RESEARCH PAPER

Serum Magnesium Levels in Children With and Without Migraine: A Cross-Sectional Study

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Objective: To study the association between serum magnesium level and migraine in children. **Methods:** This cross-sectional study enrolled children aged 5–18 years diagnosed with migraine, and age- and sex-matched controls without a headache disorder. International Classification of Headache Disorders 3 **(**ICHD-3) was used for the diagnosis of migraine. The association between serum magnesium level and migraine headache was analyzed. **Results**: A total of 35 children with migraine were enrolled with 35 control subjects. The median (IQR) serum magnesium levels were comparable among children with migraine and controls [2.0 (2.0,2.1) vs 2.2 (1.9, 2.2) mg/dL; *P*=0.23], respectively. In adolescent subgroup, median (IQR) serum magnesium levels were significantly low among the children with migraine as compared to those without migraine [2.0 (1.9, 2.1) vs 2.2 (2.0, 2.2 mg/dL); *P*<0.045]. **Conclusion:** We found a statistically significant association between low serum magnesium levels and the occurrence of migraine in adolescents, which may have treatment implications.

Keywords: *Adolescents, Diagnosis, Headache, Supplementation.*

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Migraine is a common cause of headache in children, particularly during adolescence [1]. The International Classification of Headache Disorders beta 3 version (ICHD-3) is currently used for the diagnosis of migraine [2]. Magnesium plays a key role in the active transport of ions across neuronal membranes [3]. Low serum magnesium can increase neuronal irritability. Reduced magnesium levels can lead to opening of calcium channels, increased intracellular calcium with release of glutamate, and increased extracellular potassium, which cause cortical spreading depression (CSD) leading to migraine [4].

Serum magnesium levels have been shown to be significantly lower among adults with migraine as compared to controls [5]. Although, there are similarities in the clinical presentation among children and adults, the treatment approaches differ [6,7]. There is limited information on serum magnesium levels among children with migraine, as it may have treatment implications. [8]. Hence, we studied the association between serum magnesium levels and occurrence of migraine among children and adolescents.

METHODS

This cross-sectional study with controls was done between 1 July, 2018 and 31 March, 2020, in the pediatric department of a tertiary care hospital, after permission from the institutional ethics committee. Children aged 5 to 18 year with headache were screened and those diagnosed with migraine were enrolled after getting informed consent from the parents, and assent from the adolescents aged 12 years and above. Based on the previous adult study with the mean (SD) serum level of magnesium of 1.86 (0.41) mg / dL in cases and 2.10 (0.23) mg/dL in controls, the sample size calculated was 29 rounded up to 35, with power of 80%, alpha error of 5%, and with effect size of 0.76 [5].

A detailed history and physical examination of children with headache was performed as part of the routine evaluation, with ophthalmological, ear, nose and throat examinations to exclude secondary headaches as per the standard of care [9]. The diagnosis of migraine was made as per ICHD Beta-3 classification, which was independently confirmed by a pediatric neurologist. Weight was measured using digital weighing scale with minimal clothing and barefoot. Height was measured using a stadiometer. Body mass index (BMI) was calculated as per standard formula. The interpretation of the nutritional status was done using revised IAP growth charts, 2015 for both genders [10]. Blood pressure was measured in the left upper arm with a sphygmomanometer, in sitting position, using the appropriate cuff size. Those with chronic illnesses (renal, cardiac, respiratory, and gastrointestinal disorders), malnourishment in the form of underweight or overweight/ obesity, and on magnesium supplements, were excluded.

A venous blood sample of 3 mL was collected from each participant, during the period of normalcy (without an acute headache episode), and serum magnesium level was measured using Xylidyl blue method by automatic analyzer (Beckman Coulter - AU5800). Age- and sex-matched controls were selected from the pediatric outpatient department on the same day, and blood samples for serum magnesium levels were collected after informed consent, and assent, if appropriate. These children were not on any magnesium supplements and had normal BMI. Age was matched with an accepted maximum of 3 months difference between the cases and controls. The serum magnesium levels were informed to the participants, and management was planned for those with hypomagnesemia. Hypomagnesemia was defined as serum magnesium concentration <1.8 mg/dL.

Statistical analysis: The association between serum magnesium level in children with migraine and controls was analyzed and a sub-group analysis for adolescents (10-18 years) was performed. We used SPSS version 20.0 for analysis. Shapiro-Wilk test was performed for testing the normality of the data. Non parametric statistical analysis using Mann-Whitney test was done for those variables that were not normally distributed.

RESULTS

A total of 122 children with headache were screened and 35 with migraine were finally enrolled (**Fig. 1**). Another 35 age- and sex-matched control subjects were also enrolled. None of the patients with migraine had any aura, and 29% had a positive family history. All had normal blood pressure with no difference in the baseline values between the cases and controls.

