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# Molecular genetic basis of petrified ear and review of literature

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***Abstract:*** *"Petrified ear" or calcification of auricular cartilage is a rare condition commonly associated with local trauma, frost bite, and repeated inflammation, without visible changes in the appearance of the ear. Adrenal insufficiency is the most frequent systemic disease associated with auricular calcification. A case of idiopathic adult-onset petrified ear with unilateral auricular calcification was seen in our out-patient department. Recognition of the association between auricular calcification and adrenal insufficiency can be an important step towards identification of a life-threatening cortisol deficiency.*

***Keywords:*** **Adrenal insufficiency, auricular calcification, auricular ossification**

## 1. Introduction

Petrified ear is a rare condition associated with calcification of auricular cartilage. By ***definition it occurs in soft tissues which do not normally ossify***. This condition may be associated with calcification or ossification. The auricular cartilage is highly malleable and painless to manipulate. With calcification or ossification of the auricle, it becomes difficult to maneuver and auricle becomes rock hard in consistency. Petrification is caused more often by calcification than ossification. Auricular calcification may be an indicator of an underlying adrenal insufficiency with life-threatening cortisol deficiency [1]. Dystrophic calcification occurs when a patient has normal serum calcium and phosphorous levels, but calcium is deposited in previously damaged tissues [2].

**Types of Tissue Calcification Includes**

- Dystrophic - Deposition of calcium into damaged soft tissues in the presence of normal calcium metabolism
- Metastatic Calcification - Calcium deposition caused by hypercalcemia
- Iatrogenic calcification - after calcium gluconate therapy
- Idiopathic calcification - unknown underlying cause
- Ectopic ossification - including ossification of the auricle Petrification is due to
- Dystrophic calcification
- Metastatic calcification
- Ectopic ossification

The common causes for petrified ears

- ✓ Local trauma
- ✓ Frost bite
- ✓ Inflammation- chondritis, Perichondritis, syphilis
- ✓ Endocrine or metabolic disorder that lead to hypercalcemia and Cutaneous ossification is classified as
  - Primary - arises de novo
  - Secondary - occurs within a preexisting lesion.

Local causes of ossification of auricles are

- Repeated exposure to cold,
- mechanical trauma,
- repeated manipulation of the auricle,
- radiation therapy,
- acne scarring and
- Insect bites [3].

The majority of petrified auricles are caused by calcification without ossification. Auricular ossification is

a rare cause of petrified ear, and the diagnosis requires ***histological*** examination in contrast to auricular calcification. Dystrophic, metastatic, iatrogenic and idiopathic causes are the more common causes of petrified ear.

| Endocrine/Metabolic | Local tissue injury | Idiopathic |
|---|---|---|
| Hyperparathyroidism | Repeated cold exposure | |
| Addison's disease | Inflammation | |
| Acromegaly | Frostbite | |
| Adrenal insufficiency | Chondritis | |
| Diabetes mellitus | Perichondritis | |
| Hypopituitarism [4] | Physical trauma/manipulation | |
| Hyperthyroidism | | |
| Ochronosis | | |
| Hypercalcemia | | |
| Systemic chondromalacia | | |

**Table: 1. Diseases or conditions correlated with ossification of auricular cartilage (Benedicte Louise Hegelund Krogh Et Al)**

Previously published and histologically verified causes of auricular ossification are
- ✓ Hypercholesterolemia
- ✓ Repeated manipulation of the auricles –may be associated with hearing loss
- ✓ Prolonged Calcium intake
- ✓ Addison's disease associated with Diabetes Mellitus
- ✓ Idiopathic-Hearing loss
- ✓ Repeated exposure to cold
- ✓ Frost bite
- ✓ Trauma
- ✓ Perichondritis with multiple seromas.

The most common causes of auricular ossification are
- Severe Frost bite
- Recurrent exposure to cold

**Auricular ossification has been associated w ith**

- ✓ benign melanocytic nevi,
- ✓ pilomatricomas,
- ✓ chondroid syringomas, and
- ✓ external auditory canal exostoses Auricular ossification is also associated with syndromes such as
- ✓ congenital plaque-like osteomatosis,
- ✓ Albright's hereditary osteodystrophy,
- ✓ Fibro dysplasia ossificans progressiva, and
- ✓ osseous heteroplasia Collagen vascular diseases associated with auricular ossification are
- ✓ Morphea (localized Scleroderma)
- ✓ scleroderma,
- ✓ CREST syndrome(Calcinosis, Raynaud phenomenon, Esophageal dysmotility, Sclerodactyly and Telangiectasia) and
- ✓ childhood dermatomyositis can demonstrate areas of both calcification and ossification

## 2. Case Report

32 years old male patient from west Bengal, India presented to plastic surgery out-patient Department with history of progressive stiffening of the right auricle for the past six years. The patient had no other specific complaints or illness.

