CASE REPORT

Familial hypomagnesaemia with secondary hypocalcaemia

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SUMMARY

Magnesium is the second most abundant intracellular cation and plays an essential role in neuronal, skeletal and cardiac tissue. Hypomagnesaemia can cause hypocalcaemia by inhibiting parathyroid hormone release and inducing resistance at its receptor sites. Untreated hypomagnesaemia can lead to tetany, recurrent seizures, status epilepticus and life-threatening arrhythmias. Primary hypomagnesaemia with secondary hypocalcaemia (HSH) is a rare metabolic disorder of intestinal magnesium absorption. The condition typically presents in the neonatal period with neuromuscular excitability and seizures refractory to antiepileptic therapy. Early diagnosis and prompt magnesium replacement are essential to prevent death or long-term neurodevelopmental sequelae. Fewer than a hundred cases are reported in the literature. Recent advances have added significantly to our understanding of the genetic basis of HSH. We report the presentation and long-term follow-up of an affected female who was found to have a mutation in the transient receptor potential melastatin 6 (*TRPM6*) gene, encoding a transient receptor potential cation channel.

BACKGROUND

Familial hypomagnesaemia with secondary hypocalcaemia (HSH) is a rare autosomal recessive disorder. Affected individuals have a defect in the magnesium permeable ion channel encoded for by the transient receptor potential melastatin 6 (*TRPM6*) gene on chromosome 9q22.¹ This gene is expressed in the intestine and the kidney, but the defect primarily affects the intestine, leading to serum hypomagnesaemia. Presentation is usually in the neonatal period with hypocalcaemia refractory to calcium supplementation. The condition is treatable but failure to diagnose early can lead to intractable seizures with irreversible cerebral damage and mental retardation, or even death. Recent reports have suggested initial investigations for neonates presenting with seizures do not always include assessment for serum magnesium abnormalities. Calcium supplementation alone in these scenarios will fail to be effective and result in significant morbidity or mortality. Genetic diagnosis of HSH is now possible but treatment remains lifelong high-dose magnesium supplementation. This condition should be included in the differential diagnosis of any neonate presenting with seizures.

CASE PRESENTATION

A female neonate presented 15 days after birth. Her mother reported the baby had a brief generalised tonic-clonic seizure at home, lasting less than a

minute. Jerking movements of the limbs had also been witnessed several days before this. The newborn had otherwise been well. She was moving all her limbs normally and her eye movements were also reportedly normal. There was no associated fever and she had not exhibited any features of infection in the preceding days.

There had been no antenatal or perinatal complications. The neonate had been delivered at term by caesarean section because of failure to progress in labour and was of normal birth weight. There were no early problems with feeding. She was born to consanguineous parents of Bangladeshi origin who already had two healthy male children. The newborn was not taking any regular medication and there was no background of maternal recreational drug use. Family history was unremarkable, with no convulsive, metabolic or genetic disorders.

On examination, her vital signs were within the normal range and she was not hypoglycaemic. Her pupils were reactive and symmetrical in size and the Babinski sign was bilaterally positive. Her head circumference was within average limits. Neurological examination was unremarkable at the time of presentation, with normal tone and reflexes and spontaneous movement of all four limbs.

INVESTIGATIONS

The neonate was admitted for neurological observation and a full investigative work-up for neonatal seizures was performed. This primarily consisted of neurological and metabolic assessment, and exclusion of infection.

Imaging, electroencephalography and a lumbar puncture were all indicated. Serum sodium, potassium and glucose were normal. Serum calcium was low at 1.61 mmol/L (normal range 2.1–2.6 mmol/L) and serum magnesium was extremely low at 0.2 mmol/L (normal range 0.7–1.0 mmol/L). Further investigations and monitoring were therefore performed to ensure that these deficiencies were not disturbing the electrical rhythm of the heart and to investigate whether renal losses might explain the low serum electrolyte levels.

The role of each of these investigations in helping to identify the cause of the seizure is shown in [table 1](#) alongside the results of the investigations.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for seizures in the neonatal period is broad and shown in [table 2](#). In addition to the metabolic disturbances that can cause seizures in adults, febrile convulsions, epilepsy syndromes, inborn errors of metabolism and traumatic brain injury from difficult labour must all be considered.

