Cognitive impairment and severe hypocalcemia in a patient with hypoparathyroidism and systemic sclerosis. Report of a case

Hipocalcemia severa y deterioro cognitivo en paciente con hipoparatiroidismo y esclerosis sistémica. A propósito de un caso

Systemic sclerosis (SS) is a multisystemic autoimmune disease of connective tissue that causes vascular damage and fibrosis. The incidence of thyroid dysfunction is significantly higher in patients with SS compared to the general population, and thyroid gland fibrosis has been reported in up to 14% of patients in autopsy studies. However, only two cases of hypoparathyroidism (HP) have been reported to date in patients with SS, and the two diseases were simultaneously diagnosed in both. An autopsy of the first patient showed fibrosis of all four parathyroid glands, while computed tomography (CT) of the brain of the second patient disclosed bilateral, symmetrical calcifications in the basal ganglia and cerebellum, a condition also known as Fahr’s disease (FD), whose association with HP was first reported by Eaton et al. in 1939.

We report here the case of a 57-year-old male patient diagnosed 17 years before with HP and SS with cutaneous, esophageal, and pulmonary involvement for which he was receiving treatment, who attended the emergency room for paresthesia, tremor, coldness and cramps in all four limbs, associated with memory loss and behavioral changes over the previous year. The patient’s history included high blood pressure (HBP), chronic obstructive pulmonary disease (COPD), superficial gastritis, macrocytic anemia, calcific tendinopathy, and subcapsular cataract. Current treatment consisted of methotrexate 5 mg: 1 comp/8 h (Wednesday and Thursday), prednisone 7.5 mg: 1 comp/day, nifedipine retard 20 mg: 1 comp/day, acfol 1 comp weekly, Ideos-20 vitamin D 1 comp/8 h, magnesium 1 comp/8 h. A physical examination showed, in addition to tremor and coldness, sclerodactily and cyanosis in all four limbs, associated with bradyhypoaemia and depressive mood. Laboratory test results included: total calcium 6.6 mg/dL (8.4–10.2); ionic calcium 0.85 mmol/L (1.12–1.32), phosphate 5.6 mg/dL (2.7–4.5), magnesium 1.62 mg/dL (1.80–2.60), C-reactive protein (CRP) 22.2 mg/L (0–5), PTH <3 pg/mL (12–65), (25(OH)) vitamin D 51 ng/mL (30–100), TSH 2.02, and T4 1.01. CT of the head revealed multiple bilateral, symmetrical intracerebral calcifications (Fig. 1). Six days after the start of treatment with calcium (oral and intravenous), magnesium, and 25-OH vitamin D, biochemical normalization and symptomatic improvement were achieved. A neurological study, including an examination of cerebrospinal fluid, allowed for a diagnosis of cortical-subcortical mild to moderate dementia. Alzheimer’s disease, demyelinating diseases, and tuberculosis were ruled out. Three cerebral aneurysms were incidentally found. After hospital discharge, low thyroxine levels were detected (TSH 2.60, T4 0.80), and a neck ultrasound examination showed a slight increase in thyroid size (an AP diameter of 18 mm) with no evidence of focal lesions or parathyroid glands. Treatment was started with levothyroxine sodium 50 µg daily. An immunological study ruled out the presence of peroxidase antibodies (<2.00 IU/mL), thyroglobulin (<2.00 IU/mL), and parathyroid antibodies (undetectable). Both the patient and his family stated that they were unaware of the importance of adequate compliance with calcium and 25-OH vitamin D treatment, and reported intolerance to the various preparations prescribed, with frequent treatment noncompliance.

FD was initially described by Delacour en 1850. FD is usually due to phosphorus and calcium metabolism disorders, occurring in up to 73–78% of patients with idiopathic HP, but may also be induced by other metabolic, infectious, or genetic causes (such as diabetes mellitus, AIDS or osteopetrosis). Today, the term “Fahr’s syndrome” tends to be used for congenital forms of the disease only. The differential expression of various osteogenic molecules in the caudate nucleus and gray matter of the brain appears to account for the preferential location of intracerebral calcifications in these areas. Their occurrence correlates to the duration...
of hypocalcemia and the presence of choroid plexus calcification, seizures, and cataract, and progression depends on the serum calcium/phosphorus ratio during follow-up. The reported patient had, in addition to subcapsular cataract, a long-standing history (17 years) of HP, and probably also of hypocalcemia because of erratic treatment compliance (with a low calcium/phosphorus ratio).

