Growth hormone deficiency and secondary adrenal insufficiency in petrified ear syndrome: a case report and literature review

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Abstract

Petrified ear is a rare clinical entity characterized by the progressive hardening of normal, flexible auricular cartilage, leading to partial or complete auricular stiffness. In many cases, it provides a valuable clinical clue that allows the clinician to detect endocrinopathies (particularly Addison's disease) in a patient who has not received a diagnosis. We present the first documented case of petrified ears, which resulted in the diagnosis of both secondary hypoadrenalism and growth hormone deficiency (GHD). Additionally, we review the relevant literature. Petrified ear syndrome is probably an underreported clinical manifestation of other systemic disorders. It may, at times, serve as a valuable and simple clinical clue to suspect underlying endocrinopathies even in the absence of typical features.

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Introduction

Petrified ear, also known as stony pinna, is a rare clinical entity characterized by progressive hardening of normal flexible auricular cartilage, leading to partial or complete auricular stiffness. Approximately 150 cases have been reported worldwide, but the real incidence of this condition is unknown because it is not a commonly evaluated sign in clinical practice. In a previous paper, we hypothesized a first representation of this rare disease in a 1st-century Roman mosaic and, fascinatingly, in the remains of a 17th-century skull with ears that reemerged in 2019 during the restoration works of the church of Santa Luciella ai Librai in Naples.[1] Various systemic, metabolic, and endocrine disorders have been reported over time as causative factors in the development of pinna petrification. The most common endocrinopathy associated with this syndrome is primary adrenal insufficiency.[2] It has also been reported as a rare manifestation of acromegaly, while it has never been reported in growth hormone deficiency (GHD).[3] Here, we report the first case of petrified ears associated with secondary hypoadrenalism and GHD and a review of the literature.

Case Report

A 38-year-old man with a medical history of psoriasis, seborrheic dermatitis, and allergic rhinitis presented to medical attention with progressive bilateral stiffness of both auricles over the last 5 years. Clinical examination showed bilateral rigidity of both auricles without alteration of the overlying skin (Figure 1). Audiometry demonstrated mild sensorineural hearing loss in both ears. Nose examination was without any significant abnormal findings. The patient denied frostbite, wrestling, boxing, or any other contact activity that could cause local injury, physical trauma, or ear inflammation. CT scan of the skull revealed auricular cartilage calcifications without any bony deposits within the auditory canal (Figure 2). A comprehensive laboratory workup, including rheumatological, infectious disease, and hormonal evaluation, was conducted to identify potential underlying diseases. Phosphocalcium metabolism parameters were within the normal range (calcium 2.19 mmol/L [2.1-2.6], phosphate 0.9 mmol/L [0.8-1.5], PTH 57 pg/mL [15-65], 25-OH vitamin D 32 pg/mL, albumin 42.3 g/L [35-50]). Central adrenal insufficiency was suspected (adrenocorticotropic hormone [ACTH] 5 pg/mL, cortisol 10 ng/mL) and then confirmed by a standard dose (250 mcg) tetracosactrin test

(cortisol peak 32 ng/mL). Surprisingly, the patient didn't complain about any signs or symptoms of hypoadrenalism. No other pituitary deficiencies were found except for low levels of insulin growth factor (IGF-1) (TSH 3.67 mcUI/mL [0.1-4.5], fT4 0.97 ng/dL [0.93-1.7], fT3 3.81 pg/mL [2-4.4], LH 7.6 mU/mL, FSH 6mU/mL, testosterone 3.12 ng/mL [2.48-8.38], PRL 9.4 ng/mL, IGF-1 34 mcg/L [60-200]). To determine the hypothalamic or pituitary origin of hypoadrenalism, a corticotropin-releasing hormone (CRH) test was performed, leading to an ACTH and cortisol peak of 7.2 pg/mL and 5 ng/mL, respectively. Pituitary MRI showed an empty sella without any evidence of intrasellar masses or any other hypothalamic-pituitary abnormalities (Figure 3).