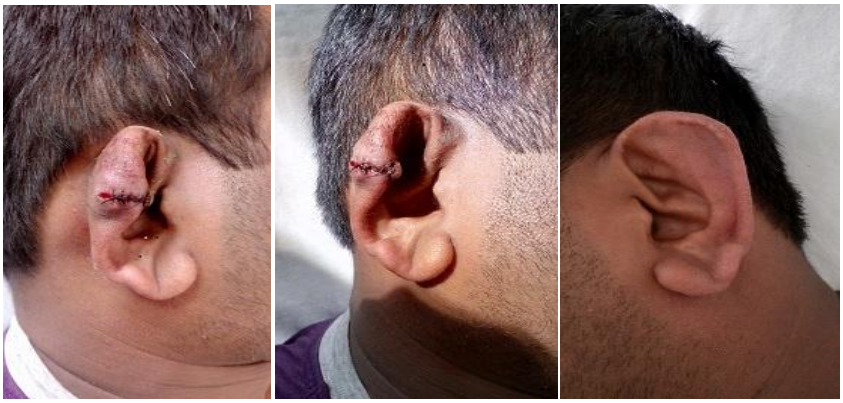

**Fig:1. The right auricle ossification with deformity and bony hard in consistency. The left ear is normal.**

Examination of the right ear showed a deformed auricle stony hard in consistency. ***The lobule of the ear was normal***. X-ray of the right auricle showed ossification.

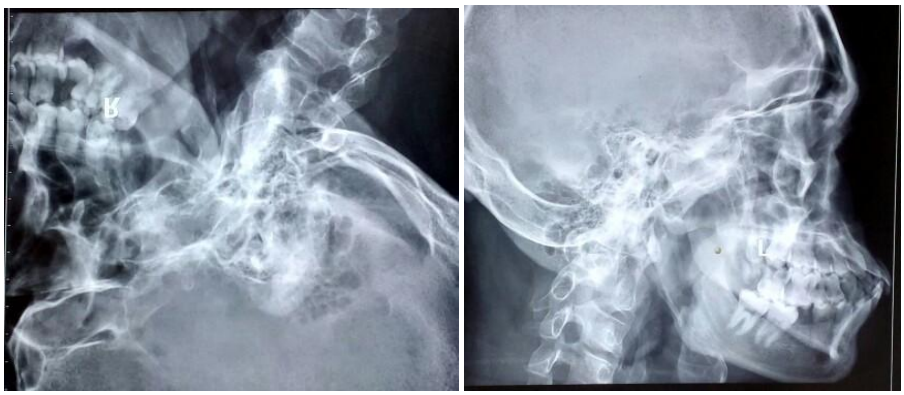

**Fig:2. X-ray shows ossification of the right auricle**

The left ear was found to be normal. The patient was evaluated by the Endocrinologist. Single serum Cortisol level by CLIA method was normal at 11.33 ug/dl (Biological reference interval 6.7-22.6). Other routine investigations were within normal limits. **Biopsy** from the right ear showed *lamellar ossification*. It was concluded the cause of the condition to be Idiopathic. The patient wanted ear reconstruction and it was explained to him regarding the limited reconstructive options and also warned of the possibility of calcification or ossification in the reconstructed ear.

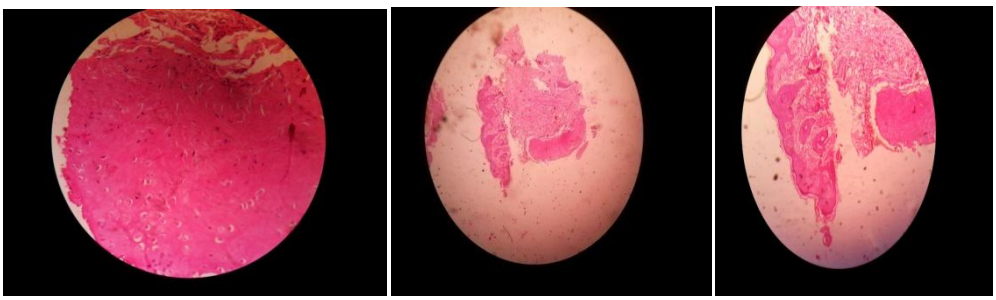

**Fig:3. Histology shows the dermis with fibrocollagenous tissue with focus of spicules of lamellar bone formation surrounded by fibrous tissue.**

