



Hypocalcemic convulsions secondary to hypomagnesemia; a case report

Faheemullah Khan¹, Bilal Sethi², Iftikhar Ali³, Bilal Khan⁴

Abstract

Hypomagnesemia with secondary hypocalcemia (HSH) is a rare inherited disorder, characterized by low levels of serum magnesium associated with symptomatic hypocalcemia. This condition manifests with the defect in the intestinal trans-epithelial transport system-defective intestinal absorption of magnesium, which impairs the function of the parathyroid gland. The condition typically presents in the infancy with neuromuscular excitability and convulsion refractory to antiepileptic therapy. We described a 2-year-old patient presented with generalized tonic convulsions refractory to antiepileptic therapy. The clinical examination demonstrated stiffening of hands and feet. The laboratory investigations showed severe hypomagnesemia with associated hypocalcemia. Parathyroid hormone level was in the lower normal range (25 pg/mL). Based on the presentation and laboratory findings, magnesium sulphate intravenous (IV) and calcium (oral + I.V.) replacement therapy was initiated. Parathyroid hormone level normalized and symptoms resolved. Magnesium levels should always be investigated while confirming the etiologic basis for seizures. Early diagnosis and prompt magnesium replacement are essential to prevent death or long-term irreversible neurologic damage.

Keywords: Hypomagnesemia, Hypocalcemia, Convulsions.

Please cite this paper as: Khan F, Sethi B, Ali I, Khan B. Hypocalcemic convulsions secondary to hypomagnesemia; a case report. *J Parathyroid Dis.* 2019;7:13-15.

Copyright © 2019 The Author(s); Published by Nickan Research Institute. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Introduction

Hypomagnesemia with secondary hypocalcemia (HSH) is a rare genetic autosomal recessive condition which generally presents in early childhood (1,2). There is decreased magnesium blood concentration associated with hypocalcemia, secondary to magnesium induced hypoparathyroidism (3). The affected patients present with increased neuromuscular excitability in the form of muscle cramps, spasms or tetany and generalized convulsions with the majority of them present with latter sign (4-6). Magnesium is normally absorbed through an active process in the intestine through a channel called transient receptor potential channel melastanin 6 (TRPM6). The same channel is responsible for the magnesium reabsorption in the kidneys. In HSH, there is genetic mutation in this channel, that leads to the defective absorption of magnesium through the intestinal epithelium and increased clearance through kidneys (7, 8). The low magnesium blood concentration leads to decreased synthesis and release of parathyroid hormone and its increased target tissue resistance (9-11). The symptoms resolve by correcting the serum magnesium

level (1.5-2.5 mg/dL). The associated hypocalcemia also resolves (3). The condition requires lifelong magnesium supplementation to keep the magnesium and calcium in normal ranges (1,11). Failure to diagnose the condition in time, leads to irreversible neurologic damage (10). We report a female patient who presented with convulsions, profound hypomagnesemia with hypocalcemia. To the best of our knowledge, this is the first case we are reporting from Pakistan.

Case Presentation

A 2 years old female patient, born to Pakistani parents with no parental consanguinity, without any significant family history, presented to outpatient pediatric medicine department with stiffening of hands and feet. She has one to two episodes of convulsions daily. The first episode of convulsions was noted when she was 2-month old. Since then she was experiencing convulsions regularly. The convulsions are generalized and of tonic variety associated with shortness of breath, central cyanosis and urinary incontinence. The patient has no history of trauma or cerebrovascular accident. The patient was afebrile. She

Received: 30 June 2019, Accepted: 3 August 2019, ePublished: 12 August 2019

¹Department of Pediatric Medicine, Northwest General Hospital and Research Centre, Peshawar, Pakistan. ²Department of Pediatric Medicine, Northwest General Hospital and Research Centre, Peshawar, Pakistan. ³Department of Pharmacy, University of Swabi, Khyber Pakhtunkhwa, Pakistan.

⁴Department of Pediatric Medicine, Northwest General Hospital and Research Centre, Peshawar, Pakistan.

