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CASE REPORT

Hypokalemic periodic paralysis in a patient with acquired growth hormone deficiency

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ABSTRACT. ***Context:*** **Hypokalemic periodic paralysis (HypoPP) is a rare disorder consisting of sudden episodes of muscle weakness with areflexia involving all four limbs, which spontaneously resolve within several hours or days. Primary HypoPP is genetically determined, while secondary acquired HypoPP has been described in association with thyreotoxycosis, hyperaldosteronism, kidney diseases, diuretics and liquorice abuse, gastrointestinal potassium loss, or cysplatinum therapy.** ***Objective:*** **To report a case of HypoPP associated with GH deficiency.** ***Patient:*** **A 33 yr-old man with hypopituitarism and diabetes insipidus secondary to pituitary stalk-localized sarcoidosis, and documented HypoPP episodes.** ***Clinical Presentation:*** **Neurologic exam outside HypoPP episodes was normal. Needle electromyography was normal without myotonia or other spontaneous electric activity. Muscle biopsy documented a vacuolar myopathy with tubular aggregates. However, genetic analysis ruled out common mutations of the voltage-gated calcium channel observed in primary HypoPP. Common causes of secondary HypoPP were also ruled out. The patient was diagnosed with severe GH deficiency with modest fasting hyperinsulinemia and insulin resistance and started on GH replacement therapy, an α-glucosidase inhibitor (acarbose) and a diet low in simple carbohydrates.** ***Conclusions:*** **GH replacement therapy, acarbose and a diet low in simple carbohydrates resulted in the complete long-term (>2 yr) remission of HypoPP episodes. This is consistent with the hypothesis that the hyperinsulinemia associated to GH deficiency may trigger HypoPP episodes by increasing Na^+/K^+ ATPase activity and K^+ transport into the intracellular compartment with subsequent hypokalemia.**
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INTRODUCTION

Hypokalemic periodic paralysis (HypoPP) is a rare disorder characterized by sudden episodes of muscle weakness with areflexia involving all four limbs, usually occurring on awakening, after exercise or carbohydrate-rich meals (1, 2). Prodromic symptoms include xerostomy, thirst, and tachycardia. Spontaneous recovery may take several hours or days. Involvement of respiratory muscles and arrhythmias secondary to electrolyte imbalance are rare (1, 2). Primary HypoPP is an autosomal dominant disease, caused by mutations in the voltage-gated calcium channel gene CACNA1S (3) or, less frequently, by mutations in the voltage-gated sodium channel gene SCNA4A (4-6). Muscle biopsy (2) and response to acetazolamide (6) are used to differentiate between these two forms of primary HypoPP. Secondary or acquired forms of HypoPP are mostly observed during adulthood and may be associated with thyreotoxycosis (7), hyperaldosteronism (8), kidney diseases (9), diuretics and liquorice abuse (10), gastrointestinal potassium loss (11), and cysplatinum therapy (12). Primary forms are treated using the carbonic anhydrase inhibitors acetazolamide and dichlorophennamide (13, 14). In case of life-threatening hypokalemia, intravenous potassium supplementation is mandatory. In

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secondary or acquired forms of HypoPP, the treatment of the underlying disease will prevent further HypoPP episodes. In both primitive and secondary forms of HypoPP patients are advised to avoid precipitant factors. We report the case of HypoPP occurring in an adult male with hypopituitarism secondary to neurosarcoidosis, who had regression of HypoPP episodes with combined GH replacement and acarbose therapy.

CASE REPORT

A 33-yr-old man was referred to the Endocrinology Unit at the San Raffaele Scientific Institute in Milan, with a 2-yr history of progressive weight gain, fatigue, myalgias and recurrent post-prandial episodes of sudden limb weakness evolving to complete paralysis. Several of those episodes required admission to an emergency department, where severe hypokalemia was repeatedly documented (lowest value reported during paralysis: 1.8 mmol/l). Paralysis would resolve spontaneously after many h of rest or after iv potassium administration.

Family history was negative for HypoPP or muscle-weakness episodes. Repeated neurologic exams outside the paralytic episodes were normal. Two years before admission the patient was diagnosed with hypopituitarism and diabetes insipidus secondary to stalk-localized sarcoidosis. Pathology on a stereotactic biopsy showed chronic giant cell-, non-caseating-granulomatous hypophysitis. The patient received

Table 1 - *Antropometric parameters, biochemical and hormonal profile of the patient.*