## 3. Discussion

Petrified ear seems to occur more commonly in men than in women [5]. Physical examination shows the superior pinna is rigid and immobile. The ear lobule is spared. Patients may have subjective and/or objective hearing loss which may be evaluated with an audiogram. External otalgia may be present if the process involves the ear canal. Generally the patients are asymptomatic and this condition may be an incidental finding. There is stiffening of the auricular cartilage which may be unilateral or bilateral [6]. There is progressive stiffening of

the auricular cartilage and is characterized by a stony-hard auricular cartilage which results in a rigid and immalleable ear in which only the ear lobule is spared. It is important to bear in mind this condition may be associated with potentially serious and life-threatening cortisol deficiency. Idiopathic adult-onset pituitary insufficiency with associated auricular calcification is due to the following reasons [7].

- a sequel to head injury
- subarachnoid hemorrhage
- cerebrovascular accident
- following radiation
- Lymphocytic hypophysitis.

Lymphocytic hypophysitis is usually a disease of women, particularly in peri-partum period with the following features.

- ACTH deficiency,
- diabetes insipidus, and
- Hyperprolactinemia.

Petrified auricle with irreversible hardening of the elastic cartilage was first described in 1866 by Bochdalek et al.[8]. Calcification of the auricular cartilage was first recognized in a cadaver by Bochdalek. Wassmund first reported the X-ray findings of this condition in 1899. This cutaneous condition has been reported under a variety of terms. In 1932, Scherrer examined 800 apparently healthy patients of ages between 15-75 years and no evidence of calcification was documented [9]. In 1963, Gordon examined for inflexibility of the ears in a random study of 300 patients with radiological evidence of calcification of the ear cartilage in 11 patients (3%) [10]. In 1998, Bowers and Gould reported that auricular calcification was found more frequently in older people, especially those who have worked outdoors for many years [11].

Severe hypothermia is the common cause of auricular ossification. Since then, less than 200 cases have been described in literature. ***Rapid cooling induces vascular thrombosis and occlusion with resultant ischemia that induces lamellar bone proliferation***. Ossification involves new bone development resembling trabacular bone. Calcification of soft tissues may be

- dystrophic calcification
- Metastatic calcification.

Dystrophic calcification occurs due to deposition of the minerals in damaged tissues. The auricle of the ears is vulnerable to local trauma and frost bite, which are the common etiological factors in the hardening of the auricular cartilage. Metastatic calcification is deposition of mineral in normal soft tissue due to presence of high calcium and phosphorous levels in the serum. Metastatic calcification may be a causative factor, and hypercalcemia may be a feature of adrenal insufficiency [12]. Adrenal insufficiency is the most frequent systemic disease leading to the development of stiffening of the auricular cartilage. Jarvis *et al*. reported a high incidence of this phenomenon in patients with Addison's disease, with varying severity from moderate stiffness to stony hard ears. The etiology of this phenomenon in adrenal insufficiency is not clear and is believed to be due to cortisol deficiency. Long-term 11-desoxycorticosterone acetate (DOCA) therapy was implicated, but this is unlikely, as stiffening of the auricular cartilage has been found in patients who had never received DOCA. Calcification of auricular cartilage has been described in patients with both primary adrenal insufficiency as well as in secondary adrenal insufficiency and in adrenogenital syndrome. Auricular calcification has only been described in males and gonadal steroids may play a role in the evolution of this condition.

Other endocrinopathies reported with auricular calcification are

- diabetes mellitus,
- hypothyroidism, and
- Acromegaly.

Systemic diseases associated with the condition are

- familial cold hypersensitivity,
- hypertension,
- alkaptonuria,
- scleroderma, and
- Systemic chondromalacia.

Clinical presentation of petrified auricle may include

- Asymptomatic
- Discomfort on application of pressure
- Gradual stiffening of the appendage
- Bilateral involvement is more frequent than unilateral involvement
- Adrenal insufficiency presents as bilateral rigid auricles.

Physical examination:

- There is a rigid auricle which may be deformed
- the lobule is spared
- No obvious cutaneous abnormality.

Clinical Progression

- External auditory canal, tympanic membrane may be involved
- Nasal, thyroid and cricoids cartilages may be involved
- Epiglottis, and arytenoids involvement must be evaluated on laryngoscopy
- Pure-tone audiogram of the external ear should be performed.

