소아 뇌전증 환자에서 발열이 동반된 경련을 하는 것과 저 이온화 마그네슘 혈증과의 관련성

고려대학교 병원 소아청소년과

서선희 · 김경주 · 변정혜 · 은소희 · 은백린 · 김건하

Association of Low Serum Ionized Magnesium Level with Fever-Triggered Seizures in Epileptic Children

Purpose: Several studies have shown that magnesium plays an important role in modulating N-methyl-D-aspartate (NMDA)-related seizures by blocking NMDA ion channel receptors. Clinicians usually measure total serum magnesium levels instead of biologically active ionized magnesium levels. We compared the serum ionized magnesium (iMg^{2+}) level between epileptic children with and without a history of fever-triggered seizure (FTS).

Methods: All epileptic children who visited the outpatient clinic or pediatric emergency department at Korea University Guro Hospital between January 2015 and July 2017 were included. Only epileptic children aged 1–8 years who were newly diagnosed within 2 years were included.

Results: There were 12 children with FTS and 16 without FTS. Median serum iMg^{2+} level was 0.93 (0.85–1.14, quartile) mEq/L. Serum iMg^{2+} level was significantly lower in epileptic children with FTS (0.86 mEq/L) compared to those without FTS (1.10 mEq/L) ($P=0.005$). No difference was noted in clinical variables between the two groups. Lower serum iMg^{2+} level significantly increased the risk of having FTS in epileptic children based on multivariable logistic regression analysis (odds ratio [OR]=0.028).

Conclusion: Serum iMg^{2+} level was significantly lower in epileptic children with FTS than in those without FTS. Measurement of biologically active serum iMg^{2+} level could be considered in epileptic children with recurrent FTS. A large-scale prospective study is warranted.

Key Words: Epilepsy, Magnesium, Febrile convulsion, Child

Sunny Suh, MD, Kyungju Kim, MD, Jung Hye Byeon, MD, PhD, So-Hee Eun, MD, PhD, Baik-Lin Eun, MD, PhD, Gun-Ha Kim, MD, PhD

Department of Pediatrics, Korea University College of Medicine, Seoul, Korea

This article was presented at the annual conference of the Korean Pediatric Society at fall, 2017.

Submitted: 23 July, 2018

Revised: 20 September, 2018

Accepted: 27 September, 2018

Correspondence to Gun-Ha Kim, MD, PhD
Department of Pediatrics, Korea University College of Medicine, Gurodong-ro 148, Guro-gu, Seoul 08308, Korea
Tel: +82-2-2626-1114, Fax: +82-2-2626-1599
E-mail: gunhaaa@korea.ac.kr

Introduction

Magnesium is an essential mineral involved in a variety of physical functions¹⁾ and diseases²⁻⁴⁾. Several studies have shown that magnesium plays an important role in modulating N-methyl-D-aspartate (NMDA)-related seizures by blocking NMDA ion channel receptors, and has been an emerging research subject in the past few decades⁵⁻⁷⁾. Several controlled studies have shown a relationship between magnesium and seizures⁸⁻¹⁰⁾. Use of magnesium sulfate in epilepsy, febrile seizures, infantile spasm, or refractory status epilepticus has shown some efficacy¹¹⁻

¹⁴⁾. Some epileptic children are prone to fever-triggered seizures (FTSs), even in the absence of genetic risk.

Clinicians usually measure total serum total magnesium levels instead of serum ionized magnesium (iMg^{2+}) levels, knowing that the total magnesium level in the body can represent the ionized magnesium status in normoproteinemia. However, biologically active iMg^{2+} was not reflected upon analysis of total magnesium in 25% of the patients even with normal albumin level¹⁵⁾. Therefore directly measuring the active form of magnesium is more accurate. Serum iMg^{2+} is the physiologically active form of magnesium, and plays a key role in neurotransmission within the nervous system. Thus, we compared serum iMg^{2+} levels between epileptic children with and without a history of FTS.

