

## A dangerous mixture

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### ABSTRACT

A 59-year old woman was admitted for fatigue and arm paresthesias with Trousseau sign. Her medical history included thyroidectomy and hypercholesterolemia recently treated with simvastatin. Laboratory tests showed severe hypokalemia and hypocalcemia, severe increase in muscle enzymes, metabolic alkalosis; low plasma renin activity, increased thyroid-stimulating hormone, normal free thyroxine, increased parathyroid hormone, decreased vitamin D3; alterations in electrolyte urinary excretion, cortisol and aldosterone were excluded. Hypothesizing a statin-related myopathy, simvastatin was suspended; the patient reported use of laxatives containing licorice. Electrolytes normalized with intravenous supplementation. Among many biochemical alterations, none stands out as a major cause for muscular and electrolyte disorders. All co-factors are inter-connected, starting with statin-induced myopathy, worsened by hypothyroidism, secondary hyperaldosteronism and vitamin D deficiency, leading to hypocalcemia and hypokalemia, perpetrating muscular and electrolyte disorders. The importance of considering clinical conditions as a whole emerges with multiple co-factors involved. Another issue concerns herbal products and their potential dangerous effects.

### Case Report

Emilia, a 59-year old woman was hospitalized due to fatigue, cramps and paresthesias involving her arms with a spontaneous Trousseau sign (spasm of the wrist and metacarpophalangeal joints, extension of distal and proximal interphalangeal joints, adduction of the fingers).<sup>1,2</sup> Urgent biochemical tests showed hypernatremia (150 mmol/L), hypokalemia (2.3 mmol/L), hypocalcemia (total calcium 7.3 mg/dL, ionized calcium 0.89 mmol/L).

Her medical history included: thyroidectomy for Graves's disease, now treated with levothyroxine, vi-

tiligo, mild carotid arteries atherosclerosis treated with acetylsalicylic acid, recently diagnosed hypercholesterolemia treated with simvastatin, started the previous month.

On admittance to hospital the patient was alert and collaborative; general examination did not show any particular alteration except for vitiligo and mild hyperreflexia. Blood pressure was high (140/100 mmHg) and other vital parameters were normal.

Routine laboratory tests confirmed hypernatremia, hypocalcemia and hypokalemia and showed: metabolic alkalosis (pH 7.50, pCO<sub>2</sub> 44 mmHg, HCO<sub>3</sub> 34 mmol/L); mild hypomagnesemia (1.54 mg/dL; n.v. 1.58-2.55); albuminemia, phosphatemia, blood urea nitrogen and creatinine were normal, but with slightly increased urinary protein excretion (0.29 g/24 h); urinary excretion of calcium was low (31.2 mg/24 h; n.v. 100-320); urinary sodium excretion was elevated (290 mmol/24 h; n.v. 40-220); urinary excretion of phosphate and potassium was normal; muscle enzymes were very elevated (creatinine kinase 2509 U/L; myoglobin 466 ng/mL; aldolase 34.9 UI/L); cortisol and aldosterone level were normal, plasma renin activity was low (0.5 pg/mL in orthostatism and 1.5 pg/mL in clynostatism), thyroid-stimulating hormone (TSH) level was high (22.9 uUI/mL) with normal free thyroxine (FT<sub>4</sub>) (0.92 ng/dL); parathyroid hormone (PTH) level was high (70.8 pg/mL; n.v. 7-53); vitamin D<sub>3</sub> was low (19.2 nmol/L; n.v. 75-100). Blood cell count, plasma osmolarity, C-reactive protein, cholesterol and triglycerides levels were normal.

Electrocardiogram (EKG) showed sinus rhythm with normal heart rate (60 bpm), prolongation of QT interval. Chest X-ray was regular, upper and lower limbs electromyography showed only a mild

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and chronic radicular impairment (C6-C7 level).

We hypothesized statin-related muscle damage, therefore simvastatin was suspended at admission. Later on, the patient reported to have taken laxative products (herbal decoction and tablets) containing low doses of licorice in the previous weeks.

Hypokalemia was corrected with slow intravenous potassium solution, followed by oral potassium administration. The patient presented a new and short episode of carpo-metacarpal and finger tetany, successfully managed with slow intravenous calcium gluconate. Hypothesizing a form of hyperaldosteronism, a potassium-sparing diuretic was prescribed for the first week; chest X-ray and abdomen computed tomographic-scan did not show abnormalities.

Muscle enzymes, electrolytes and EKG normalized after a few days. At discharge, Emilia was prescribed vitamin D and an increased dose of levothyroxine.

## Discussion

The main change occurred in Emilia's habits had been the start of statin therapy. This provoked muscular damage, as was verified by biochemical tests.<sup>3-5</sup> However, hypothyroidism and hyperaldosteronism, with consequent hypokalemia and hypocalcemia, can all have contributed to statin-induced myopathy.<sup>6-8</sup>

Our patient underwent total thyroidectomy 16 years ago because of Graves's disease. Subsequently she started levothyroxine replacement therapy; since then, thyroid function was always reported to be normal. However, from our biochemical screening, subclinical hypothyroidism (TSH level was 22.9 uIU/mL, with normal FT4) emerged. It is well known that hypothyroidism can provoke muscular weakness and can worsen statin-induced myopathy.<sup>6</sup> At that stage, anyway, impaired thyroid function was not serious yet, so we do not regard this as a major cause of myopathy, considering it as one of many triggers.

Hypokalemia surely worsened muscular cramps and weakness.<sup>8</sup> It could be the result of laxative use: in addition, herbal laxative products contained low amounts of licorice, that lead to a secondary hyperaldosteronism, which contributed to myopathy.<sup>7-10</sup> and could be also linked to hypocalcemia.<sup>11</sup> Regarding other possible causes of hypokalemia, diuretic use, hypercortisolism and nephropathies were excluded.<sup>8</sup>

Hypocalcemia can cause muscular spasm, tetany and EKG alterations.<sup>12</sup> Our patient presented all these pathological characteristics that regressed after electrolyte values normalized. Among the major causes of hypocalcemia, only vitamin D deficiency emerged.<sup>13-15</sup> Regarding other possible causes of hypocalcemia, our patient never received diuretic therapy; massive intestinal loss of electrolytes was excluded because Emilia had occasional constipation, which she resolved taking

small amounts of herbal products; anti-transglutaminase antibodies were absent. She never presented pancreas nor kidney disease except a slightly increase in urinary protein excretion, and phosphatemia was normal. Hypoparathyroidism was excluded: PTH level was high to compensate hypocalcemia.<sup>13,14</sup>

## Conclusions

Among the many clinical and biochemical alterations we observed, none stands out as a major cause of muscular damage and electrolyte disorders. All co-factors that we examined appear to be inter-related, and could have contributed to worsen Emilia's clinical conditions. Therefore, we hypothesize a multifactorial etiology, consisting in statin-induced muscular damage, worsened by hypothyroidism, secondary hyperaldosteronism and vitamin D deficiency, which led to hypocalcemia and hypokalemia, that could worsen muscular damage and symptoms.

What we point out is the importance of considering clinical conditions as a whole, because multiple co-factors can be involved. Another relevant issue concerns herbal over-the counter products and their potential dangerous effects, that must always be taken into account.

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