassemic patients was very low compared to that of the general children population. Thus, iron overload may be a major factor involving the brain metabolism that prevents febrile seizures.*

Keywords : *Febrile seizures, Thalassemia, Brain metabolism*

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Febrile seizures are the most common seizures in children[1]. Their incidence ranged between 2-5%[1-4] or 4.8/1000 person-years[5]. The pathophysiology of febrile seizures is unknown[6-8]. However, there are several hypotheses stating that it might relate to plasma iron level[9-11]. This was based on the theoretical background that iron plays a major role in the metabolism of neurotransmitter such as monoamine, aldehyde oxidase. This neurotransmitter was decreased in iron deficiency anemic patients[12].

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Besides, to date there are few studies that accesses to the role of plasma iron level in febrile seizures. Among these, the results were controversial. Kobrinsky et al concluded that iron deficiency may be a protective mechanism of febrile seizures[9]. In contrast, Piscane et al reported that in iron deficiency anemic patients, there was a significantly higher incidence of febrile seizures compared with the control group[10]. Recently, Daoud et al found that plasma ferritin in the first attack of febrile seizures was significantly lower than in the control group[11].

There is general acceptance that moderate to severe thalassemic patients almost always have

iron overload[12]. But, to the authors' knowledge, no study has reported the rate of febrile seizures among thalassemic patients. So the study for febrile seizures in these patients would provide more information to this issue.

The present study determined such a rate and compared it with the corresponding rate in the general population.

Patients and Method

Patients

The present study was approved by the Institutional Review Board of Khon Kaen Medical Center. All thalassemic patients aged 6 months to 10 years who came to hematology clinics at Srinagarind and Kalasin hospital, Thailand between February 2003 and January 2004 were recruited. The authors excluded patients who had a history of central nervous system abnormalities such as tumors, cyst, abscess, mental retardation, intracranial hematoma and cerebral palsy. Informed consent was obtained from all of the patients' guardians.

Outcome and outcome measurements

All medical records of thalassemic patients were thoroughly reviewed. The authors summarised data regarding percentage of hemoglobin, type of thalassemia, history of central nervous system abnormalities, history of febrile seizures and family history of febrile seizures.

The authors defined febrile seizures as an event in neurologically healthy infants and children between 6 months and 5 years of age, associated with a fever > 38°C, but without evidence of intracranial infection or a defined cause and with no history of prior afebrile seizures[13]. The children who were diagnosed as thalassemic patients were based on clinical manifestations, complete blood count and hemoglobin electrophoresis[14].

Then the authors interviewed the patients' parents about febrile seizures. If the parents reported that their children had febrile seizures, a pediatric neurologist would seek more information to differentiate them from shivering, temper tantrums, myoclonus, CNS infection, and other types of seizures. This interview also sought information about the onset of seizures, the number of episodes, the place of diagnosis, the doctor who made the diagnosis, the method of treatment, the courses of seizures and the results of treatment. From this information, the authors directly contacted the doctors who made the diagnosis to confirm and find out more information by reviewing the histories of the patients.

The incidence of febrile seizures in the general children population was obtained from Verburgh et al[5]. This was the only available source for such information.

Statistical methods

The rate of febrile seizures was calculated as an incidence density per 1,000 person-years. It's confidence intervals were estimated based on poisson distribution. STATA (StatCorp, College Station, TX) was used for all statistical analysis.

Results

A total of 431 thalassemic patients were recruited. One case with porencephalic cyst was excluded. The 430 eligible patients contributed 2,734 person-years as duration of observation.

Baseline characteristics of the patients are shown in Table 1. About one third were aged was less than 5 years. Most of them, 65.81%, were Hb E beta thalassemia. There were 6 patients who gave a history of febrile seizures but when contacting the doctors who made the diagnosis, it was found that 2 cases were upper respiratory tract infection with shivering. One was a temper tantrum without fever. Only 3 pa-

Table 1. Baseline characteristics

Characteristics	n (%)
Sex	
Male	208 (48.4%)
Female	222 (51.6%)
Age	
6 months to 5 years	167 (38.8%)
over 5 to 10 years	263 (61.2%)
Type of thalassemias	
Hb H disease	36 (8.4%)
Hb E beta thalassemia	283 (65.81%)
Homozygous beta thalassemia	7 (1.6%)
Beta thalassemia heterozygote	6 (1.4%)
Hb E homozygote	2 (0.5%)
Hb E heterozygote	4 (0.9%)
Hb EA Bart's disease	27 (6.3%)
Hb H disease with Hb Constant Spring	41 (9.5%)
Hb EA Bart's and Constant Spring	17 (4%)
Hb EF Bart's disease	4 (0.9%)
Homozygous Hb Constant Spring	3 (0.7%)
Family history of febrile seizures	
Yes	20 (4.7%)
No	410 (95.3%)

Table 2. Details of thalassemic patients with febrile seizures

	Case I	Case II	Case III
Sex	male	male	female
Age	4 years	5 years	6 years
Type of thalassemia	Hb E beta thalassemia	Hb E beta thalassemia	Hb E homozygote
Family history of febrile seizures	No	No	No
Age of the first attack	10 months	2 years	2 years
Number of episode	1	1	1
The last episode	10 months	2 years	2 years
Prophylactic drug	Phenobarbital	Diazepam	none

tients had true febrile seizures, one episode for each patient. Their histories are shown in Table 2.