Materials and Methods

All epileptic children who visited the outpatient clinic or pediatric emergency department at Korea University Guro Hospital between January 2015 and July 2017 were included. To minimize the bias from other factors such as long term anti-epileptic drug use or other underlying disease or environmental factors, only epileptic children newly diagnosed within 2 years were included. We limited the study patient age to 1–8 years, as this group is prone to febrile seizures. We divided all patients into groups with and without at least 1 FTS. A total of 32 patients were initially included. Of these, we excluded four: two with Dravet syndrome, one with protocadherin 19 (PCDH19) epilepsy, and one with brain tumor. A total of 28 patients were finally included: 12 with FTS and 16 without FTS. This study was approved by the institutional review board of the Korea University Guro Hospital (2018GR1412).

1. Statistical analyses

Statistical analyses were performed with SPSS version 19 (SPSS Inc., Chicago, IL, USA). As the number of patients was small, Fisher's exact test and the Mann-Whitney U test were used for comparisons between 2 groups, with significance level $P < 0.05$. Median values and interquartile ranges were used, and multivariate logistic regression was used with adjustment for other co-factors, such as age, sex, and serum sodium level. Thereafter, in order to compensate for the fewer seizures likely to occur during the relatively short observation period, the rate of seizure frequency per observation period in each group was calculated and compared with the t-test.

Results

1. Patient demographics

A total of 12 epileptic children with FTS and 16 without FTS were included. Patient demographics are shown in Table 1. The 28 patients included 15 males and 13 females, with median age of 32 months at diagnosis; 13 had generalized epilepsy and 15 had focal epilepsy. Median serum iMg^{2+} level was 0.93 mEq/L (0.85–1.14, quartile). Serum ionized magnesium level was measured at emergency department in 12 patients (6 FTS, 6 non-FTS) and at outpatient clinic in 16 patients (6 FTS, 10 non-FTS) without significant difference ($P=0.783$).

2. Comparison between patients with and without fever-triggered seizure

Comparison of clinical variables and laboratory values is shown in Table 1 and Table 2. There were no differences in clinical va-

Table 1. Comparison of Clinical Variables according to the Presence of Fever-Triggered Seizures

	Total	With FTS (n=12)	Without FTS (n=16)	P-value
Male/Female, n	15 (53%)/13 (47%)	8/4	7/9	0.276
Age, months		57.03 (48.36–63.78)	67.90 (31.87–76.36)	0.57
Age at epilepsy diagnosis, months	32.00 (17.50–54.27)	35.30 (19.73–48.48)	32.00 (13.00–58.42)	0.837
Type of epilepsy				
Focal/Generalized	15/13	7/5	8/8	0.718
Underlying cause of epilepsy				
Genetic	1	0	1	1.00
Structural	10	5	5	
Unknown	17	7	10	
Antiepileptic drug use, n	1.0 [1.0;1.0]	1.0 [1.0;1.5]	1.0 [1.0; 1.0]	0.871
Follow-up duration since diagnosis, months		24.80 (10.23–30.53)	15.21 (11.90–22.60)	0.48
Total number of seizures since onset		7.5 (3–9)	3.5 (4–5)	0.16
Number of fever-triggered seizures		3.5 (1–4)	0	

Data are presented as number of patients or median (quartile) if not described.
FTS, Fever-triggered seizure.

riables between groups with and without FTS. The duration of the observation period and the number of total seizures after diagnosis were similar in both groups. Median serum iMg^{2+} level was significantly lower in those with FTS than in those without FTS (0.86 vs. 1.10 mEq/L, $P=0.005$), and serum sodium level was also significantly lower in those with FTS than in those without FTS group (138 vs. 139 mmol/L, $P=0.047$). There was no difference in total calcium and phosphorus level. Using multivariable logistic regression (Table 4), the odds ratio for FTS increased by 3.8 for every 0.1 mEq/L decrease in serum iMg^{2+} concentration ($P=0.028$). Serum sodium, sex, and age were not associated with increased risk of FTS ($P=0.10$).

Discussion

Median serum iMg^{2+} level was significantly lower in epileptic children with FTS as compared to those without FTS (0.86 vs. 1.10 mEq/L). The odds ratio for FTS increased by 3.8 for every 0.1 mEq/L decrease in serum iMg^{2+} concentration.

Reference ranges for normal serum iMg^{2+} level vary, with reported adult values of 0.7–1 mmol/L (1.5–2 mEq/L); however, limited data are available for pediatric patients. Based on some studies, we can approximate the pediatric reference range as 0.5–0.6 mmol/L (1–1.2 mEq/L)^{16–18}.

