

# Endocrine Glands and Hearing: Auditory Manifestations of Various Endocrine and Metabolic Conditions

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## Abstract

The aetiology of hearing loss in humans is multifactorial. Besides genetic, environmental and infectious causes, several endocrine and metabolic abnormalities are associated with varying degrees of hearing impairment. The pattern of hearing loss may be conductive, sensorineural or mixed. The neurophysiology of hearing as well as the anatomical structure of the auditory system may be influenced by changes in the hormonal and metabolic milieu. Optimal management of these conditions requires the integrated efforts of the otolaryngologist and the endocrinologist. The presence of hearing loss especially in the young age group should prompt the clinician to explore the possibility of an associated endocrine or metabolic disorder for timely referral and early initiation of treatment.

**Keywords:** Endocrine systems, hearing loss, Pendred syndrome, Turner syndrome

## INTRODUCTION

Hearing loss is a common problem encountered in clinical practice. In addition to aging, various genetic and environmental factors play an important role in hearing loss. Some disorders and syndromes of endocrine system have shown to be associated with deafness. They may either cause or adversely influence diseases of the ear.

Diabetes mellitus, hypothyroidism, hypogonadism, acromegaly, osteogenesis imperfecta (OI), hypoparathyroidism, and Paget's disease of bone are some of the diseases which may have varying degrees of hearing abnormalities attributable to different mechanisms. This brief review attempts to describe the association of hearing impairment with disorders of various endocrine glands.

## HEARING AND HYPOTHALAMIC-PITUITARY DISORDERS

### Acromegaly

Acromegaly, a state of growth hormone (GH) excess due to a somatotroph adenoma, has been shown to be associated with hearing loss. There is an increased prevalence of both conductive and sensorineural deafness in patients with acromegaly. It has been suggested that deafness in acromegaly occurs because of bone hypertrophy and narrowing of internal

auditory canals.<sup>[1]</sup> The mechanism of conductive hearing loss is postulated to be due to inadequate ventilation of the middle ear due to eustachian tube dysfunction as a result of redundant soft tissue and mucosa.<sup>[2]</sup> In addition, hearing loss may be caused by middle ear pressure dysregulation, sclerosis of mastoid, recurrent otitis, plaque formation, and GH excess associated increase in perilymph formation.<sup>[3]</sup>

### Growth hormone deficiency

Hearing loss has been reported in mutations of genes encoding insulin-like growth factor 1 (IGF 1) and the GH receptor. IGF 1 and its receptor are expressed abundantly in the central nervous system, including the inner ear. Being the chief effector molecule of GH, IGF 1 is required for the differentiation of neurons and the maturation of inner ear cells. IGF 1 influences hearing by protecting hair cells from undergoing apoptosis, suppressing the downregulation of proapoptotic genes and regulating glucose transporters of the outer hair cells, thereby promoting neuronal survival.<sup>[4]</sup> The prevalence of misophonia (reduced sound tolerance) and

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**DOI:**  
10.4103/ijem.IJEM\_10\_17

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**How to cite this article:** Cherian KE, Kapoor N, Mathews SS, Paul TV. Endocrine glands and hearing: Auditory manifestations of various endocrine and metabolic conditions. *Indian J Endocr Metab* 2017;21:464-9.

high-tone sensorineural hearing loss was shown to be more in individuals with untreated congenital isolated GH deficiency than in controls. Misophonia may be related to changes in the limbic and autonomic nervous system and an absence of the stapedial reflex secondary to a reduction in depth of skull and facial height.<sup>[5]</sup>

### Neurohypophyseal diabetes insipidus

Diabetes insipidus, diabetes mellitus, optic atrophy, and deafness DIDMOAD syndrome is a rare autosomal recessive disorder caused by mutations in the wolframin (WFS 1) gene which is expressed in pancreatic beta cells, neurons, and neuroendocrine tissues. Although diabetes mellitus and optic atrophy are the defining features of this complex disorder, diabetes insipidus occurs in about 70% and sensorineural deafness in about two-thirds of all patients. WFS 1 gene on chromosome 4p encodes a calcium channel that is responsible for maintaining the homeostasis of the endoplasmic reticulum (ER). Mutated wolframin forms intracellular aggregates<sup>[6]</sup> and contributes to unresolvable ER stress leading to apoptosis of beta cells and neurons.<sup>[7]</sup>