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Table 1 The role of investigations for neonatal seizures and results

Investigation	Role of investigation	Results
Cranial ultrasound	A non-invasive imaging modality which can identify gross parenchymal lesions and haemorrhage. It will also show any ventricular system defects. If gross abnormalities are identified, CT or MRI may be performed.	Reports for this patient no longer available.
EEG	Abnormalities in electrical activities can be matched to epilepsy syndromes. Normal background activity is a good prognostic marker for normal neurodevelopment and for seizure resolution.	Reports for this patient no longer available.
CSF examination	This is primarily to exclude infection as part of a septic screen.	Reports for this patient no longer available.
Serum glucose	Hypoglycaemia has an established epileptogenic potential and is more common in the neonatal period.	The neonate was normoglycaemic.
Serum electrolytes	High or low potassium, calcium and magnesium levels, all have epileptogenic potential.	Serum calcium 1.61 mmol/L Serum magnesium 0.2 mmol/L Normal serum sodium and potassium
Urine electrolytes	If serum electrolytes are low and there is no evidence of intestinal electrolyte wasting, urine assays can identify renal salt wasting.	Low urine magnesium and calcium excretion
Parathyroid hormone and vitamin D	Low parathyroid hormone may explain hypocalcaemia but as magnesium ions are required for normal parathyroid hormone function, severe hypomagnesaemia will lead to hypocalcaemia even in the absence of primary parathyroid gland dysfunction.	Raised serum parathyroid hormone (220 pg/mL, normal range <120 pg/mL) and normal vitamin D (25-hydroxy vitamin D 16.7 ng/mL, normal range 3–30 ng/mL)
ECG	Hypocalcaemia can cause narrowing of the QRS complexes, shortened PR intervals and prolonged S-T and Q-T segments. Prominent U waves may also be seen. Hypomagnesaemia on the other hand, will lengthen the Q-T segment. These changes suggest electrical instability and increase the propensity for arrhythmias.	The ECG showed narrow QRS complexes.
Septic screen	The 'TORCH' (toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus) organisms responsible for perinatal infection in particular, require exclusion. Serum, CSF and other obtained samples will require microscopy and culture. White cell count and inflammatory markers also require assessment.	Serological and CSF testing excluded an infective aetiology.

CSF, cerebrospinal fluid.

Table 2 Differential diagnosis for neonatal seizures

Causes of neonatal seizures	Underlying aetiology
Brain injury	Haemorrhage, parenchymal lesions, arteriovenous and cerebral malformations
Intracranial infection	Meningitis, encephalitis
Febrile convulsion	Secondary to respiratory tract infection, commonly respiratory syncytial virus or influenza viruses
Metabolic disorders	Hypoglycaemia, hypocalcaemia, hypomagnesaemia, inborn errors of metabolism
Seizure syndromes	West syndrome, Salaam syndrome
Benign idiopathic neonatal seizures	

Intracranial abnormalities were excluded by ultrasonography. A septic screen excluded intracranial and other systemic infections, and the likelihood of a convulsion secondary to febrile illness. The absence of birth trauma made conditions such as hypoxic ischaemic encephalopathy less likely and there were no reported electroencephalographic changes consistent with seizure syndromes (including West syndrome and Salaam syndrome). Hypoglycaemia was excluded quickly and deranged serum electrolytes were identified early. As all other investigations were normal, the working diagnosis was that the neonate had presented with a seizure secondary to hypocalcaemia and hypomagnesaemia.

TREATMENT

While the cause of the electrolyte derangement was being investigated, parenteral magnesium sulfate and calcium gluconate were administered to prevent further seizures and to stabilise myocardial electrical activity. The intravenous route for replacement was selected to achieve rapid correction of serum

electrolytes as the route of electrolyte wasting—intestinal, renal or both—was unclear. This resulted in a return to normal serum levels of magnesium. Serum calcium remained in the low-normal range. Regular venepuncture was required for monitoring.