Magnesium is known to play an important role in modulating seizures by blocking NMDA ion channel receptors. Resting NMDA receptors are normally blocked by magnesium and activated by glutamate and glycine binding at the activation site, thereby releasing the magnesium. NMDA receptors can be more easily activated when there is a deficiency of magnesium^{19,20}. Isolated idiopathic hypomagnesemia, a familial condition caused by defective renal reabsorption of magnesium, can present as aphasia and generalized motor seizures in children⁸. Chronic magnesium deprivation in mice lowered the threshold of NMDA receptor-related seizures⁶. In addition, magnesium supplementation is reportedly effective in animal studies and several clinical situations. A single oral dose of magnesium inhibited NMDA-induced

convulsions in mice in a dose-dependent manner⁵. Magnesium supplementation had therapeutic effects in patients with refractory status epilepticus^{11,12,14}. Combining intravenous magnesium sulfate with adrenocorticotrophic hormone showed improved response to treatment in infantile spasms¹³.

Fever can be a trigger factor for the NMDA-related seizures. Pedder showed that NMDA receptor antagonists attenuated febrile seizures in epileptic chicks⁷. Our study results also suggested that lower serum iMg^{2+} level might be associated with FTS. Only one study reported no significant correlation between serum total magnesium level and febrile convulsions²¹. However, total magnesium concentration was measured, instead of biologically active serum ionized magnesium. About 1% of body stores of magnesium reside in extracellular fluid. Thus, it is reasonable to measure the free ionized form of magnesium because it is physiologically active and about half is found in extracellular fluid.

In our study, serum sodium level was also different between the groups (138.0 vs. 139.0, $P=0.047$), but was not a risk factor for FTS. As previously reported, hyponatremia-associated seizures are usually associated with levels <120 mmol/L¹⁹; only 1 patient had a seizure with a level of 120–124 mmol/L. Hyponatremia has been commonly reported in febrile seizures but was not predictive of seizure recurrence^{22,23}. Hyponatremia in febrile seizures could be due to an excess of arginine vasopressin associated with febrile illness itself²⁴.

As low total calcium level can lead to hypocalcemia induced seizure²⁵, we compared total calcium level between FTS and without-FTS group. There was no difference of total calcium

Table 3. Risk Factors for Fever-Triggered Seizures in Epilepsy

	Odds ratio	95% CI		P-value
		Lower	Upper	
Serum ionized magnesium level	3.819	1.153	12.647	0.028*
Serum sodium level	4.617	0.727	29.448	0.105
Sex	6.495	0.524	80.448	0.145
Age	0.976	0.911	1.046	0.495

Adjusted value with multivariable logistic regression, Variable entered in step 1: iMg , sex, age, Na. iMg 1 unit=-0.1, Na 1 unit=-1.

* $P<0.05$.

Table 2. Comparison of Laboratory Values according to the Presence of Fever-Triggered Seizures

	Total	With FTS (n=12)	Without FTS (n=16)	P-value
Sodium, mmol/L	139.00 (138.00–140.00)	138.00 (137.00–139.00)	139.00 (138.00–140.00)	0.047*
Ionized magnesium, mEq/L	0.93 (0.85–1.14)	0.86 (0.79–0.89)	1.10 (1.01–1.17)	0.005*
Total calcium, mg/dL	9.40 (9.17–9.72)	9.35 (9.20–9.72)	9.50 (9.00–9.73)	0.909
Phosphorus, mg/dL	4.90 (4.67–5.42)	4.85 (4.57–5.62)	4.95 (4.77–5.33)	0.802

Data are presented as median (quartile). Mann-Whitney U test

FTS, Fever-triggered seizure.

* $P<0.05$.

level in FTS and without-FTS group.

Limitations of our study should be mentioned. We did not consider the effect of anti-epileptic drugs on laboratory results including electrolytes. To minimize the effect of anti-epileptic drugs, we only included children newly diagnosed within 2 years. In addition, we did not compare baseline laboratory data because we recently started measuring serum iMg^{2+} instead of total magnesium levels. A larger number of patients in a prospective setting are required to overcome this limitation.

