Clinical Letter

Dermal osteomata as first symptom of Albright’s hereditary osteodystrophy in a 10-month-old girl

History

A 10-month-old girl presented with progressive congenital subcutaneous hardening, starting on the back, and spreading over the shoulders and legs. There was no pruritus or pain. Her mother described an otherwise normal development of her daughter. Further characteristics were a round face and obesity (Figure 1). While the girl’s height (73 cm) fell within the 50th percentile, her weight (11.5 kg) exceeded the 97th percentile. The child also had a medical history of gastroesophageal reflux disease and an allergy to cow’s milk. Her two-year-old sister developed normally. Consanguinity of the parents was negated.

Clinical examination showed irregular livedoid maculae on her back, the right dorsal thigh (Figure 2) and the right clavicular region. Clearly delineated hardening could be palpated deep to these.

Histological examination showed well-defined areas of dermal calcinosis with secondary ossification devoid of inflammation (Figure 3).

The patient was examined in our pediatric department and underwent laboratory blood tests. Calcium, phosphate, parathormone and vitamin D3 levels were normal, but subclinical hypothyroidism was found and treated with levothyroxine. Molecular genetic examination revealed a \textit{GNAS1} mutation (c.348dupC; p. Val117Argfs*23).

Based on the \textit{GNAS1} mutation, histological findings and the clinical presentation, the patient was diagnosed with Albright’s hereditary osteodystrophy (AHO).
Discussion

The GNAS1 mutation (OMIM 139320) is rated as pathogenic and is the most likely cause of the patient’s disease. GNAS encodes for the alpha subunit of the stimulatory guanine nucleotide binding protein (Gsα). The detected GNAS1 mutation is a frame shift mutation at chromosome 20q13.32 with an earlier stop codon that results in reduced Gsα-protein activity [1]. Inactivating mutations in GNAS can cause various disorders characterized by heterotopic ossification. One of these is AHO, an autosomal dominant hereditary disease that was first described in 1942 by Albright et al., who recognized the typical AHO phenotype [2]. It is characterized by obesity, a typical round face with short nose and neck, brachydactyly with short metacarpals and metatarsals, and other skeletal deformations [3]. Moreover, 75% of the patients have a cognitive disability [4].

Histology commonly shows calcification in the mid to deep dermis with secondary ossification. However, dermal osteomata do not usually occur until an advanced age. Histological differential diagnoses include idiopathic calcinosis, posttraumatic calcinosis or calcification due to disorders of calcium-phosphate-metabolism [5]. Compared to primary ectopic bone formation, secondary ossification is characterized by the presence of calcification as well as osteomata.

Differential diagnoses caused by GNAS1 mutations include pseudohypoparathyroidism, pseudo-pseudo-hypoparathyroidism (PPHP, OMIM 612463) and progressive osseous heteroplasia (POH, OMIM 166350) [1]. The epigenetic concept of imprinting plays an important role in understanding the development of a certain phenotype. Depending on their parental origin, chromosomes are uniquely modified leading to changes in expression of genes located on these chromosomes.

Heterozygous, inactivating mutations on the paternal allele lead to pseudohypoparathyroidism type 1a (OMIM 103580) [1, 6]. PHP type 1a shows end organ resistance of the kidneys as well as the skeleton toward parathormone. This results in increased resorption of phosphate within the tubules of the kidney and hypocalcemia due to decreased mobilization of calcium from the bone. Hormone resistance also affects TSH, LH, FSH and GHRH, resulting in the typical AHO phenotype as well as obesity, intellectual disability or developmental delay.

A heterozygous, inactivating mutation on the paternal allele leads to PPHP or POH [1, 7]. The reason why paternal inheritance of the GNAS1 mutation leads to PPHP in some cases and to POH in other cases is still unclear. PPHP is a limited form of PHP type 1a, revealing an AHO phenotype without hormone resistance or obesity [1]. Progressive osseous heteroplasia is an even more restricted variant of PPHP. Beginning in infancy, patients with POH show heterotopic ossification extending from the dermis to deeper tissues [1].

An activating, usually postzygotic somatic mutation within the GNAS gene can cause a rare genetic disorder called McCune-Albright syndrome (MAS). This disorder is characterized by polyostotic fibrous dysplasia of the bone, precocious puberty, café-au-lait pigmentation and endocrinopathies including hyperthyroidism, growth hormone excess and hypercortisolism [8].

Another example of heterotopic ossification is fibrodysplasia ossificans progressiva (FOP; OMIM 135100), a rare autosomal dominant disease that leads to progressive ossification of muscles and tendons. In contrast to AHO and POH, FOP is not caused by a GNAS1 mutation but instead by a point mutation in the ACVR1 gene [9].

Most cases of GNAS1 mutations arise as de novo mutations. However, in regard to family planning it is still advisable to test parents and siblings [10]. While AHO is usually diagnosed during childhood, some cases have been described in which the initial diagnosis did not occur until adulthood [11].

In our case this systemic disease was diagnosed at an early stage, based on the clinical appearance, histology with dermal calcinosis and subsequent molecular genetic investigations. Early supportive therapy is essential for patients with AHO. Close supervision to detect secondary endocrinological disorders such as hypoparathyroidism should also be implemented.

This case stresses the importance of biopsy examination of ambiguous skin lesions and interdisciplinary collaboration to enable early diagnosis of systemic diseases in childhood.

Conflict of interest

None.

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