For continual neurological observation, the neonate was managed as an inpatient for several days. Serial ECGs were also performed to monitor for arrhythmias. The primary side effect from therapy was diarrhoea. This was monitored while the mode of replacement was being altered. No clinically significant consequences resulted from the diarrhoea.

OUTCOME AND FOLLOW-UP

The newborn had a further generalised tonic-clonic seizure while initial neurological and metabolic investigations were in progress. Features of neuromuscular excitability were also observed during the first 48 hours of hospital admission. Once the electrolyte derangement had been corrected, however, no signs of abnormal electrical activity were detected and the baby remained seizure-free. Intramuscular replacement with magnesium sulfate was initiated before discharge. At this stage, calcium replacement was discontinued. Urinary magnesium, although inappropriately normal, was not raised to suggest renal electrolyte wasting such as might occur in Gitelman and Bartter syndromes. It was presumed that chronic magnesium malabsorption was underlying the serum hypomagnesaemia. The baby remained well following discharge.

Genetic mapping was not possible at the time of presentation. A genetic defect was nonetheless presumed to underlie the hypomagnesaemia and a clinical diagnosis of HSH was made. Management would require lifelong magnesium supplementation.

The next clinical challenge was to maintain normomagnesaemia in a growing child; this required regular monitoring and dose adjustment. Daily intramuscular supplementation with 1.6 mmol/kg of magnesium sulfate was continued for most of the

child's first year of life. At age 2, a trial of stopping intramuscular magnesium resulted in a seizure after 11 days; treatment was therefore restarted, initially as oral magnesium glycerophosphate, eight tablets daily (0.4 mmol magnesium per tablet). This was well tolerated. At age 5 years, the dose was increased to 10 tablets daily, at 8 years, 15 tablets per day were required, at 12 years, 19 tablets and progressively, the requirements for magnesium continued to increase, guided by serial serum magnesium measurements. Serum magnesium levels remained consistently in the low-normal range, at 0.6–0.8 mmol/L despite increasing doses of magnesium supplements. Serum calcium, on the other hand, remained within normal limits. The patient remained seizure-free after age 2 years, while remaining on magnesium replacement.

During the 29-year follow-up period, magnesium glycerophosphate was well tolerated; when magnesium glycerophosphate was briefly unavailable she was treated with magnesium oxide but this caused diarrhoea. At age 29 years, this patient is currently requiring 39 tablets daily in divided doses. Her most recent serum magnesium concentration was 0.6 mmol/L and serum calcium concentration was 2.24 mmol/L.

Neurological insult following neonatal seizures and suboptimal therapy for electrolyte abnormalities can have serious adverse effects on neurodevelopment. However, this patient exhibited normal developmental milestones, she completed her education including acquiring a university science degree and went on to pursue an academic career as an adult.

At age 22 years, she reported worsening blurred vision. Bilateral keratoconus was diagnosed and has been managed with contact lenses. Keratoconus has been described in association with hypomagnesaemia secondary to other pathology but hitherto, has not been described in HSH.² The patient has had no other significant reported health problems over 29 years of follow-up.

A clinical diagnosis of HSH was made at the time of her presentation in 1986. Since then, the genetic mutation responsible for this condition has been identified. This patient recently underwent genetic testing which confirmed she has a pathogenic mutation in the *TRPM6* gene, which encodes a transient receptor potential cation channel required for ionic magnesium influx. A homozygous deletion of exon 2 and flanking intronic sequences were found. Genetic testing thus confirmed the clinical suspicion of HSH.

DISCUSSION

We have described a case of familial HSH. The diagnosis was made clinically within a few days of birth and subsequently confirmed by genetic analysis. Over the 29 years of follow-up, the patient has been fully compliant with treatment, tolerating magnesium replacement which has been closely titrated throughout this period. She demonstrates normal physical and mental development, though has recently been diagnosed with keratoconus which is being managed satisfactorily by conservative measures.