Parameters	Before therapy	After 6 months of therapy
BMI (kg/m^2)	32.4	31.2
IGF-I (ng/ml, nv 115-307)	107	158
TSH (mU/l, nv 0.27-4.20)	0.01	0.01
fT_4 (ng/dl, nv 0.93-1.70)	1.06	1.18
fT_3 (ng/l, nv 1.8-4.6)	3.5	3.7
Glycated hemoglobin (%, nv 3.5-6.0)	4.9	4.7
S-fasting glucose (mg/dl, nv 65-110)	80	84
S-fasting insulin (μU/ml, nv 5-25)	15	12
HOMA-S %	53.7	65.9
HOMA-β %	188.8	147.5
S-creatinine (mg/dl, nv 0.5-1.25)	0.7	0.8
Microalbuminuria (mg/dl, nv<15)	11	Not evaluated
U-pH (nv 5-6.5)	6.2	Not evaluated
S-potassium (mmol/l, nv 3.5-5.0)	3.6	4.12
S-sodium (mmol/l, nv 135-148)	138	140
S-total calcium (mmol/l, nv 2.10-2.60)	2.29	2.36
S-ionized calcium (mmol/l, nv 1.18-1.30)	1.22	1.25
S-phosphate (mmol/l, nv 0.8-1.5)	1.29	1.37
S-chloride (mmol/l, nv 96-108)	103	102
U-potassium (mmol/24 h, nv 30-90)	49	52
U-sodium (mmol/24 h, nv 40-220)	135	128
U-calcium (mmol/24 h, nv 2-10)	1.9	8.0
U-phosphate (mmol/24 h, nv 11-32)	56.07	36.50
U-cytrate (mg/24 h, nv 349-956)	440	Not evaluated
S-aldosterone clin (pg/ml, nv 30-150)	35	43
S-aldosterone ort (pg/ml, nv 70-350)	73	81
P-renin activity clin (ng/Al/ml/h, nv 0.2-2.8)	1.47	1.38
P-renin activity ort (ng/Al/ml/h, nv 1.5-5.7)	2.81	2.5
P-parathyroid hormone (pg/ml, nv 10-65)	58	30
S-osteocalcin (ng/ml, nv 1.1-7.2)	5.8	7.7
25OH-D_3 vitamin D (ng/ml, nv 10-68)	15	21
Hemogasanalisis:		
pH (nv 7.35-7.45)	7.387	
pCO_2 (mm Hg, nv 35-45)	38.4	
pO_2 (mm Hg, nv 80-110)	80	
Bicarbonate (mmol/l, nv 22-26)	22.6	
CO_2 (mmol/l, nv 23-27)	20	
Base excess (mol/l, nv 2.0-3.0)	–2.1	
O_2 saturation hemoglobin (%, nv 95-98)	96.7	

BMI: body mass index; HOMA-S: homeostasis model assessment for insulin sensitivity; HOMA-β: homeostasis model assessment for β-cells function; nv: normal values; fT_3: free T_3; fT_4: free T_4; P: plasma; U: urine; S: serum.

immunosuppressive therapy with oral prednisone (1 mg/kg/day) that was progressively tapered and replaced with cortisone acetate and oral methotrexate (the latter stopped after 1 yr). At the time of admission the patient was on cortisone acetate (25 mg/day), testosterone enantate (250 mg/15 days), l-thyroxine (75 µg/day) and intranasal desmopressin (0.125 mg b.i.d.) replacement therapy. Anthropometric, biochemical and hormonal parameters are shown in Table 1. Replacement therapy was adequate. Free T_3, free T_4 levels, plasma renin activity, and serum aldosterone levels in clino and orthostatism were within the normal range. Kidney function was normal with unremarkable urinalysis. Sarcoidosis-related renal tubular acidosis (15) was ruled out based on a normal urinary pH and urinary citrate excretion (Table 1). The patient had no diarrhea, and reported no use of diuretics or licorice, nor history of cysplatinum exposure. Furthermore, serum electrolyte levels and urinary electrolyte excretion were normal. Needle electromyography (EMG) was normal with no myotonia or other spontaneous electric activity recorded. Nerve conduction velocity was also normal. Muscle biopsy showed a vacuolar myopathy with tubular aggregates (Fig. 1A, B, C, D), as observed in skeletal muscle channelopathies. However, genetic analysis ruled out the common mutations on the voltage-gated calcium channel gene CACNA1S Arg528Hys and CACNA1S Arg1239Hys and of the voltage-gated sodium channel gene on domain D2 Arg672Hys/Gly, Arg669Hys, and Arg672Ser.

A GHRH (1 µg/kg iv) + arginine (0.5 µg/kg iv) stimulation test documented severe GH deficiency (GH peak 1.7 µg/l), confirmed by the finding of low circulating IGF-I levels (107 ng/ml, nv 115-307). Magnetic resonance imaging of the hypothalamic-pituitary region showed slight thickening of the pituitary stalk with enhancement after gadolinium administration, compatible with the previous diagnosis of stalk-localized sarcoidosis. We estimated insulin sensitivity and β-cell function using the homeostasis model assessment (HOMA-S and HOMA-β, respectively) (16). Hyperinsulinemia and insulin resis-tance were documented (Table 1), as expected in hypopituitary adults with GH deficiency (17).

GH replacement therapy was started at a dose of 0.3 mg/day sc. The patient was also prescribed an α-glucosidase inhibitor (acarbose 200 mg t.i.d.) and a diet including 50% of complex carbohydrates, both aimed at reducing insulin peaks in response to meals. Since the start of treatment in February 2004, the patient reported no further HypoPP episodes or complaints of fatigue and muscle pain.