In conclusion, serum iMg^{2+} level was significantly lower in epileptic children with FTS than in those without FTS. Measurement of biologically active serum iMg^{2+} level could be considered in epileptic children with recurrent FTS. A large-scale prospective study is warranted.

요약

목적: 마그네슘은 N- 메틸 -D- 아스 파르 테이트(NMDA) 이온 채널 수용체를 차단하여 NMDA 관련 발작을 조절하는 데 중요한 역할을 한다는 것이 밝혀져 있다. 경련 시 총 혈청 마그네슘 수치를 주로 측정하고 있는데, 생물학적으로 활성화된 형태인 이온화 마그네슘 수치를 측정하는 것이 체내 마그네슘 양을 평가하기 위한 보다 적절한 방법이다. 이에 연구자는 뇌전증 환아들 중 발열과 동반된 경련 발작(FTS) 이 있었던 환아들과 없었던 환아들에서 혈청 이온화 마그네슘(iMg^{2+}) 수치를 비교해 보았다.

방법: 2015년 1월부터 2017년 7월까지 고려 대학교 구로 병원 외래 또는 소아 응급실을 방문한 뇌전증 환아들 중 2년 이내에 새로 진단 받은 1-8 세의 환아들을 대상으로 하였으며 열과 동반된 경련을 할 수 있는 뇌전증 증후군(드라베 증후군, PCDH19 뇌전증 증후군 등)은 제외하였다.

결과: 12명의 발열을 동반한 경련 발생군(FTS)과 16명의 발열을 동반한 경련이 없었던 군(without FTS)으로 분류를 하였으며, 혈중 iMg^{2+} 농도는 0.93 (0.85-1.14, quartile) mEq/L이었다. 혈청 iMg^{2+} 수치는 without FTS 군(1.10 mEq/L)에 비해 FTS군에서 0.86 mEq/L으로 유의하게 낮았다($P=0.005$). 두 군간의 임상 적 변수에는 차이가 없었다. 혈청 iMg^{2+} 수준이 낮을수록 다 변수 로지스틱 회귀 분석($OR=0.028$)에 근거하여 뇌전증 환아에서 FTS를 가질 위험이 유의하게 증가했다.

결론: 혈청 iMg^{2+} 수치는 FTS 가 있었던 뇌전증 환아들에서 FTS가 없었던 환아들보다 유의하게 낮았다. 반복적인 FTS를 가진 뇌전증 환아들에서 생물학적으로 활성화 형태인 혈청 iMg^{2+} 수치를 측정을 고려할 수 있겠으며, 앞으로 대규모 전향적 연구가 필요할 것으로 생각된다.

