Hypomagnesemia, a diagnosis to consider

Hipomagnesemia, un diagnóstico a considerar

Dear Editor,

Magnesium is one of the main electrolytes in the human body and is involved in multiple mechanisms necessary for the correct functioning of the body.

The normal range for magnesium levels in serum is 0.7–1.03 mmol/L. Hypomagnesaemia (level <0.7 mmol/L)[1] can manifest with different symptoms, such as weakness, cramps or heart arrythmias, although it is usually asymptomatic if the levels are greater than 0.5 mmol/L.[1] Some genetic disorders are associated with increased renal excretion of magnesium.[2]

We present the case of a boy aged 9 years in follow-up in the department of paediatric endocrinology due to colloid cysts in the thyroid gland and transient elevation of thyroid-stimulating hormone (TSH) (peak level, 11.67 mU/L; normal range, 0.60–4.84 mU/L) with a normal level of free thyroxine (FT4) normal and negative thyroid peroxidase (TPO) antibodies. Thyroid function normalised and the cysts stabilised, but the patient exhibited persistent hypomagnesaemia during the follow-up (levels ranging between 0.53–0.57 mmol/L).

The relevant findings of the personal history were the diagnosis of attention-deficit hyperactivity disorder (ADHD) managed with methylphenidate, pectus excavatum and malposition of teeth.

The patient had never experienced headaches, dizzy spells, muscle weakness or cramps.

There was no family history of interest.

In the physical examination, the patient was not obese (body mass index: 15.68 kg/m^2, 20th percentile, $z = -0.6$) and neurodevelopment was adequate for age.

In the laboratory tests performed to identify the aetiology of hypomagnesaemia, the levels of albumin, parathyroid hormone (PTH), vitamin D, calcium and creatinine (Cr) were normal (estimated glomerular filtration rate, 169.9 mL/min/1.73 m^2). The fractional excretion of magnesium was elevated (8%; normal range, 2%–4%), as was the urine calcium level (Ca/Cr 0.32 mg/mg; normal range, <0.2 mg/mg) which suggested that the cause of hypomagnesaemia was renal.

An abdominal ultrasound ruled out renal and urinary tract anomalies, such as nephrocalcinosis.

Genetic testing, consisting in exome sequencing of 9 genes associated with hypomagnesaemia, identified a de novo, heterozygous likely pathogenic mutation in exon 1 of gene *CNNM2* (c.1310G>A; p.(Gly437Glu)) associated with autosomal dominant renal hypomagnesaemia type 6 (HOMG 6; OMIM 613882).

Initially, given the absence of symptoms, treatment was limited to a diet rich in magnesium, but since the low levels of magnesium persisted (0.57 mmol/L), supplementation with magnesium tablets (300 mg/day) was initiated.

The kidneys are the main regulators of the concentration of magnesium in blood. Certain proteins, like cyclin M2 (*CNNM2*) facilitate the excretion of magnesium in the kidney. This protein is encoded by gene *CNNM2*, and changes in this gene can cause HOMG6 or primary hypomagnesemia, seizures, and impaired intellectual development 1 (HOMGSMR1; OMIM 616418). In addition, some variants at the *CNNM2* locus have been associated with neuropsychiatric disorders, intellectual disability and language disorders.[2]

In the variant identified in our patient, the amino acid change p.(Gly437Glu) occurs in a domain that is important for the function of the protein (Bateman domain, amino acids 429–578). It has been hypothesised that the activity of protein CNNM is regulated by conformational changes in this domain associated with the binding of Mg^{2+} and ATP.[3] The replacement of a glycine, a small hydrophobic amino acid, by glutamic acid, a polar amino acid with a negative charge, causes an essential change in the protein. Furthermore, in silico tools used for pathogenicity prediction (PolyPhen2, Sift, Mutation Taster, etc.) predict a pathogenic effect.

Hypomagnesaemia was present in the patient before he started treatment with methylphenidate, so this drug did not seem to be the cause.

Most described individuals with changes in the *CNNM2* genes present severe neurologic symptoms associated with hypomagnesaemia.[4] In our patient, ADHD is the only neurologic manifestation present to date. Petrakis et al.[5] also described a case of HOMG6 and ADHD and discussed the possibility of a milder neurologic phenotype in HOMG6. However, given the high prevalence of ADHD in the paediatric population, it is not possible to rule out a chance association with hypomagnesaemia.