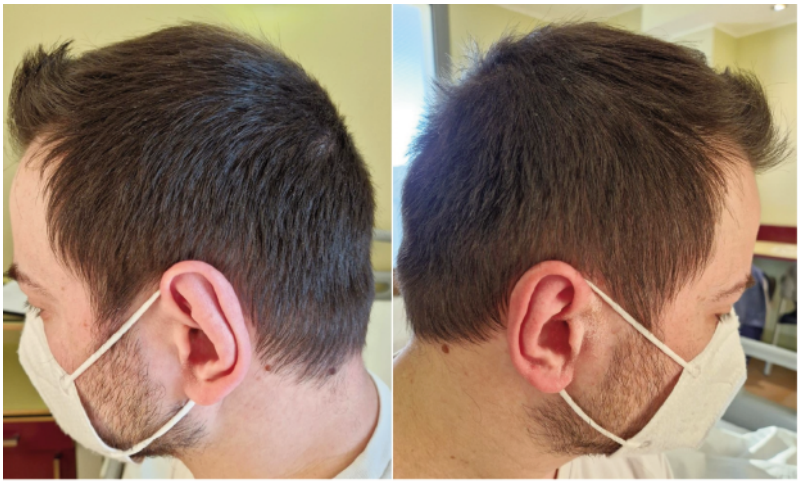

Figure 1. Bilateral auricular rigidity without cutaneous alteration.

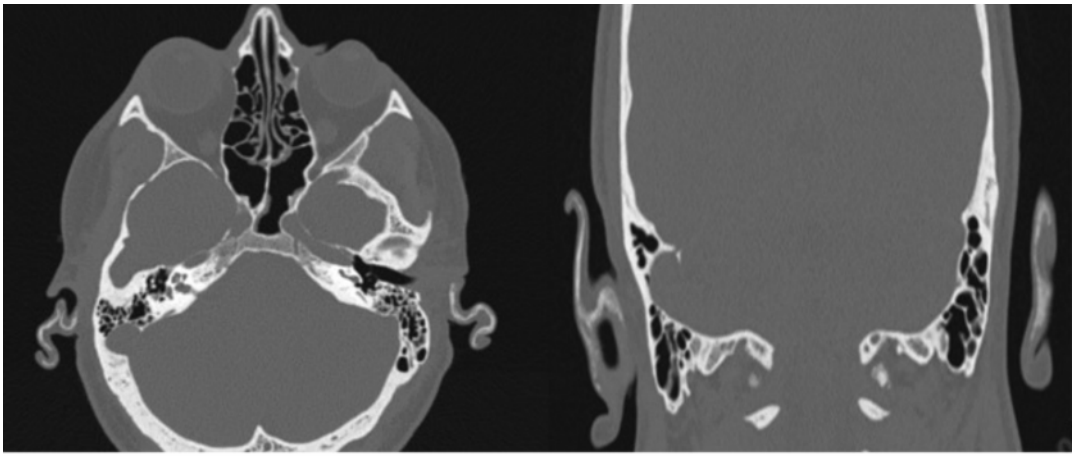

Figure 2. Skull CT showing bilateral auricular cartilage hyperdensities compatible with calcifications.

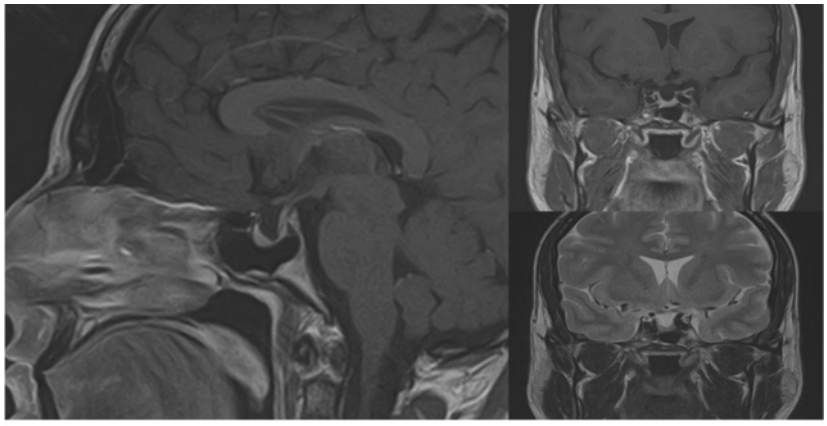

Figure 3. Pituitary MRI showing partial empty sella.

Replacement therapy with cortisone acetate 25 mg per day was started. Reduced level of IGF-1 (34 mcg/L [60-200]) persisted despite corticosteroid replacement therapy. Therefore, a glucagon stimulation test was performed, showing an insufficient GH response (GH peak 0.1 ng/mL). Before starting GH replacement therapy, the patient underwent a DEXA scan, which showed a Z-score of +2.8 standard deviation (SD), +2.3 SD, and +0.9 SD at lumbar, femoral, and radial scans, respectively. The total body scan demonstrated increased adiposity without lean mass depletion: body fat percentage 22.7%, Fat Mass Index (FMI) 22 kg/m^2, Free Fat Mass Index (FFMI) 22 kg/m^2, and Appendicular Skeletal Muscle Mass Index (ASMMI) 9.92 kg/m^2. The patient is currently under corticosteroid and GH replacement therapy. Dermatological and otolaryngological follow-ups were also advised.

