CASE REPORT

Vitamin D deficiency in a patient with HDR syndrome

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SUMMARY

The case of a patient with clinical symptoms, laboratory and imaging findings of hypoparathyroidism, sensorineural deafness, renal dysplasia HDR, or Barakat syndrome (hypoparathyroidism, deafness, renal dysplasia), and vitamin D deficiency, is presented. A Caucasian man aged 51 years with a history of chronic hypocalcaemia since childhood, was admitted with hypertonia of the body and extremities, and loss of consciousness. On admission, he was found to have severe hypocalcaemia, hyperphosphataemia, severe hypoparathyroidism, low serum magnesium and mild renal insufficiency. Calcium gluconate was administered intravenously supplemented with magnesium, and the patient recovered consciousness while clinical and laboratory findings improved. Evaluation revealed left renal aplasia and sensorineural deafness affecting both ears. Vitamin D deficiency was also present. He was given calcium and vitamin D supplements orally, and the hypocalcaemia was corrected. This case is described as it is an extremely rare case of HDR syndrome with concurrent vitamin D deficiency.

BACKGROUND

HDR, or Barakat syndrome (hypoparathyroidism, deafness, renal dysplasia), is an extremely rare clinical entity, characterised by the simultaneous presence of hypoparathyroidism, sensorineural deafness and various forms of renal dysplasia.^{1–2} It is due to mutations of the *GATA3* gene, which is situated in the short arm of chromosome 10, rendering the gene absent or non-functioning, and is acquired by autosomal-dominant inheritance. *GATA3* is related to the embryonic development of ears, parathyroid glands and kidneys.³ At a clinical level, hypoparathyroidism causes hypocalcaemia, chronic fatigue, episodes of muscle spasm and occasional crises of tetany. Parathyroid hormone levels vary from the lower levels of normality to non-detectable. Hearing loss may be mild to complete, is most often bilateral, and appears postnatally. It mainly affects the higher frequencies.⁴ Finally, as far as the renal defect is concerned, it appears as dysplasia, hypoplasia or, rarely, full renal aplasia, disorders of the pericalicular renal architecture, renal scars and vesicoureteral reflux. These disorders gradually lead to functional renal insufficiency with haematuria, proteinuria, nephrotic syndrome and gradually evolving renal failure. Diagnosis of the syndrome may be performed at any age in relation to the time and severity of the symptoms during the life course of the affected patient. The prognosis varies and depends on the severity of renal disease. Vitamin D deficiency has not so far been reported in the context of HDR syndrome.

CASE PRESENTATION

An unmarried and childless 51-year-old Caucasian man was transferred to the emergency department, unconscious, with hypertony of the trunk and arms. According to his next of kin, for 10 days prior to the event, the patient was not taking his medications, calcium and vitamin D supplements, and experienced gradual deterioration of cognitive function, hypertony of the extremities, crises of tetany, saliva loss and episodes of sleep apnoea.

His history revealed the presence of chronic hypocalcaemia, for which he was on therapy with calcium and vitamin D supplements; bilateral hearing loss since childhood; left renal aplasia; and repeated hospitalisations due to tetanic crises. Alcohol abuse during the past 8 years was reported and the patient had been submitted to surgery for bilateral cataract correction 8 years prior. Concerning therapy, the patient was intermittently taking calcium and vitamin D orally; he did not comply with medical instructions for continuous use of these medications.

Physical examination on admission revealed positive Chvostek sign, spasm of the feet and hands, contraction of the muscles of the abdominal wall, tachycardia (104 bpm), hypotension (arterial pressure 95/54 mm Hg), increased perspiration and paleness, with good respiratory function and no signs of obstruction of the respiratory tract observed. The patient's skin was hard and coarse, and micrognathia, tooth disorders and fragile nails were observed. In EEG, sinus rhythm was observed with mild prolongation of QT and ST (figure 1).

INVESTIGATIONS

Initial laboratory investigations revealed severe hypocalcaemia with mild renal insufficiency. In particular, serum glucose was 111 mg/dL, serum urea 29 mg/dL, creatinine 1.9 mg/dL, glomerular filtration rate 42.4 cc/min, serum sodium 139 mmol/L, potassium 3.7 mmol/L, serum calcium 3.5 mg/dL (normal values 8.5–10.2 mg/dL), phosphate 8.0 mg/dL (3.5–5.0 mg/dL), magnesium 1.6 mg/dL (1.7–2.6 mg/dL), lactic dehydrogenase 496 U/L, alkaline phosphatase 58 U/L, C reactive protein 3.23 mg/L, parathyroid hormone 0.7 pg/mL (10.0–65 pg/mL), 25 (OH)D₃ 17 ng/mL (>30 ng/mL) and thyroid-stimulating hormone was 2.6 mIU/L. On admission, blood gasses were also abnormal, as mild hypoxaemia was observed, pO₂ being 65 mmol/L, pH 7.399, PCO₂ 46.1 mmol/L and HCO₃⁻ 27 mmol/L in arterial blood, in the context of fully compensated respiratory acidosis. A brain CT scan performed was normal, while abdomen ultrasonography revealed the absence of the left

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Figure 1 Sinus rhythm with mild prolongation of QT and ST intervals, as shown on ECG performed on admission (QTc=550 ms).

kidney. Audiography revealed bilateral sensorineural hearing loss (figure 2). Genetic tests were not performed.