Our patient did not have nephrocalcinosis, a feature described in other individuals with hypomagnesaemia and disorders of phosphate and calcium metabolism secondary to changes in the *CNNM6* gene.[6]

As was the case of our patient, most changes in the *CNNM2* gene are sporadic.

To date, changes in this gene have not been associated with thyroid disorders, and we did not find any reports in the literature of variants causing both hypomagnesaemia and thyroid disorders.

Changes in the *CNNM2* gene are infrequent, so we thought it would be relevant to report this case. Hypomagnesaemia, which may be oligosymptomatic, and disorders like ADHD could be manifestations of the same disease.

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Immune-mediated necrotizing myopathy: antibodies and forecast. A literature review

Miositis necrotizante autoinmune: anticuerpos que marcan el pronóstico. Revisión de la literatura

Dear Editor:

Autoimmune inflammatory myopathies constitute a broad clinical spectrum and, depending on the involved autoantibodies, can have an unfavourable prognosis with involvement of different organs. Anti-signal recognition particle (SRP) antibodies are present in fewer than 1% of children with these diseases and are associated with a poor prognosis, giving rise to necrotising myopathy with poor response to steroid therapy and multiple system involvement, and a high morbidity and mortality.

We present the case of a girl aged 11 years who reported progressive muscle weakness and myalgia with onset 3 months prior, with inability to climb steps or get up from the floor in the past week. She had no personal or family history of interest. The physical examination evinced significant muscle weakness in the axial muscles of the neck, the pelvic girdle, the shoulder girdle and dorsal and lumbar back, and occasional choking on ingestion of fluids, with a score of 9/52 in the Childhood Myositis Assessment Scale. The patient weighed 52 kg and had a body surface area of 1.51 m^2. Blood tests evinced elevation of creatine phosphokinase (CPK, 11 426 U/L [normal range, 26–192]), aldolase (94.2 IU/L; [normal range, 1–7.5]), lactate dehydrogenase (LDH, 1513 U/L [normal range, 120–300]), alanine aminotransferase (ALT, 137 IU/L [normal range, 5–31]) and aspartate aminotransferase (AST, 193 U/L [normal range, 10–31]).

An extensive differential diagnosis was performed during the hospital stay, ruling out infectious, neurologic, metabolic, toxic, endocrinological and oncological causes. The autoimmunity study was positive for anti-SRP-54 and anti-52 kDa Ro/SSA antibodies. Electromyography evinced significant inflammatory myopathy and magnetic resonance imaging muscle changes with a bilateral, symmetrical and multifocal patchy myofascial pattern and oedema predominantly found in the pelvic girdle and the proximal lower extremity muscles (Fig. 1a). Based on the suspicion of immune-mediated inflammatory myositis, high-dose systemic steroid therapy was initiated, which did not achieve a clinical response or, initially, a change in laboratory markers (intravenous boluses of methylprednisolone at 125 mg/day for 5 days followed by prednisone at a dose of 60 mg/day). The muscle biopsy showed myopathic changes with some necrotic and some regenerating fibres and little inflammation. The immunohistochemical analysis revealed focal sarcolemmal HLA class I expression and diffuse expression in the cytoplasm of p62 forming aggregates in scattered fibres, all features compatible with immune-mediated necrotising myositis (Fig. 1b and c). On account of the possibility of systemic involvement, the patient underwent an extensive evaluation that included: cardiological assessment with echocardiography, which evinced adequate biventricular function and absence of valve insufficiency, spirometry and lung diffusion testing evincing adequate lung function, and assessment of swallowing with an upper gastrointestinal series in which the video fluoroscopy findings were normal. Given the lack of response to steroid therapy, intravenous immunoglobulin (1 g/kg), methotrexate (6.6 mg/m^2/week: 10 mg) and rituximab (375 mg/m^2; first dose: 500 mg with a second dose 15 days later) were added, in addition to intensive physical therapy, which achieved a progressive decrease of muscle enzymes. At present, 2 years after diagnosis, the patient receives methotrexate weekly (5 mg) and intravenous immunoglobulin monthly (1 g/kg), and remains stable in terms of both clinical and laboratory features. The patient has not developed additional symptoms, does not suffer from dysphagia and the cardiovascular and pulmonary assessments show no complications, and her muscular strength has improved significantly, allowing her

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