



Familial Hypocalciuria – Hypercalcemia

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Editorial

History

It is a rare pathological entity and it was first described by Fanconi under the name of idiopathic hypercalcemia as a state characterized by hypercalcemia, hypercalciuria most often, normal phosphatemia, and variable phosphaturia. Idiopathic infantile hypercalcemia was associated with vitamin-D supplementation in the 1950's. Blood tests showed hypercalcemia and borderline high vitamin-D levels [1]. The hypercalciuria initially described was interpreted as secondary to the administration of high doses of vitamin D or as a particular reaction of these patients. Recently it has been found that one of the causes of hypercalcemia in the child is-familial benign hypercalcemia that is transmitted in an autosomal dominant manner. It is also known as Familial Hypocalciuria-Hypercalcemia (FHH). FHH is generally characterized by lifelong hypercalcemia without hypercalciuria [2]. For this condition hypercalcemia and very low level of urinary calcium are considered to be characteristic.

Diagnosis

FHH is a genetic disease caused by the mutation of the CASR gene (Ca²⁺ sensing receptor gene) located on 3q chromosome. The hypercalcemia causes a characteristic symptomatology when it has values between 12 to 15 mg/dl. It affects especially the nervous system and the gastrointestinal system, but also the osteoarticular system. The effects of hypercalcemia on the nervous system consist of anorexia, vomiting, diminished growth process, headache, depression, irritability, confusion. The gastrointestinal manifestations consist of paralytic ileus, ectopic calcifications that may cause pancreatitis or abdominal pain and vomiting. The osteoarticular manifestations are more discrete, appear later and are detected in the form of joint pain and/or in the form of heterotopic ossifications. When these manifestations are noticeable, radiological and imaging investigations are required. Clinically, repeated episodes of anorexia and vomiting are particularly noticeable, and particularly the slowing down or stopping of the growth. The physiognomy of these patients is characteristic: The jaw is hypoplastic, the upper lip is more developed, the pavilions of the ears are larger and the eyes are globular. The children with microcephaly have a varying degree of psychomotor retardation. Hepatosplenomegaly or nephrocalcinosis can also be noticed. Renal ultrasound revealed medullary nephrocalcinosis [1,3]. The radiological examination reveals bone and soft parts lesions caused by increased concentration of calcium salts. The cortices of the long bones are thickened and denser and the medullary canal narrowed or clogged. At the spinal level the vertebral plates are more opaque and the vertebral discs have often calcifications. The bones of the skull and especially the base of the skull may appear more opacified. The calcium salts can be detected radioimagnostically especially on the large vessels walls and at the kidney level. The diagnosis of this rare disease is established having as a starting point two events: a) either an X-ray or b) increased calcium levels. The radiography is most of the time performed as a result of a trauma or other condition. When it reveals "something abnormal", apart from the underlying condition, a diffuse endosteal skeletal hyperostosis in the long bones complementary investigations are required, that allow the diagnosis to be established. Diffuse Idiopathic Skeletal Hyperostosis (DISH) is an under diagnosed condition that leads to ossification of ligaments and entheses of the spine and peripheral skeleton. An association between FHH and DISH has not been previously reported. Although most cases of hypercalcemia are found to have decreased bone mineralization, inactivation of calcium sensing receptor may induce a prometogenic response to hypercalcemia resulting in increased bone density [4]. In case of asymptomatic increased

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calcemia or symptomatic calcemia, additional investigations aim at obtaining a biochemical balance of phosphocalcial metabolism, followed by other investigations. Mild hypercalcemia was recognized by Foley in a 7-year-old boy during a headache assessment [5]. FHH is a rare, lifelong, benign condition. It is important to separate this condition from other hypercalcemic states such as hypercalcemia of malignancy and Primary Hyperparathyroidism (PHPT). Differential diagnoses include mainly PHPT, but in some cases also hypercalcemia of malignancy and use of thiazide diuretics. Similar to PHPT, FHH is characterized by hypercalcemia, unsuppressed or elevated plasma parathyroid hormone, and typically normal renal function. The phenotype is normal, and hypercalcemic symptoms are generally absent. The hallmark is a relatively low urine calcium excretion in contrast to PHPT, in which urine calcium excretion is increased [6].

Treatment

The treatment of heterotopic pains and ossifications is done by means of a calciprivia diet and calcium chelators. This treatment diminishes the extension of an existing ossification outbreak and diminishes the risk of other heterotopic ossification outbreaks. Surgical treatment is performed when the ossifications are symptomatic and is aimed at their ablation. The risk of recurrence is increased especially when the calcemia cannot be stabilized at normal values both before and after the surgery. Renal consequences include nephrocalcinosis with distal tubular dysfunction, nephrolithiasis, and finally renal failure. Early diagnosis and appropriate treatment is life-saving in such cases [7].

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