Clinical evaluation of these patients should include

- a complete blood cell count,
- serum levels of calcium and phosphorus,
- alkaline phosphatase,
- glucose test,
- thyroid function test, and
- Parathyroid hormone level estimation.

## 4. Radiological diagnosis

X-ray both mastoids: Law's view of the mastoids and CT scan of the local part confirm the diagnosis. CT scans with minute radiolucent air spaces within bony opacities may indicate bone formation [13].

## 5. Molecular Genetics

Munroe et al (1999) studied the gene for matrix Gla protein as a causative factor for Keutel syndrome because of its localization to the same chromosomal region as the disorder and the known function of its protein product. By mutation analysis of the MGP gene in the 3 unrelated proband of the Turkish and Belgian families, they identified 3 different mutations, (154870.0001-154870.0003) all of which predicted a nonfunctional protein. Hur et al (2005) identified homozygosity for a splice site mutation in the MGP gene (154870.0004) in 3 siblings from a consanguineous Kuwaiti family with Keutel syndrome. The unaffected parents were heterozygous for the mutation.There are two common syndrome associated with auricular calcification.

### 5:1. Keutel syndrome

Keutel syndrome (KTLS) is caused by homozygous mutation in the gene encoding the human matrix Gla protein (MGP:154870) on chromosome 12p12. Khosroshahi (2014) stated that the estimated prevalence of Keutal syndrome is 1 in one million. Keutal syndrome is an autosomal recessive disorder characterized by

- multiple peripheral pulmonary stenosis,
- brachytelephalangy,
- inner ear deafness, and
- abnormal cartilage ossification or calcification (Khosroshahi et al 2014)

Keutel syndrome is a rare autosomal recessive disorder characterized by

- diffuse cartilage calcification,
- characteristic physiognomy,
- brachytelephalangism,
- peripheral pulmonary stenosis,
- hearing loss, and
- Borderline to mild mental retardation.

Keutel syndrome associated cerebral calcification was identified in a 15 years old patient while being investigated for a seizure disorder. The parents are phenotypically normal first cousins. Thirteen cases from 9 families have been published. Six families were consanguineous, two had multiple affected Siblings (Males and females) and 4 families originated from the Middle East countries.

### 5:2. Schmidt's Syndrome

When immune dysfunction affects two or more endocrine glands and associated with Non-endocrine immune disorders, the polyglandular autoimmune (PGA) syndromes should be considered. The PGA syndromes are classified as two main types

- PGA type I
- PGA type II.

PGA type I consists of Addison's disease, hyperparathyroidism and chronic mucocutaneous candidiasis. The type II syndrome (PGA2) is much more prevalent than the type I syndrome. It is associated with HLA-DR3and/or HLA-DR4 haplotypes. The pattern of inheritance is autosomal dominance with variable expressivity and a female-to-male ratio of 3-4:1, it occurs in the third or fourth decade of life. Primary adrenal insufficiency, autoimmune hypothyroidism and insulin dependent diabetes mellitus was diagnosed as "Schmidt's syndrome" (PGA type II). This syndrome is a very rare autoimmune disorder. The diagnosis is difficult since the symptoms depend on the gland which gets involved first. The patients were treated with corticosteroid, thyroxin and insulin and patients responded well to treatment.

## 6. Management

Most cases are asymptomatic and there are no guidelines for treatment of this condition. An improvement has been reported after conchal reduction surgery in localized involvement of the conchal region. Attempts to reconstruct badly deformed auricle has not been successful. The possibility of recurrent Petrification following reconstruction has not been documented beyond doubt.

## 7. Conclusion

Ectopic ossification represents an uncommon cause of petrified ear. It is caused by deposition of calcium and phosphorus in a proteinaceous matrix as hydroxyapatite crystals. Radiological findings show it has the same opacity as the normal bone and histologically similar to the lamellar bone found elsewhere in the body. Stiff ears are usually asymptomatic and give very little burden to the patients. Patients report mainly due to secondary problems. It is important to identify recognition of adrenal insufficiency. This sign has been reported in both primary and secondary adrenal insufficiency, cortisol deficiency is likely to play a role, regardless of the calcium and phosphorus levels. Furthermore, the rigid ears in association with endocrine disorders are reported in male patients only, therefore gonadal hormones could be involved. Pertrified ear is an uncommon entity with unclear pathogenesis. It is important to bear in mind the associated serious diseases like endocrinopathies. They are mostly asymptomatic with little discomfort. In case of extreme discomfort, surgical intervention like conchal reduction through a posterior approach has been done with some improvement in symptoms.

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