Thus, there were 3 episodes in 2,734 person-years giving an incidence of 1.10 per 1,000 person-years (95% confidence interval: 0.23 to 3.20) (Table 3). This was statistically lower than that of the general population (p-value = 0.002). That is, the incidence rate difference was 3.7/1,000 person-years (95% confidence interval: 1.6 to 5.9). In other words, the rate in thalassemic patients was 4.4 times less than that of the general population (95% confidence interval: 1.4 to 22.6).

Discussion

In accordance with the present study, the incidence of febrile seizures in thalassemic patients is lower than that of the general population. To the authors' knowledge, this is the first study that has reported evidence of association between thalassemia which was presumably iron overload and febrile seizures. The findings support what has been concluded by Piscane and Daoud[10,11]. The authors concluded that iron overload in thalassemic patients is likely responsible as a protective factor of febrile seizures. The following are the explanations to support this conclusion.

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[15-17]. Iron chelators, desferrioxamine and prochlorperazine, could produce a disturbance of serotoninergic and noradrenergic systems[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.

The authors acknowledge that this is a descriptive study, involving interviewing, that may lead to recall bias. The authors tried to minimize this by selecting only young patients aged 6 months to 10 years. Febrile seizures are very terrifying events that the guardians can hardly forget. The present study didn't perform an iron study to elicit iron overload. But only patients who came to the hematology clinic who had moderate to severe thalassemia and had an iron overload were selected[20]. In addition, we used the rate of febrile seizures from the Netherlands was used as the reference rate for the general population[5]. This could yield different results if the rate of our own setting was used. The authors did this due to the lack of data in our setting. But we believe that our conclusion will not change. To get an accurate magnitude of the rate difference, a further cohort study should be carried out.

The authors concluded that the incidence of febrile seizures in thalassemic patients was very low compared to that of the general children population. Thus, iron overload may have a major factor that

Table 3. Incidence of febrile seizures comparing between thalassemic patients with general population

Group	Number of patients	Number of person-years	Incidence Irate/1,000 person-years	95% CI
Normal	23,801	6,195	4.8	3.27 to 6.91
Thalassemia	430	2,734	1.10	0.23 to 3.20

Incidence rate difference = 3.7/1,000 person-years (95% confidence interval: 1.6 to 5.9);
Incidence rate ratio = 4.4 (95% confidence interval: 1.4 to 22.6);
p-value = 0.002

affects brain metabolism and thereby prevents febrile seizures.

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อุบัติการณ์ไข้ชักในผู้ป่วยธาลัสซีเมีย

ภารดี เอื้อวิชญาแพทย์, ณรงค์ เอื้อวิชญาแพทย์, อรุณี เจตศรีสุภาพ, บัณฑิต ถิ่นคำรพ, สกุลรัตน์ ศรีโรจน์, ทิวาวรรณ ปิยกุลมาลา, ศิริอร พหลภาคย์, จินตนาภรณ์ วัฒนธร

ภาวะไข้ชักเป็นการชักที่พบได้บ่อยที่สุดในเด็ก มีอุบัติการณ์ร้อยละ 2-5 พยาธิสรีรวิทยาและพยาธิกำเนิดของไข้ชักที่แท้จริงยังไม่ทราบแน่ชัด แต่มีสมมุติฐานที่คาดว่าอาจมีความสัมพันธ์กับระดับธาตุเหล็กในเลือด

เป็นที่ทราบกันดีว่าในผู้ป่วยธาลัสซีเมีย จะมีธาตุเหล็กเกินร่วมด้วยเสมอ การศึกษาครั้งนี้ทำในผู้ป่วยธาลัสซีเมียที่มาคลินิคโรคเลือด โรงพยาบาลกาฬสินธุ์และโรงพยาบาลศรีนครินทร์ในระหว่างเดือนกุมภาพันธ์ 2546ถึงมกราคม 2547 จำนวน 430 ราย โดยผู้ป่วยจะได้รับการทบทวนแฟ้มประวัติผู้ป่วยและสัมภาษณ์ประวัติการเป็นไข้ชักโดยละเอียด

ผลการศึกษาพบว่ามีผู้ป่วยเป็นชาย 208 คน หญิง 222 คน อายุเฉลี่ย 6.36 ปี (6 เดือนถึง 10 ปี) มีประวัติพี่น้องเป็นไข้ชัก 20 คน (ร้อยละ 4.7) มีการเกิดไข้ชัก 3 ครั้ง ใน 2734 คน-ปี คิดเป็นอุบัติการณ์ 1.10/1000 คน-ปี (ช่วงเชื่อมั่นร้อยละ 95 เท่ากับ 0.23 ถึง 3.20) ซึ่งต่ำกว่าเด็กปกติอย่างมีนัยสำคัญทางสถิติ(p = 0.002) กล่าวคือมีอุบัติการณ์ไข้ชักในคนปกติเป็นประมาณ 4 เท่าของผู้ป่วยธาลัสซีเมีย (ช่วงเชื่อมั่นร้อยละ 95 เท่ากับ 14 ถึง 22.6) อุบัติการณ์ไข้ชักในผู้ป่วยธาลัสซีเมียพบได้น้อยมากเมื่อเทียบกับประชากรปกติ ทั้งนี้อาจสนับสนุนสมมุติฐานที่ว่าระดับของธาตุเหล็กในเลือดที่สูงมีผลต่ออัตราเมแทบอลิซึมของสมองซึ่งป้องกันการเกิดไข้ชักได้