References

- 1) Vormann J. Magnesium: nutrition and metabolism. *Mol Aspects Med* 2003;24:27-37.
- 2) Burch GE, Giles TD. The importance of magnesium deficiency in cardiovascular disease. *Am Heart J* 1977;94:649-57.
- 3) Chaya A, Yoshizawa S, Verdelis K, Myers N, Costello BJ, Chou DT, et al. In vivo study of magnesium plate and screw degradation and bone fracture healing. *Acta Biomater* 2015;18:262-9.
- 4) Stahlmann R, Förster C, Shakibaei M, Vormann J, Günther T, Merker HJ. Magnesium deficiency induces joint cartilage lesions in juvenile rats which are identical to quinolone-induced arthropathy. *Antimicrob Agents Chemother* 1995;39:2013-8.
- 5) Decollogne S, Tomas A, Lecerf C, Adamowicz E, Seman M. NMDA receptor complex blockade by oral administration of magnesium: comparison with MK-801. *Pharmacol Biochem Behav* 1997;58:261-8.
- 6) Maurois P, Pages N, Bac P, German-Fattal M, Agnani G, Delplanque B, et al. Threshold to N-methyl-D-aspartate-induced seizures in mice undergoing chronic nutritional magnesium deprivation is lowered in a way partly responsive to acute magnesium and antioxidant administrations. *Br J Nutr* 2009;101:317-21.
- 7) Pedder SC, Wilcox RI, Tuckek JM, Johnson DD, Crawford RD. Attenuation of febrile seizures in epileptic chicks by N-methyl-D-aspartate receptor antagonists. *Can J Physiol Pharmacol* 1990;68:84-8.
- 8) Dharnidharka VR, Carney PR. Isolated idiopathic hypomagnesemia presenting as aphasia and seizures. *Pediatr Neurol* 2005;33:61-5.
- 9) Oladipo OO, Lesi FE, Ezeaka VC. Plasma magnesium and calcium levels in children with epilepsy in lagos. *Niger Postgrad Med J* 2007;14:26-9.
- 10) Chen BB, Prasad C, Kobrzynski M, Campbell C, Filler G. Seizures related to hypomagnesemia: a case series and review of the literature. *Child Neurol Open* 2016;3:2329048X16674834.
- 11) Zeiler FA, Matuszczak M, Teitelbaum J, Gillman LM, Kazina CJ. Magnesium sulfate for non-eclamptic status epilepticus. *Seizure* 2015;32:100-8.
- 12) Jang SH. Magnesium treatment for patient with refractory partial status epilepticus. *EC Neurology* 2017;87-91.
- 13) Zou LP, Wang X, Dong CH, Chen CH, Zhao W, Zhao RY. Three-week combination treatment with ACTH + magnesium sulfate versus ACTH monotherapy for infantile spasms: a 24-week, randomized, open-label, follow-up study in China. *Clin Ther* 2010;32:692-700.
- 14) Tan WW, Chan DWS, Lee JH, Thomas T, Menon AP, Chan YH. Use of magnesium sulfate infusion for the management of febrile illness-related epilepsy syndrome: a case series. *Child Neurol Open* 2015;2:2329048X14550067.
- 15) Johansson M, Whiss PA. Weak relationship between ionized and total magnesium in serum of patients requiring magnesium

- status. *Biol Trace Elem Res*. 2007 Jan;115(1):13-21.
- 16) Liu J, Yuan E, Zhang Z, Jia L, Yin Z, Meng X, et al. Age- and sex-specific reference intervals for blood copper, zinc, calcium, magnesium, iron, lead, and cadmium in infants and children. *Clin Biochem* 2012;45:416-9.
- 17) Hamed SA, Abdellah MM, El-Melegy N. Blood levels of trace elements, electrolytes, and oxidative stress/antioxidant systems in epileptic patients. *J Pharmacol Sci* 2004;96:465-73.
- 18) Greenway DC, Hindmarsh JT, Wang J, Khodadeen JA, Hébert PC. Reference interval for whole blood ionized magnesium in a healthy population and the stability of ionized magnesium under varied laboratory conditions. *Clin Biochem* 1996;29:515-20.
- 19) Halawa I, Andersson T, Tomson T. Hyponatremia and risk of seizures: a retrospective cross-sectional study. *Epilepsia* 2011;52:410-3.
- 20) Blanke ML, VanDongen AMJ. Activation mechanisms of the NMDA receptor. In: Van Dongen AM, editor. *Biology of the NMDA receptor*. Frontiers in Neuroscience. Boca Raton (FL) 2009:283-312.
- 21) Khosroshahi N, Ghadirian L, Kamrani K. Evaluation of magnesium levels in serum and cerebrospinal fluid of patients with febrile convulsion hospitalized in Bahrami Hospital in Tehran in 2010-2011. *Acta Med Iran* 2015;53:778-81.
- 22) Thoman JE, Duffner PK, Shucard JL. Do serum sodium levels predict febrile seizure recurrence within 24 hours? *Pediatr Neurol* 2004;31:342-4.
- 23) Heydarian F, Ashrafzadeh F, Kam S. Simple febrile seizure: The role of serum sodium levels in prediction of seizure recurrence during the first 24 hours. *Iran J Child Neurol* 2009;3:31-4.
- 24) Hasegawa H, Okubo S, Ikezumi Y, Uchiyama K, Hirokawa T, Hirano H, et al. Hyponatremia due to an excess of arginine vasopressin is common in children with febrile disease. *Pediatr Nephrol* 2008;24:507-11.
- 25) Pengcheng Han, Bradley J. Trinidad, Jiong Shi. Hypocalcemia-induced seizure – demystifying the calcium paradox. *ASN Neuro* 2015 Mar-Apr; 7(2) 1759091415578050.