Discussion

The first case of petrified ear was described in 1866 by the Czech anatomist Vincent Bochdalek in Prague,[4] while Wassmund,[5] in 1899, first reported the corresponding X-ray findings. Although it seems uncommonly found in clinical practice, the real incidence of this syndrome is unknown.

Data from a randomized study conducted in 1963, analyzing a series of 300 patients, found radiological evidence of calcification of the ear cartilage in 11 patients (3%).[6] More recently, in 1998, Bowers and Gould reported that auricular petrification is found more frequently in older people, especially those who have worked outdoors.[7]

Petrification can arise from either calcification or ossification. Calcification is the deposition of amorphous, insoluble calcium onto the auricular cartilage, whereas ossification describes new bone formation with both calcium and phosphorus in areas that are not normally ossified. Calcification can either be dystrophic or metastatic in origin. Dystrophic calcifications, which describe the deposition of the mineral in damaged or necrotic tissue despite normal serum calcium levels, could be more common in the auricle of the ears, as it is vulnerable to injury, such as local trauma, inflammation, and cold exposure with or without frostbite. In contrast, metastatic calcium deposition stems from alterations in calcium and phosphorus metabolism, with subsequent deposition of calcium-phosphorus product and calcium hydroxyapatite crystals into tissues. Vitamin D intoxication, milk-alkali syndrome, primary renal end-stage disease associated with secondary and tertiary hyperparathyroidism, hyperphosphatemia, and sarcoidosis have been associated with metastatic calcification.[8]

Ectopic ossification refers to new bone formation in tissue that does not normally ossify. This new bone has the same X-ray diffraction pattern as the apatite crystals in normal bone and is histologically identical to lamellar bone. Ectopic ossification can be either primary or secondary. Primary ectopic ossification occurs in rare congenital syndromes, including osseous heteroplasia, fibrodysplasia ossificans progressiva, Albright hereditary osteodystrophy, and congenital plaque-like osteomatosis. Secondary ectopic ossification most commonly occurs after trauma (fracture, joint dislocation, soft-tissue trauma, or surgery). It has been hypothesized that trauma produces a bone morphogenic protein, which causes the differentiation of mesenchymal cells into osteoprogenitor cells.[9] Furthermore, collagen vascular diseases, such as scleroderma, CREST syndrome, and dermatomyositis, may also demonstrate areas with ectopic ossification, except for cutaneous calcification.[10]

Auricular ossification occurs much less frequently than calcification, with fewer than 20 pathologically confirmed cases. The majority of the patients with petrified auricles are asymptomatic, and the auricle does not change its configuration. Thus, it may be incidentally recognized by imaging or, more rarely, by physical exam, as patients rarely come to medical attention. If symptomatic, patients could complain about ear pain or discomfort occurring with pressure, especially at night while sleeping, or, more rarely, auricle paresthesia and skin ulceration. In some cases, bony deposits extend to the external auditory canal in the form of exostoses, resulting in otalgia and hearing impairment.

Our patient was slightly symptomatic as presented to medical attention because of progressive bilateral stiffness of both auricles that started 5 years before. He had neither pain nor perception of hearing loss. The rigidity is progressive over time, and bilateral involvement is more frequent than unilateral involvement. Physical examination shows a partially or completely stiff, stony hard, inflexible, and unmalleable external ear, usually without visible cutaneous involvement. Therefore, the diagnosis can easily be presumed by palpation and the patient's clinical history, as in the present case. Notably, both ossification and calcification spare the earlobes. Diagnosis is supported by radiological findings, as the skull X-ray shows hyperdense areas where calcification or new bone formation has occurred. However, since ossification and calcification of the auricle are clinically and radiographically identical, a temporal CT scan may be performed to differentiate these two entities: calcifications appear as uniform hyperdensities. At the same time, radiolucent spaces within hyperdense areas represent the trabecular bone formation seen in ossification.[11]

In our patient's skull, a CT scan showed bilateral auricular hyperdensities suggestive of areas of calcifications. Definitive diagnosis may require a histopathological exam to distinguish between these two conditions. Clinical and radiological features of our patient were consistent with the diagnosis of petrified ear syndrome. Therefore, no biopsy was performed, as it was deemed not clinically necessary. The detrimental aspect of this syndrome is that it could represent a clue – sometimes being the first manifestation – of associated systemic, metabolic, and endocrine disorders, as in the present case. Identifying and treating the possible underlying disorder may help prevent further tissue hardening of the external ear. On the other hand, detecting the petrified ear syndrome may help to diagnose and treat other potentially life-threatening conditions such as Addison's disease.[2]

