SCIENTIFIC LETTERS

Hyponatremic rhabdomyolysis in Addison’s disease in a child with autoimmune polyglandular syndrome type 2

Rabdomiólisis hiponatrémica en enfermedad de Addison en niño con síndrome poliglandular autoinmune tipo 2

Autoimmune polyglandular syndromes (APS) are defined as the coexistence in a same individual of at least two autoimmune polyglandular diseases, and other non-endocrine autoimmune diseases may be associated.1 There are two main types of APS, which differ in age at onset, type of inheritance, and the diseases characteristic of each of them.2 APS type 1 is highly uncommon, of autosomal recessive inheritance, and monogenic (AIRE gene mutation in chromosome 21 q 22.3), and occurs in childhood and adolescence as the triad of chronic mucocutaneous candidiasis, hypoparathyroidism, and primary adrenal insufficiency.1 APS type 2 has polygenic inheritance, with autosomal dominant transmission and incomplete penetrance. Its prevalence is much greater (1:20,000), and is more common in females. Occurrence in children is however very unusual. Primary adrenal insufficiency occurs in 100% of cases, together with autoimmune thyroid disease (70–75%) (Schmidt syndrome) or with type 1 diabetes mellitus (50–60%) (Carpenter syndrome).2,4

In the setting of APS type 2, Addison’s disease is the initial manifestation in 50% of patients; occurs simultaneous with thyroid disease or type 1 diabetes mellitus in 20% of cases, and after these diseases in 30%.2

Adrenal insufficiency may occur with musculoskeletal abnormalities, but association with rhabdomyolysis is extremely uncommon. Concomitant hyponatremia is found in most cases.6,8

Rhabdomyolysis may be associated to hyponatremia, usually in situations of water intoxication or inadequate ADH secretion (SIADH). However, there are less than 10 reports of hyponatremic rhabdomyolysis in the setting of Addison disease.6

We report the case of a 9-year-old boy with type 1 diabetes mellitus since the age of 3 years who was diagnosed with adrenal insufficiency during an acute episode of hyponatremia and rhabdomyolysis. This case is of interest both because of the uncommon association of both conditions and the low incidence of autoimmune polyglandular syndrome type 2 (APS type 2) in childhood.2

The patient reported loss of strength and leg pain for the past three days, with no fever. He was receiving intensive insulin therapy at doses of 0.71 IU/kg/day. The patient had experienced in the previous week frequent hypoglycemia episodes, none of them severe, for no apparent cause, but no seizures. Results of recent laboratory tests showed normal thyroid function: TSH, 5.3 µU/mL (0.35–5.35) and free T4 0.9 ng/dL (0.81–1.76), with negative thyroglobulin and microsomal antibodies.

He had blood-related parents of Arab origin. His mother was with type 1 diabetes mellitus and celiac disease.

Examination revealed a good overall status, signs of mild dehydration, and tenderness of calf muscle masses. Laboratory test results included: urea, 85 mg/dL (12–42); creatinine, 0.68 mg/dL; GOT, 123 IU/L (6–31); GPT, 93 IU/L (7–40); Na, 120 mEq/L (136–145); and K, 6.8 mEq/L (3.5–5.1). After rehydration for 24 h with physiological saline, a trend to hypotension and mucocutaneous hyperpigmentation was found. Laboratory tests showed slight metabolic acidosis (pH 7.3; HCO3, 19.7 mmol/L; BE, −6.3); blood glucose, 319 mg/dL; CPK, 1043 IU/L (30–200) (not measured previously); Na, 127 mEq/L; K, 6.7 mEq/L; serum osmolality: 289 mOsm/kg; urine: specific gravity 1015, osmolality 536 mOsm/kg; Na, 126.4 mmol/L; K, 22.7 mmol/L; Cl, 133 mmol/L; Transtubular K gradient (TTKG), 1.8 (suggests absence of mineralocorticoid activity). Despite adequate water and electrolyte replacement, Na levels of 131.9 mEq/L and K levels of 5 mEq/L persisted at 72 h, with normalization of CPK.

