Mitochondrial cytopathy presenting with features of Gitelman's syndrome

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Mitochondria are essential for the homeostasis of every cell except red blood cells.[1] Therefore, mitochondrial disorders cause a wide range of clinical presentations; however, organs with higher aerobic metabolism tend to be more severely affected.[1] These symptoms, although severe, can be non-specific. Gitelman syndrome (GS) is a primary renal tubular disorder with hypokalemic metabolic alkalosis, hypocalciuria, and magnesium deficiency.[2] Gitelman et al described it in 1966, in 3 female patients, 22-47 years old. It is more typical of adults and age at presentation is usually 5 years or more. Failure to thrive and short stature has been described occasionally, and it could be included as an association.[3] However, recently 3 cases of GS and growth hormone (GH) deficiency were reported,[4,5] and considered as a new phenotype of GS with a new complex hereditary renal-tubular-pituitary syndrome.[5] We report another case of GS that was associated with GH deficiency, partial adrenocortical hormone (ACTH) deficiency, and mitochondrial encephalopathy.

A 9-year-old boy presented with repeated episodes of carpopedal spasms, constipation, fatigue, muscle cramps, and muscular weakness with on/off tetanic episodes since the age of 3 years. His height was 104 cm [–5.1 SDS below the mean] and his weight was 14.5 kg [–3.6 SDS below the mean]. He had a normal upper to lower segment ratio. He had bilateral ptosis but no other dysmorphic features. His blood pressure was 90/50, and the rest of systemic examination was unremarkable apart from generalized muscular weakness. His parents reported that he was of normal intelligence, and his performance was above average at school. There was no relevant family history and parental consanguinity between parents. He had 2 healthy siblings. His father's height was 173 cm [-0.6 SDS] while mother was short with height of 142 cm [-3.6 SDS] and his target height was 164 cm [-1.9 SDS]. His serum calcium was low (1.86 mmol/l) with simultaneous low urinary calcium level of 0.35 mmol/l. He was hypomagnesemic with a serum level of 0.58 mmol/l and urinary magnesium was normal. He had a metabolic alkalosis with a pH of 7.48 and bicarbonate of 25mmol/l. He had low serum potassium of 2.9 mmol/l and urinary potassium of 41.7 mmol/l. Urine chloride was normal. He had normal full blood count with hemoglobin of 13.5 g/dl. He had a normal liver function tests, muscle enzymes and serum lactate. Celiac screen was negative, including IgA-antigliadin, antiendomysium, and anti-tissue transglutaminase antibodies with normal total IgA level. He was diagnosed as GS based on hypokalemia, hypocalcemia, hypomagnesemia, high urinary chloride, and metabolic alkalosis on multiple occasions. In the view of his extreme short stature, a growth hormone stimulation test was performed using both clonidine and glucagon. There was a poor GH response with a peak of 5.6 ng/ml (normal >10 ng/ml). He had a normal parathyroid hormone level of 1.4 pmol/l, normal thyroid function tests with thyroid stimulating hormone of 4.6 u/L and free thyroxine of 15.7 pmol/l. There was no evidence of nephrocalcinosis on renal ultrasound. Rennin and aldosterone levels were normal. Magnetic resonance imaging revealed a pituitary gland of normal size, shape, and intensity with a normal infundibulum. He was treated with potassium supplementation, magnesium citrate, and calcium. His serum calcium and magnesium were normalized, however, his potassium remained low at 3-3.4 mmol/l. At the age of 9.5 years, he was commenced on rhGH initially at 0.5 mg/day. Response was initially poor, and therefore the dose was increased gradually to 1 mg every night. There was a partial response with improvement in his growth velocity. Ten days before rhGH was commenced, he presented to the emergency room with acute onset of drowsiness, low-grade fever, and confusion. Cerebrospinal fluid analysis revealed high protein and lymphocytes. There was no microbial growth and his electroencephalogram showed changes of encephalitis. He was treated with a 10 day course of intravenous acyclovir, and he made a full recovery. A year after starting the rhGH, he presented twice with generalized fatigability and weakness associated with an upper respiratory tract infection. His electrolytes were normal on both occasions. Diurnal cortisol (at 8 am) was 301 nmol/l (138-635) with the maximum response with insulin tolerance test of 415.5 nmol/l (partial response). A diagnosis of partial ACTH deficiency was made, and he was commenced on hydrocortisone (8mg/m^2/day). He responded well to hydrocortisone with significant improvement on daily activity and general well being. Because of these repeated episodes of drowsiness that seemed to be triggered by infections, and because of his external ophthalmoplegia, he was evaluated for an underlying mitochondrial cytopathy. Serum lactate and pyruvate during these episodes were not documented, however, muscle biopsy revealed features consistent with mitochondrial cytopathy, which was confirmed by mitochondrial DNA (mtDNA) testing.