*Corresponding author: Faheemullah Khan, Email: islamianfellow@hotmail.com

■ Implication for health policy/practice/research/medical education

Magnesium deficiency continues to be under recognized and may be responsible for serious consequences on the part of patient. Simply, the magnesium correction can revert serious sequelae like convulsions. In our case the diagnoses was delayed for three months due to the under recognition of the fact that magnesium deficiency can affect parathyroid hormone synthesis and release. 1) It should routinely be investigated when an infant present with hypocalcemia or convulsions. Investigations should not be restricted to EEG and routine electrolytes while dealing with infants presenting with convulsions. 2) Every physician should be aware of the magnesium hemostasis and its connection with parathyroid hormone. 3) Physicians should also be updated with the genetic mutations implicated so far related to magnesium deficiency.

was born at term and delivered vaginally. Clinically, the neonatal status of the patient was unremarkable. Examination was unremarkable with the exception of stiffening of the hands and feet. The patient had no clinical signs of rickets and had presented to the same outpatient department twice before. Previously this was presumed to be a case of primary hypoparathyroidism and was sent home on calcium supplementation. The patient was admitted to the pediatric unit and was investigated. After receiving those investigations, the patient was started on parenteral magnesium sulphate and calcium gluconate therapy. The convulsions were controlled immediately after starting said therapy. Her investigations were repeated three days later as shown in Table 1.

Complete blood count, serum electrolytes and urea were in the normal range. Beside these investigations an electroencephalogram (EEG) was also performed to rule out the possibility of an epileptic disorder, which was unremarkable.

The patient was discharged after receiving the above investigations and was prescribed Oral magnesium sulphate (thrice a day), oral calcium and vitamin D drops as home medications. The same patient was followed further in time with the laboratory reports given in Table 1.

Discussion

HSH is a rare inherited disorder characterized by very low magnesium levels associated with hypocalcemia (1). The hypocalcemia is secondary to parathyroid failure and parathyroid hormone resistance at organ level (3). HSH typically presents in early infantile age with signs of increased neuromuscular excitability (muscle spasms or tetany) or generalized convulsions (2-5). Failure to diagnose and start the therapy in time, may result in serious neurologic sequelae (10). The underlying pathophysiology of HSH is related to the defective trans-epithelial transport of magnesium in the intestine and increased renal clearance. Mutation in the gene encoding the TRPM6 has been linked to the defective absorption of magnesium through intestine and increased renal clearance (7,8). Our patient has the typical presentation of HSH i.e generalized convulsions refractory to vitamin D, calcium and anticonvulsant therapy.

Shalev et al reported generalized convulsions as the most common presenting event, with the mean age of 4.9 weeks (6).

The unresponsiveness to vitamin D ruled out rickets (nutritional insufficiency). The unresponsiveness to the calcium supplementation and parathyroid hormone levels in the lower normal range ruled out the possibility of parathyroid disorder. Similarly, electroencephalogram taken of the patient was unremarkable. Serum magnesium levels were low (0.37 mg/dL). Parenteral magnesium and calcium supplementation therapy was initiated. The symptoms reversed immediately without the need of further anticonvulsant therapy. Serum calcium and magnesium levels obtained three days later were 9.53 mg/dL and 1.28 mg/dL respectively. The acute reversal of clinical symptoms with intravenous magnesium supplementation and normalization of serum calcium were suggestive of HSH. Shalev et al also reported that despite high doses of enteral magnesium, the blood concentration of those patients was still in the subnormal range (6).

Due to affordability issue and the relief of clinical symptoms with magnesium supplementation, genetic

Table 1. Laboratory results

Parameter	Normal Range	Previous visits		Current visit		Follow up visit(1 st)	Follow up visit(2 nd)	Follow up visit(3 rd)
		1 st visit	2 nd visit	Upon admission	Three days later			
Total calcium (mg/dL)	8.5-10.5	8.15	6.1	6.6	9.53	9.7	10.6	-
Ionized calcium (mg/dL)	1.14-1.35	-	0.67	0.62	1.10	1.89	1.29	-
Magnesium (mg/dL)	1.5-2.55	-	-	0.37	1.28	1.48	0.81	2.26
Phosphorus (mg/dL)	3.2-6.3	6.3	-	-	-	-	-	-
Alkaline phosphatase (U/L)	35-307	212	-	-	-	-	-	-
Alanine transaminase (U/L)	7-55	-	-	53	-	-	-	-
Parathyroid hormone (pg/mL)	15-65	-	-	-	25	25	-	36.13

analysis of the patient was not done. Early recognition and treatment compliance can prevent permanent neurologic damage (6). The patient was started on lifelong oral magnesium supplementation. The follow-up period was of good neurologic outcome.