On the other hand, neuropsychological impairment occurs in up to one third of patients with HP, and has been correlated to the duration of symptoms of hypocalcemia, serum calcium levels, and the serum calcium/phosphorus ratio. In elderly patients, it also appears to be associated with the volume, number, and location of calcifications through its impact on blood flow and synaptic transmission. In our patient, FD due to long-standing HP was considered to be the most probable cause of cognitive impairment, as well as chronic hypocalcemia due to treatment noncompliance. However, the degree of dementia appeared to be more severe than would normally be expected for classical FD, and the extensive calcification found in the patient was also striking, as he had a greater number and volume of intracerebral calcifications than usually reported in FD and than a patient previously reported with SS, HP, and FD. It should be noted that neurocognitive impairment may affect activities of daily living, promoting drug noncompliance, as suspected in our patient.

The detection of HP at 41 years of age and in parallel with SS diagnosis, the absence of prior surgery or radiation therapy in the neck area, and the findings of the immunological study suggest, by exclusion, a possible infiltrative origin of HP in this patient. Since SS may induce parathyroid gland fibrosis and HP, the prevalence of subclinical parathyroid changes in patients with SS is probably higher than that found to date. It is therefore advisable to increase the index of suspicion and to perform regular monitoring of phosphorus and calcium metabolism in patients with SS, especially in those with cognitive impairment, behavioral changes, or cerebral calcifications. Once HP is diagnosed, it is essential to inform both patients and their families about the importance of good treatment compliance and the potential risks of inadequate medication intake. Noncompliance may be both the cause and the consequence of cognitive impairment associated with HP, as it promotes the occurrence and progression of FD through a long-term maintenance of hypocalcemia and a low calcium/phosphorus ratio.
Conflicts of interest

The authors state that they have no conflicts of interest.

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Reference values and universal screening of thyroid function in the first trimester of the population of pregnant women in Toledo (Spain)∗

Valores de referencia y cribado universal de la función tiroidea en el primer trimestre de la población de mujeres gestantes del área de Toledo

Because of the physiological changes which occur during pregnancy, pregnant women have reference thyroid hormone levels different from those of the general population. Both the Spanish Society of Endocrinology and Nutrition (SEEN) and North American and European scientific bodies recommend that thyroid hormone levels be assessed according to the reference values for each trimester and population using adequate laboratory procedures. This study aimed at establishing the reference values of TSH, free T4 and free T3 during the first trimester of pregnancy, the prevalence of autoimmune thyroid disease, and the current degree of implementation of universal thyroid screening in our healthcare area. This is the only study published to date that provides two reference ranges for the first trimester of pregnancy (<11 weeks and 11–13 weeks).

A prospective study was conducted enrolling all pregnant women who attended the clinical laboratory of our hospital complex for prenatal screening for aneuploidy (weeks 11 to 13) during June–July 2004. In addition to the sample for detecting fetal chromosome diseases, a blood sample was taken for measuring TSH, free T4, free T3, thyroid peroxidase antibodies, and thyroglobulin antibodies. All laboratory parameters were tested using a two-step chemiluminescent microparticle immunoassay with Chemiflex® protocols in an Architect® i2000sr analyzer from Abbott-Diagnostics (USA). For each variable, the confidence interval of the 2.5th and 97.5th percentiles, corresponding to the lower and upper limits of reference values, were calculated following the recommendations of the International Federation of Clinical Chemistry. The sample size was 454 pregnant women, i.e. 12% of the 3516 deliveries occurring in our healthcare area in 2014. One hundred and nineteen women (26.2%) were excluded from the calculation of the reference values, 74 (16.3%) for thyroid autoimmunity, 33 (7.3%) for a history of thyroid disease, 4 (0.9%) for prior diabetes, and 5 (1.1%) for twin pregnancy. Finally, three pregnant women were excluded because of a missing laboratory result.

Consequently, reference values were calculated for 335 women taken as representing the healthy pregnant population. Prior laboratory tests including as a minimum TSH measurement in the first part of the first trimester (before week 11) were available for 261 (77.9%) of these women. Table 1 shows the reference values obtained for thyroid hormones and TSH before week 11 (median week