We report a case of mitochondrial encephalopathy presenting with features of GS. Mitochondrial cytopathy was suspected because of the presence of the bilateral partial ptosis, muscle weakness, and episodic drowsiness with infections. The diagnosis was confirmed late in the course of this child's disease because of the complexity and variability of his symptoms. In general, patients are considered for a mitochondrial evaluation after presenting with symptoms involving multiple systems without an obvious explanation.[1] This case is the fourth reported case of GS and GH deficiency. This case is different from that reported by Ko et al,[4] and the 2 cases reported by Bettinelli et al,[5] as it is associated with partial ACTH deficiency. Gitelman's syndrome patients usually have normal growth. However, it is associated with short stature in some patients.[3] Ko et al[4] reported a case of GH deficiency in a short child with GS who responded to treatment with GH therapy with markedly elevated growth rate. Bettinelli et al[5] described 2 unrelated children who were definitely diagnosed as GS by molecular evaluation for the mutation detected in the gene encoding the thiazide sensitive cotransporter of the distal convoluted tubules. Both cases presented with a new phenotype characterized by GH deficiency, disturbance in vasopressin secretion, empty sella, and normal values of serum magnesium and urinary calcium excretion in more than half the determinations. Our case fulfilled the criteria to diagnose GS,[2] as he had chronic renal hypokalemia unexplained by other renal abnormalities such as renal tubular acidosis, chronic hypomagnesemia, a blood pressure that is at the lower end of normal age, high urinary chloride concentration (>100mmol/l) and hypocalciuria.[2] Molecular genetics have recently demonstrated that mutations in genes encoding the thiazide-sensitive Na-Cl cotransporter of the distal convoluted tubule result in GS. Its gene has been mapped to chromosome 16q13. Growth hormone deficiency was documented in the reported case, with a partial response to GH therapy and with no effect on serum magnesium. This is different from Ko et al[4] who reported an excellent effect of rhGH on short-term linear growth and on serum magnesium which was normalized. Bettinelli et al[5] reported 2 cases with GH deficiency and partial vasopressin deficiency or delayed vasopressin secretion with a good clinical response to GH replacement. Our finding of partial ACTH deficiency agrees with the notion that the entity may be considered as a new complex hereditary renal tubular-pituitary syndrome.

Our case and previous reports indicate that GH provocative tests should be carried out in short children with GS.[4,5] However, other parameters could play a role in the pathogenesis of growth retardation in GS such as the disturbance of calcium metabolism related to osteopenia. There is no family history of similar illness in this reported case to suggest a specific mode of inheritance. However, the mode of inheritance in GS is thought to be autosomal recessive. Although, recently, some authors hypothesized that there are 2 different types of genetic transmission of GS, one autosomal recessive, and one autosomal dominant with high phenotype variability. They have observed that this genetic heterogeneity is associated with a different clinical expression.

In conclusion, we report a complex hereditary renal tubular pituitary syndrome with mitochondrial cytopathy, which may be responsible for such rare associations.

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