Conclusion

HSH is a rare disorder manifesting with convulsions and spasms in early infancy, which if left untreated, can lead to mental retardation or death. The diagnosis can be a challenge, and a high index of suspicion is needed. An inherited disorder should be suspected, and genetic studies are recommended. A simple magnesium salt supplementation can prevent permanent neurologic damage. Early diagnosis and prompt magnesium replacement are essential to prevent death or long-term neurodevelopmental sequelae. Magnesium should always be investigated while confirming the etiologic basis for seizures. Hypomagnesemia and afebrile seizures should be treated with the goal of maintaining a magnesium concentration > 1.7 mg/dL.

Acknowledgments

The authors are very thankful to the parents of the baby for providing the necessary information and permission for the publication of this case report.

Authors' contribution

FK, BS and IA wrote the paper. FK, BS and BK provided conceptual input. IA proofread and organized the manuscript. All authors reviewed the final version of the manuscript.

Conflicts of interest

None to declare.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors. The authors obtained informed consent from the patient's parents.

References

1. Walder RY, Landau D, Meyer P, Shalev H, Tsolia M, Borochowitz Z, et al. Mutation of TRPM6 causes familial hypomagnesemia with secondary hypocalcemia. *Nat Genet.* 2002;31:171-4.
2. Carrazza FR, Souza M, Romaldini C, Feferbaun R, Diniz EA. Magnesium metabolism in chronic primary hypomagnesemia. *J Pediatr (Rio J).* 2000;76:310-4.
3. Schlingmann KP, Sassen MC, Weber S, Pechmann U, Kusch K, Pelken L, et al. Novel TRPM6 mutations in 21 families with primary hypomagnesemia and secondary hypocalcemia. *J Am Soc Nephrol.* 2005;16:3061-69.
4. Zhao Z, Pei Y, Huang X, Liu Y, Yang W, Sun J, et al. Novel TRPM6 mutations in familial hypomagnesemia with secondary hypocalcemia. *Am J Nephrol.* 2013;37:541-48.
5. Visudhiphan P, Visudtibhan A, Chiemchanya S, Khongkhatithum C. Neonatal seizures and familial hypomagnesemia with secondary hypocalcemia. *Pediatr Neurol.* 2005;33:202-5.
6. Shalev H, Phillip M, Galil A, Carmi R, Landau D. Clinical presentation and outcome in primary familial hypomagnesaemia. *Arch Dis Child.* 1998;78:127-30.
7. Katayama K, Povalko N, Yatsuga S, Nishioka J, Kakuma T, Matsuishi T, et al. New TRPM6 mutation and management of hypomagnesaemia with secondary hypocalcaemia. *Brain Dev.* 2015;37:292-98.
8. Chubanov V, Gudermann T, Schlingmann KP. Essential role for TRPM6 in epithelial magnesium transport and body magnesium homeostasis. *Pflügers Archiv.* 2005;451:228-34.
9. Singh R, Bhat M, Bhansali A. Hypomagnesaemia masquerading as hypoparathyroidism. *J Assoc Physicians India.* 2006;54:411-12.
10. Apa H, Kayserili E, Agin H, Hizarcioglu M, Gulez P, Berdeli A. A case of hypomagnesemia with secondary hypocalcemia caused by *Trpm6* gene mutation. *Indian J Pediatr.* 2008;75:632-34.
11. Lainez S, Schlingmann KP, Van Der Wijst J, Dworniczak B, Van Zeeland F, Konrad M, et al. New TRPM6 missense mutations linked to hypomagnesemia with secondary hypocalcemia. *Eur J Hum Genet.* 2014;22:497-504.