TREATMENT

Fluids were administered intravenously with calcium gluconate and electrolytes, and, sequentially, calcium, magnesium and vitamin D, orally. Some hours after the initiation of therapy with the attendant calcium level increment, gradual improvement of the level of consciousness was observed in the patient, with improvement and finally full restoration of neuromuscular function as well as full restoration of cardiac function and stabilisation during the first 24 h of hospitalisation. However, as the patient improved, the presence of cognitive impairment became apparent. Sentimental instability, slowness of thought, and irritability were evident, rendering the patient uncooperative.

OUTCOME AND FOLLOW-UP

The patient improved and calcium levels were corrected. He was given instructions for continuous treatment with calcium

and vitamin D supplements. Four years later he appeared for follow-up with normal calcium and phosphate levels.

DISCUSSION

In this case, phenotype, history, symptoms and clinical picture, as well as laboratory and imaging findings, were compatible with the diagnosis of HDR, or Barakat syndrome. The patient also had vitamin D deficiency.

HDR (hypoparathyroidism, neurosensory hearing loss and renal aplasia) syndrome is known to be associated with heterozygous mutation of the *GATA3* gene,³ which encodes translational factor *GATA3*. However, not all patients with HDR syndrome exhibit all these manifestations; other clinical manifestations are evident in some cases,^{5 6} as the syndrome is correlated with secondary clinical signs such as micrognathia, dental absence and coarse skin; emotional and mental symptoms are also observed, with patients manifesting depressive symptoms and agitation. It should be noted that our patient displayed irritability.

Figure 2 Audiogram from the patient showing sensorineural hearing loss. ISO denotes International Standards Organization.

In a study performed in Japan on the clinical description and genetic analysis of *GATA3* in five Japanese patients with HDR syndrome,⁷ two patients had a genetic syndrome, all five had hypoparathyroidism and sensorineural deafness, with renal malformations being absent in four, while two female patients had genital tract disorders. The *GATA3* analysis showed newly found and already described inactivating mutations; this study showed the clinical heterogeneity of HDR syndrome. In a clinical and genetic study of patients with deletions of chromosome 10p, the short arm of chromosome 10, it was observed that all the patients had mental retardation and speech disorders.⁸ The patient described in our case had marginally low mental ability, speech difficulty and irritability.

Recently, in a case from the United Arab Emirates, a young boy with HDR syndrome and accompanying hypomagnesaemia was described with high magnesium urine disposal.⁹ Our patient also had mild hypomagnesaemia, which contributed to the severity of symptoms of hypocalcaemia. In the case of the young patient from the United Arab Emirates, a heterozygous deletion of two nucleotides in exon 2 of *GATA3* was observed. Two patients suffering from HDR syndrome and renal tubular acidosis^{5,10} have been described, one of whom had hypergonadotrophic hypogonadism and autoimmune thyroiditis.¹⁰

The discovery of *GATA3* gene, of which inactivating mutations lead to HDR syndrome, was the result of research in cases of patients with DiGeorge syndrome. The majority of patients with DiGeorge syndrome have microdeletions in chromosome 22q11; some, however, exhibit deletions in the short arm of chromosome 10.¹¹ HDR syndrome is caused by mutations of *GATA3* gene, which is also situated in the short arm of chromosome 10. The disorder seems to be acquired by autosomal dominant inheritance. It has been noted that *GATA3* is related to the embryonic development of ears, parathyroid glands and kidneys.³

The auditory phenotype in HDR syndrome has been studied,¹² with hearing loss found to be moderate to severe, slightly worse at the higher end of the frequency spectrum and occasionally progressive with age.

The patient described had vitamin D deficiency. It is not known whether the deficiency was a result of his failure to

comply with medical instructions to regularly take vitamin D supplements orally. Vitamin D deficiency along with severe hypoparathyroidism may have contributed to the severity of the hypocalcaemia observed on admission.

In conclusion, the case of a patient suffering HDR, or Barakat syndrome, and vitamin D deficiency, is described. HDR syndrome is rare, and our case of a patient suffering from HDR syndrome and vitamin D deficiency is extremely rare.

Learning points

- ▶ Hypoparathyroidism may rarely coexist with renal and hearing abnormalities.
- ▶ Hypoparathyroidism may be accompanied by vitamin D deficiency, which aggravates its symptoms.
- ▶ Treatment with calcium and vitamin D supplements corrects the biochemical abnormalities of hypoparathyroidism.

Competing interests None declared.

Patient consent Obtained.

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