### Craniopharyngioma

Although craniopharyngiomas are usually confined to the sellar-suprasellar location, a subgroup of giant craniopharyngioma may extend into the posterior cranial fossa. They account for approximately 4% of cases, and can present with unilateral or bilateral hearing loss as the initial symptom, before other neurological features become evident. Children who present with deafness should be referred to hearing specialists early and language rehabilitation should be initiated as hearing loss can compromise language development and cognitive function.<sup>[8]</sup>

### Sellar/ectopic pituitary adenoma

Hearing impairment caused by pituitary adenomas has been described in literature.<sup>[9-11]</sup> Often, these have been described in invasive prolactin-secreting adenomas of sellar origin, wherein direct extension and involvement of the cerebellopontine angle instead of the bony internal auditory canal is implicated as the cause of hearing loss.<sup>[9,11]</sup> Ectopic pituitary adenomas may also present with hearing loss due to compression of the internal auditory canal.<sup>[12]</sup>

## HEARING AND THYROID-PARATHYROID DISORDERS

### Congenital hypothyroidism (nongenetic)

Endemic cretinism occurs due to severe iodine deficiency over several generations and is invariably associated with goiter. In North India, the prevalence of endemic cretinism was reported to be 3%–5% and deaf-mutism was seen in about three-fourths of them.<sup>[13,14]</sup>

The causes for auditory abnormalities in congenital hypothyroidism include the following:<sup>[15]</sup>

- i. Increased connective tissue and osseous changes throughout the labyrinth
- ii. Alterations in the petrous temporal bone and ectatic changes in the semicircular canals and cochlea
- iii. Atrophy of the stria vascularis
- iv. Degeneration of spiral ganglion and hair cells of the organ of Corti
- v. Generalized atrophy of organ of Corti
- vi. Incomplete ossification of the stapes and anomalies of incus and malleus
- vii. Distortion of oval and round windows
- viii. The presence of hyaline streak between the organ of Corti and tectorial membrane.

### Congenital hypothyroidism (genetic)

The syndrome of sporadic goiter and hearing loss with slow development of speech was described by Vaughn Pendred in 1896. Eponymously known as Pendred syndrome (PDS), this autosomal recessive disorder is characterized by iodine organification defects, presence of goiter, sensorineural hearing loss, and a positive perchlorate discharge test. It may account for 5%–10% of all cases of congenital deafness. The hearing loss is more pronounced at higher frequencies. PDS is caused by mutations of the SLC26A4 gene on chromosome 7q31 that encodes pendrin, which is a transmembrane exchanger of chloride, iodide, and bicarbonate ions and is expressed in the thyroid, inner ear, and kidney.<sup>[16]</sup> The sensorineural deafness is usually associated with malformation of the cochlea which is hypoplastic and known as “Mondini cochlea.”<sup>[17]</sup>

### Acquired hypothyroidism

The etiology of hearing loss in hypothyroidism can be conductive, sensorineural, or mixed and has been documented to occur in more than half of the individuals.<sup>[18]</sup> The conductive hearing loss in these patients is probably due to reduced compliance because of hypertrophy and edema of the mucosa of the nose and eustachian tube leading to eustachian obstruction and also related to thickening of the tympanic membrane. Other postulated mechanisms include changes in ossicles such as distortion of incus and stapes, and obstruction of round or oval windows.<sup>[19]</sup> Sensorineural deafness has been attributed to changes in the cochlea probably secondary to accumulation of acid mucopolysaccharides and altered nerve conduction.<sup>[18]</sup>

### Resistance to thyroid hormones (Refetoff syndrome)

It has been shown that thyroid hormones and their receptors are involved in the auditory system through multiple pathways. Thyroid hormone beta receptors are expressed in the cochlea and are involved in auditory development. Refetoff syndrome is characterized by mutations in the gene encoding the beta receptor and an inability of the target tissues to take up thyroid hormones resulting in high circulating levels of thyroid hormone and high urinary iodide levels. Deafness has been reported in several patients with resistance to thyroid hormone.<sup>[19]</sup> Although some patients are asymptomatic, others may present with goiter, tachycardia, and hyperactivity.