Electrolyte changes, hyperpigmentation, decreased insulin requirements, and frequent hypoglycemic episodes suggested primary adrenal insufficiency. Hormone test results confirmed diagnosis: basal cortisol, 39.7 nmol/L (1.4 µg/dL); basal ACTH, >1250 pg/mL; basal aldosterone, <6 pg/mL (40–300); and plasma renin activity, 16.3 ng/mL/h (0.2–2.3); Anti-21-hydroxylase antibodies, 48.2 IU/mL (+). Because of patient stability, treatment was started with...
oral hydrocortisone 10 mg/m²/day and fludrocortisone 0.1 mg/day, with subsequent normalization of electrolytes. Insulin therapy dosage had to be doubled (1.4 IU/kg/day), which decreased hypoglycemia episodes. Severe hyponatremia may cause rhabdomyolysis, which has mainly been reported in cases of water intoxication. Association of rhabdomyolysis with primary adrenal insufficiency is extremely uncommon. Concomitant hyponatremia exists in almost all cases, except in one reported in 2003. The lowest sodium level seen was 97 mmol/L. Potassium levels were increased in more than half the cases (highest value reported, 5.8 mmol/L). Our patient showed hyponatremia of 120 mmol/L and hyperkalemia of 6.8 mmol/L. Children with severe hyperkalemia (>7 mmol/L) may experience ascending muscle weakness, with occasional progression to flaccid paralysis. These findings are similar to those of patients with Guillain-Barré. In adrenal insufficiency, cortisol deficiency stimulates CRH release, with increased ADH secretion and decreased sodium levels. On the other hand, aldosterone deficiency promotes renal sodium excretion, causing hypovolemia and ADH release mediated by baroreceptors. The mechanism by which rhabdomyolysis occurs in the setting of hyponatremia is not clear, and various hypotheses have been proposed: rupture of the myocyte membrane caused by fluctuation in intracellular and extracellular osmolality by an increase in intracellular calcium through the sodium–calcium exchanger; or on the other hand, correction of severe hyponatremia may also cause rhabdomyolysis because CPK increase has occasionally been seen some days after correction of electrolyte imbalance. Measurement of CPK levels in patients with adrenal insufficiency complicated with hyponatremia appears to be necessary because association with rhabdomyolysis may occur more frequently than previously recognized. Our patient is probably the first clinical case reported in children of an association of hyponatremic rhabdomyolysis and adrenal insufficiency in the setting of a Carpenter syndrome.

References

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Lixisenatide clinical experience on patients with type 2 diabetes and obesity in endocrinology offices in Malaga

Experiencia clínica con lixisenatida en pacientes con diabetes tipo 2 y obesidad en consultas de atención especializada en Málaga

Glucagon-like peptide 1 (GLP-1) agonists decrease glucose levels with a very low risk of hypoglycemia, limit weight increase associated to insulin therapy and have favorable effects on dyslipidemia, high blood pressure, endothelial function, cardiac contractility, intestinal lipoproteins, inflammation, and indirect kidney function markers. A prospective study with within-subject measures of change was conducted on 43 patients (62.8% females) with type 2 diabetes mellitus and obesity who started treatment with lixisenatide (Lyxumia®, Sanofi Aventis S.A.) to assess drug tolerability and impact on weight and metabolic control. Subgroups without and with prior antihypertensive treatment (23.3% and 76.7% respectively) and lipid-lowering treatment (41.9% and 58.1% respectively) and occurrence of side effects were analyzed. Mean age was 58 ± 13.3 years, and mean time since diabetes onset 11.9 ± 7.3 years. A family history of cardiovascular disease (CVD) and diabetes was found in 41.4% and 62.9% of patients respectively. At the baseline visit, treatment consisted of oral agents (86% of patients), GLP-1 analogues (18.6%), and insulin (79.1%; basal 37.2%, premixes 25.6%, and basal-bolus 16.3%). Mean

Please cite this article as: Roca-Rodríguez MM, Tapia-Guerrero MJ, Maraver-Selfa S, Tinahones FJ, Mancha-Doblas I. Experiencia clínica con lixisenatida en pacientes con diabetes tipo 2 y obesidad en consultas de atención especializada en Málaga. Endocrinol Nutr. 2015;62:512–514.