HSH is a rare autosomal recessive disease characterised by defective intestinal absorption and renal magnesium leak. It was first described in 1968 and was thought to be an X linked recessive disease until 1997,³ when the autosomal recessive inheritance was convincingly demonstrated.¹ The underlying causative mutations in the *TRPM6* gene were discovered just over a decade ago.⁴ This gene, located on chromosome 9q22, encodes a magnesium permeable channel expressed in the distal segment of the intestine and the distal convoluted renal tubule.^{4–5} Affected individuals appear to have an isolated defect of intestinal magnesium absorption with normal or low renal magnesium excretion at diagnosis; the renal magnesium leak only becoming apparent once the serum magnesium concentration

risks, indicating a reduced renal threshold for magnesium.⁶ This increase in fractional excretion of magnesium after adequate replacement is a valuable test to aid diagnosis.⁷ Hypocalcaemia results from reduced parathyroid hormone activity in the absence of ionised magnesium. Nearly 40 mutations of *TRPM6* contributing to HSH have now been described.⁷

Case reports of HSH to date have mostly described 4–10 years of follow-up.⁶ This case study offers important extended insight into the long-term follow-up of HSH in a female patient over nearly 30 years. In her third decade, our patient developed keratoconus, a degenerative disorder affecting the eye, in which thinning of the cornea results in loss of the normal corneal contour. There is corneal membrane thinning and fragmentation. This has previously been described in association with hypomagnesaemia.⁸ However, we believe this is the first report of an association between keratoconus and HSH.

Keratoconus with hypomagnesaemia has been linked to atopy.² Keratoconus has also been linked to South Asian ethnicity.⁹ It is interesting to note therefore, that our patient has a history of childhood eczema and is of Bangladeshi origin. Keratoconus is a progressive disease which can cause refractive errors and worsening visual acuity, hence patients with hypomagnesaemia and HSH should have regular ophthalmological assessment to ensure early detection of keratoconus and appropriate treatment.

Previous reports of HSH have demonstrated how timely diagnosis and prompt magnesium replacement facilitate normal development.¹⁰ One case series described significantly impaired neurodevelopment in two affected members of the same family who failed to receive this intervention.¹ Enteral magnesium is sufficient for replacement. Magnesium transport in the intestine occurs by both an active transcellular system which is defective in HSH and a passive paracellular pathway, which increases with rising intraluminal magnesium concentrations. Hence, lifelong high-dose magnesium supplementation (~1 mmol/kg body weight/day) is required in HSH to prevent symptoms and achieve at least subnormal serum magnesium levels. Traditionally, the dose has been modified with serial serum electrolyte monitoring. The case we report and others have shown that serum magnesium levels remain in the subnormal range (0.5–0.6 mmol/L) even with significant increases in supplemented dose.⁶ Normocalcaemia and the absence of features of neuroexcitability should therefore be the target of therapy. There is no preparation of choice for oral magnesium replacement and this should be guided by the individual's reaction to those available. Rapid diagnosis and treatment of this rare disorder can significantly improve the quality of life of affected individuals.

Patient's perspective

I've always wanted to find out how it came about. It's only when I started doing my science degree and gained a better understanding of science as a whole that I realised what significant role magnesium plays in the body. It's been a learning experience for me finding out how vital it is. Having the condition doesn't affect me or impair me in any way. I'm perfectly fine and go about my daily routine as any normal person. The only issue is having to take all the tablets. I think of it as having to take a vitamin supplement and then I get on with my day. It's like a dietary supplement that gives me an energy boost. It's only if I don't take it that I feel a bit weak. Otherwise, I work and do activities as normal.

Learning points

- ▶ A diagnosis of primary hypomagnesaemia with secondary hypocalcaemia (HSH) should be considered in all paediatric patients presenting with generalised seizures or tetany as it is a treatable disease. This is particularly important in those communities where consanguineous marriages are common.
- ▶ Enteral or parenteral magnesium replacement is key to managing this condition and the aim should be to normalise serum calcium.
- ▶ Keratoconus may be a late-onset feature of HSH and the role of transient receptor potential melastatin 6 (*TRPM6*) in the cornea merits further investigation.
- ▶ Regular ophthalmological examination should be performed in patients with a known diagnosis of HSH to facilitate early detection of keratoconus.

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