The median (IQR) serum magnesium level among adolescents (10-18 years) was 2.0 (1.9, 2.1) mg/dL in cases, while among controls it was 2.2 (2.0, 2.2) mg/dL, with a *P* value of 0.045. In children (5-18 years), the median serum magnesium level of cases was 2.0 (2.0, 2.1) mg/dL and it was 2.2 (1.9, 2.2) mg/dL in control group, which was comparable (*P*=0.23). None of the patients or controls had hypomagnesemia requiring supplementation. The differences were also comparable among preadolescents (5-9 years) and across gender (**Table I**).

DISCUSSION

In this cross-sectional study, the association between serum magnesium level and the occurrence of migraine in children was not found; although, the association in the adolescent (10-18 year) sub-group was statistically significant. None of our participants with migraine had serum magnesium level below 1.8 mg/dL.

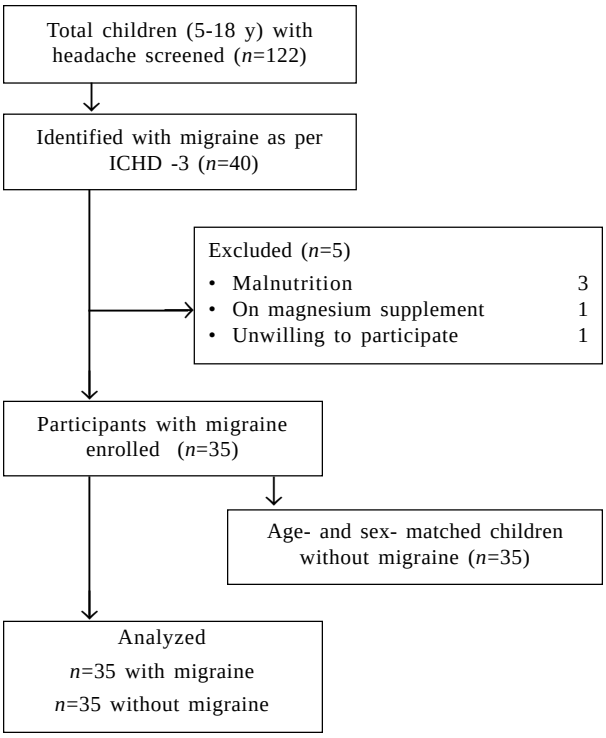

Fig. 1 Study flow chart.

In adult studies, serum magnesium levels have been reported to be low in migraine patients when compared to controls, and it was similar within and between acute episodes [5]. Adult studies have shown that women with menstrual migraine had low levels of magnesium [11]. Moreover, there is an increased frequency of migraine attacks post-puberty [11]. The increasing frequency of migraine during adolescence may develop into adult pattern [12]. The rationale for the lower magnesium levels observed among the adolescent sub-group in this study, akin to that of adult studies, may be explained by the similar pathogenetic mechanisms of adolescent and adult migraine.

In previous studies, magnesium has been used in migraine prophylaxis [13], and magnesium oxide was found to be effective. A randomized trial done in adults with migraine showed the combination therapy of magnesium

Table I Serum Magnesium Levels in Children With and Without Migraine

	Serum magnesium levels (mg/dL)		*P value*
	with migraine (n=35)	*without migraine (n=35)*	
Overall	2.0 (2.0,2.1)	2.2 (1.9, 2.2)	0.23
Male, *n*=40	2.1 (1.9, 2.2)	2.2 (1.9, 2.2)	0.5
Female, *n*=30	2.0 (2.0, 2.1)	2.1 (1.9-2.2)	0.3

WHAT THIS STUDY ADDS?

- We found a significant association between low serum magnesium levels and the occurrence of migraine in adolescents.

with sodium valproate can reduce the dosage of valproate for prophylaxis [14]. Research in the area of treatment of migraine in different age groups is quite limited [9]. There is a need for more investigations to prove safety and effectiveness of magnesium prior to use in pediatric migraine [6]. A double-blind placebo-controlled, randomized trial of patients aged 3-17 years found a statistically significant decline in headache frequency in those treated with magnesium oxide, but the difference between the placebo group and magnesium oxide group was not statistically significant [15]. It could therefore not be concluded by the authors if oral magnesium was superior to placebo in preventing frequent migraine episodes in children [15].

The major limitation of our study was its small sample size, especially among the adolescent sub-group. The post hoc power of the study was 90.7%. It is desirable to study the serum magnesium level during an acute migraine attack, rather than the period of normalcy, to further study this association.

To conclude, serum magnesium levels were comparable among children with migraine and their age- and sex-matched controls, except for low levels in adolescents with migraine. The role of magnesium supplements as either prophylaxis or treatment in children with migraine headache needs to be further explored.

Ethics clearance: IEC Sri Ramachandra Institute of Higher Education and Research; No. CSP-MED/18 JUN/44/104 dated June 23, 2018.

Note: Additional material related to this study is available with the online version at www.indianpediatrics.net.

Contributors: RB: study design, acquisition, analysis, drafting; SP: study design, analysis, interpretation and drafting; RKM: study design, interpretation, revising it critically. Final approval of the version and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved by all the contributing authors.

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