### Graves' disease and antithyroid drugs

Although hearing loss is not commonly seen in association with Graves' disease, decreased hearing ability particularly

at higher frequencies has occasionally been reported.<sup>[20]</sup> Exact mechanisms are yet to be elucidated. There have also been reports of ototoxicity secondary to ANCA-positive vasculitis in patients treated with propylthiouracil, which manifests as sensorineural hearing loss.<sup>[21]</sup>

### Hypoparathyroidism

Barakat syndrome, also known as hypoparathyroidism, deafness, and renal dysplasia (HDR) syndrome, is an autosomal dominant disorder characterized by hypoparathyroidism, sensorineural deafness, and renal dysplasia. Mutations in the GATA 3 gene located on the short arm of chromosome 10 (10p) result in the premature termination of the GATA 3 protein with loss of basic amino acids in the flanking ZnF<sub>2</sub> domain.<sup>[22]</sup> Although widely expressed in the central and peripheral nervous system, parathyroid glands, inner ear, and kidneys are the most commonly affected organs. Sensorineural deafness occurs early and is the most penetrant aspect of the HDR syndrome. The hearing loss is secondary to involvement of peripheral part of the auditory system and the absence of otoacoustic emissions and is more pronounced at higher frequencies.<sup>[23]</sup>

### Hyperparathyroidism

Deafness is not commonly encountered in hyperparathyroidism; however, a review of literature revealed occasional reports of hearing loss and aphonia in association with hyperparathyroidism. Calcification of the ear drums were noticed in these cases and were found to resolve after parathyroidectomy with complete or partial reversal of hearing loss.<sup>[24]</sup>

## HEARING LOSS AND METABOLIC BONE DISEASE

### Paget's disease of bone

Hearing loss is long recognized as a complication of Paget's disease. Previously, various mechanisms were proposed to cause hearing impairment and included loss of auditory hair cells and ganglion cells, stretching of the auditory nerve and toxic cytokines.<sup>[25]</sup> Thereafter, studies done by Khetarpal and Schuknecht on the histological appearance of pagetic temporal bone inferred that both conductive and sensory hearing loss are caused by changes in the bone density, mass and form, resulting in the dampening of the motion mechanics of the middle and inner ears.<sup>[26]</sup>

### Osteogenesis imperfecta

With an estimated prevalence of 1 in 10,000–20,000 births, OI is one of the most commonly inherited bone diseases. It occurs due to defects in the synthesis of type 1 collagen or its intracellular processing and manifests as an increased susceptibility to fractures, bony deformities, joint laxity, blue sclerae, dentinogenesis imperfecta, and hearing loss which can be conductive, sensorineural, or mixed.<sup>[27,28]</sup> In population studies, the estimated prevalence of OI-associated hearing loss is 45%–58%.<sup>[29]</sup> The mechanisms involved in the pathogenesis of deafness in OI are manifold and include the following:

- i. Atrophy of cochlear hair cells and stria vascularis
- ii. Abnormal bone formation in the cochlea and surrounding structures
- iii. Footplate fixation and deficient ossification of the ossicles
- iv. Atrophy or fractures of stapes or malleus
- v. Mucosal hypervascularization or otospongiosis-like lesions in the stapes footplate causing fixation or discontinuity of the ossicular chain.