Other endocrinopathies such as diabetes mellitus, hypothyroidism, acromegaly, pseudohypoparathyroidism, and autoimmune polyglandular syndrome have been associated with this condition.[12] Indeed, a comprehensive laboratory evaluation, including complete blood count, basic metabolic panel, thyroid function tests, phospho-calcium metabolism parameters, and morning cortisol, may be helpful in detecting underlying disease. Any additional metabolite should be added based on clinical suspicion. To date, only one familial case has been described in the literature, occurring in a father with a type 2 autoimmune polyglandular syndrome and his daughter affected by autoimmune hypothyroidism.[13] However, genetic testing wasn't performed; no pathogenetic gene mutations are currently known.

Our patient and his parents underwent a genetic evaluation and genetic testing with whole genome-array comparative genomic hybridization CGH, which resulted in a negative for mutations in genes associated with bone dysplasias and ossification diseases.

Although Addison's disease is the most frequent endocrinopathy associated with petrified ears,[2] the pathogenetic link between adrenal insufficiency and petrification is still enigmatic and a matter of debate. In the past, increased circulating ACTH has been proposed to play a causal role,[14] but the evidence that auricular

calcification has been described both in primary and secondary adrenal insufficiency does not confirm this hypothesis. In fact, ossification may be the result of endogenous cortisol deficiency.[15] Cohen *et al.* hypothesized that the condition is the result of mesenchymal cell proliferation, which ultimately forms a calcified tissue.[16] This process is facilitated by the enhanced input of calcium into the extracellular space because of underlying cortisol insufficiency, without hypercalcemia (or hyperphosphatemia) being present. As auricular calcification has been described prevalently in males, gonadal steroids may also play a role. To note, in the present case, petrified ear syndrome was the first sign of both central adrenal insufficiency and GHD. It is also noteworthy that glucocorticoids modulate GH secretion by different mechanisms in the hypothalamus, pituitary gland, and liver.

While hypercortisolism suppresses GH release, patients with glucocorticoid deficiency also show functional and reversible impairment of GH reserve and secretion. However, in our patient, low baseline IGF-1 levels persisted after cortisol deficiency treatment, and the diagnosis of GHD was confirmed by the absent GH response to the glucagon stimulation test.

Notably, although there are several reports of its association with different causes of hypopituitarism,[15] to our knowledge, this is the first case reported of petrified ears associated with both acquired secondary hypoadrenalism and GHD. Machado *et al.* described low levels of pituitary hormones, including GH, in a woman with ossified auricles and post-partum hypopituitarism. Still, no IGF-1 levels were reported, nor were further diagnostic tests performed.[17] Haider *et al.* reported the case of a patient with panhypopituitarism due to congenital pituitary hypoplasia, who underwent growth hormone replacement therapy, developing progressive hardening of the external ears.[18] In our patient, we cannot exclude that GHD could have been a collateral feature of his documented empty sella. In a recent review by Auer *et al.*, the prevalence of pituitary insufficiency was about 50% in patients with empty sella; 30% had multiple pituitary axis involvement, while isolated pituitary insufficiency was found in 21% of patients, with the somatotropic axis being the most affected.[19] Acromegaly has also been reported in petrified ear syndrome.[3] It is worth noting that apoplectic GH-secreting adenomas are anecdotally reported to cause GH level normalization or even GHD and the development of an empty sella.[20] However, this explanation seems unlikely in the present case as there were no clinical signs of acromegalic features, no report of acute headache in the past, and no enlargement of the pituitary sella. Therefore, whether GHD also plays a role in auricular calcification's pathogenesis is unknown. Nevertheless, it is well known that GH and IGF-1 are implicated in phospho-calcium homeostasis and can modulate collagen/cartilage metabolism.

Little is known about the pathogenesis of petrified ears, and there is no specific or etiological therapy since the condition is irreversible. In symptomatic cases, especially in patients complaining about serious discomfort, surgery could be considered for symptom relief. Improvement in pain and sleep disturbances has been reported with wedge biopsy removal of the calcified portion of the pinna.[13] Our patient was asymptomatic, and his hearing function was only mildly affected; therefore, no targeted treatment was pursued, and he was referred to endocrinological, dermatological, and otolaryngological follow-up.

Conclusions

Petrified ear syndrome is probably an underreported clinical manifestation of other systemic disorders. It may, at times, serve as a useful clinical clue to suspect underlying endocrinopathies even in the absence of typical features. Because of its rarity, further research is needed to clarify the pathogenetic mechanisms and define proper treatment modalities in symptomatic patients.

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