DISCUSSION

We reported a case of HypoPP secondary to GH deficiency in an adult male with hypopituitarism due to pituitary stalk-localized neurosarcoidosis. To our knowledge, this is the first report of HypoPP associated to adult GH deficiency. Conditions commonly

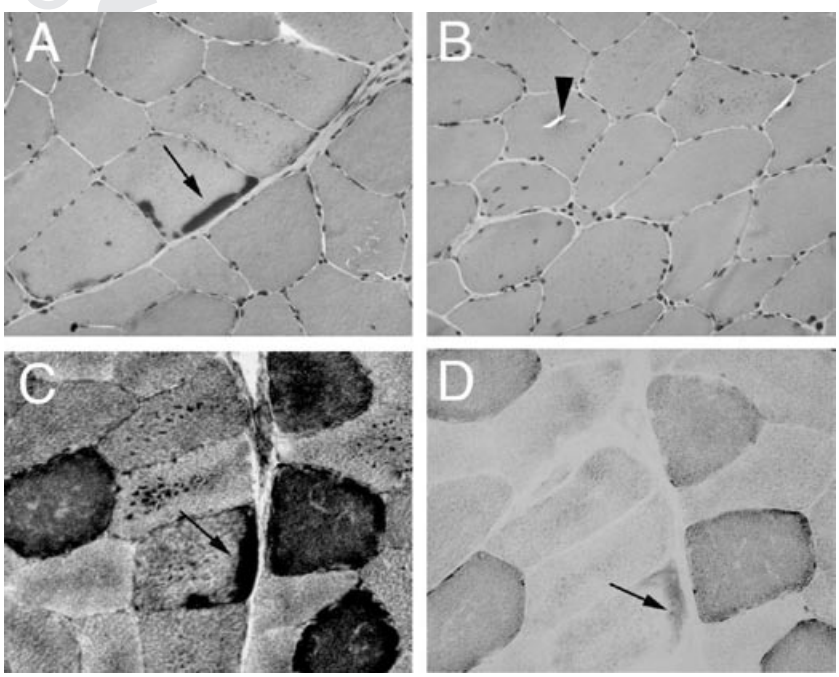

Fig. 1 - *Muscle biopsy (magnification 400x). Hematoxylin and eosin (H&E) staining shows peripheral basophilic aggregates (Panel A, arrow) and an optically empty vacuol (Panel B, arrowhead). Basophilic aggregates show intense reactivity on nicotinamide adenine dinucleotide-tetrazolium reductase (NADH-TR) staining (Panel C), but are mostly negative on succinic dehydrogenase (SDH) staining (Panel D).*

associated with HypoPP, such as hyperthyroidism, primary hyperaldosteronism, diuretics abuse, gastrointestinal potassium loss, and sarcoidosis-related renal tubular acidosis were ruled out. Glucocorticoids abuse as a cause of hypokalemia was excluded for the following reasons: 1) at the time of the hypokalemic episodes, the patient showed no clinical features of glucocorticoid excess; 2) a factitious increase of steroid dosage was likely to persist also after the start of GH replacement therapy, when the hypokalemic episodes promptly disappeared; 3) in case of glucocorticoid excess, the expected effect would be chronic hypokalemia, rather than acute hypokalemic episodes after meals or at awakening. Neuromuscular symptoms during paralytic attacks were undistinguishable from those of a primary skeletal muscle calcium or sodium channel hypokalemic periodic paralysis. However, a genetic form of HypoPP was unlikely since the patient had no family history of HypoPP and common mutations for CACN1A and SCN4A were excluded.

The mechanism triggering a HypoPP episode in a patient with GH deficiency remains a matter of speculation. A direct effect of GH on the ion channels involved in the pathogenesis of HypoPP cannot be excluded but, to our knowledge, it has never been demonstrated. We hypothesized that the hyperinsulinemia accompanying GH deficiency documented in our patient may increase Na^+-K^+ ATPase activity (18). This, in turn, would increase potassium transport into the intracellular compartment with subsequent hypokalemia. The prompt regression of HypoPP episodes observed in our patient immediately after starting treatment with GH and an α-glucosidase inhibitor is consistent with this hypothesis. The hypothesis of a decreased effectiveness of cortisone therapy because of GH-dependent inhibition of 11β-hydroxysteroid-dehydrogenase type 1 (19) seemed unlikely, since there was no need for adjustment of cortisone dose after the start of GH replacement therapy. The need for an underlying predisposing genetic or epigenetic condition, resulting in an ionic transmembrane electrolyte imbalance (7, 20), has been shown for HypoPP associated with thyreotoxicosis and may partly explain why HypoPP does not occur in all patients with GH deficiency. The need for a predisposing genetic factor is also suggested by a previous study showing that insulin-induced hypoglycemia is not associated with an increased risk of hypokalemia among hypopituitary adults with GH deficiency compared to individuals with normal anterior pituitary function (21).

In conclusion, GH deficiency may be another cause of secondary (acquired) HypoPP. GH deficiency should be considered in patients with unexplained, episodic muscle weakness with a history of hypothalamic/pituitary disorders. Replacement therapy with recombinant GH, and dietetic/pharmacological approaches to reduce hyperinsulinemia may obtain complete long-term remission of HypoPP episodes.

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