Although the conductive hearing loss caused by ossicular deformities can often be surgically corrected, outcomes are worse than in patients without OI probably due to diminished stability of the supporting bones and possible thickening and hypervascularization of the footplate.<sup>[30]</sup>

### Fibrous dysplasia

Fibrous dysplasia is a slow-growing condition of the bone, in which there is progressive replacement with fibrous tissue and disorganized bony trabeculae. The temporal bone is rarely involved in monostotic forms of the disease resulting in narrowing of the external auditory meatus, otalgia, recurrent otitis media, and formation of secondary cholesteatoma leading to hearing loss.<sup>[31]</sup>

### Hereditary hypophosphatemic osteomalacia

This forms a heterogeneous group of disorders characterized by renal phosphate wasting. They occur due to mutations in various genes such as PHEX (phosphate-regulating gene with homologies to endopeptidase on X chromosome) that causes X-linked hypophosphatemic rickets (XLH), fibroblast growth factor (FGF) 23, causing autosomal dominant hypophosphatemic rickets, dentin matrix protein (DMP) causing autosomal recessive hypophosphatemic rickets (ARHR) type 1, and ectonucleotide pyrophosphatase (ENPP) causing ARHR type 2.

Conductive hearing loss has been reported to occur in PHEX gene mutations. Mutations involving inactivation of DMP 1 have been associated with sensorineural hearing loss due to narrowing of the internal auditory canal. ENPP mutation has been reported to cause a mixed hearing loss, initially conductive and then sensorineural.<sup>[32]</sup> In XLH, the mechanism underlying deafness appears to be involvement of the cochlea, secondary to osteosclerosis of the petrous temporal bone.

### Osteoporosis

A recent meta-analysis of five studies showed a significant association between decrease in bone mineral density (BMD) and hearing loss. There was a statistically significant increased odds of hearing loss in the low BMD or osteoporosis group with OR of 1.20.<sup>[33]</sup> Osteoporosis is associated with demineralization of the skeleton and involvement of the temporal bone that contains the cochlear capsule, is considered to be responsible for the hearing loss.

### Inherited sclerotic bone disorders

Most inherited sclerosing bone dysplasias present with cranial nerve dysfunction due to compression of the narrow foramina

that carry them. Among these Voorhoeve's disease is classically described to present with hearing loss.<sup>[34]</sup>

## GONADAL DISORDERS AND HEARING LOSS

### Hypogonadotropic hypogonadism

A clinical diagnosis of Kallman's syndrome is made in the presence of hypogonadism and anosmia. Other manifestations include renal and dental agenesis, cleft lip and palate, mirror movements, and hearing loss. Deafness has been attributed to several genetic mutations in KAL1, fibroblast growth factor receptor 1, FGF 8, interleukin 17 receptor D, CHD7, and the transcriptional factor SOX 10 that regulate the development of neural crest cells.<sup>[35]</sup>

Coloboma, heart defects, choanal atresia, retardation of growth and development, genital abnormalities, and ear abnormalities (CHARGE) syndrome caused by mutations in CHD7 can present similarly with hypogonadism, anosmia, cleft palate, and hearing loss. CHARGE syndrome is associated with distortion of the semicircular canals.<sup>[35]</sup> Hearing loss is due to many factors such as ossicular malformation, eustachian tube dysfunction, otitis media secondary to craniofacial anomalies, dysplastic cochlea, and reduced diameter of auditory nerve.<sup>[36]</sup>

### Hypergonadotropic hypogonadism

Turner syndrome (TS) is characterized by short stature and gonadal dysgenesis secondary to loss of one of the X chromosomes in affected females. Hearing loss has been reported in women with TS and can be conductive, sensorineural, or mixed. It occurs in young and middle-aged women and tends to be progressive with advancing age.

Recurrent otitis media occurs due to abnormal eustachian tube structure and function that leads to scarring of the tympanic membrane causing conductive hearing loss. Other mechanisms of conductive hearing loss include ossicular necrosis and cholesteatoma in the middle ear. Anatomical malformation of the skull base resulting in poor drainage and inadequate ventilation of the middle ear also contribute to middle ear involvement. Lymphatic hypoplasia resulting in persistent lymphatic effusion also causes impaired aeration and drainage.

The patterns of sensorineural deafness include a mid-frequency dip and a high-frequency loss. The etiology of sensorineural hearing loss is thought to be an X-linked dosage effect resulting in fewer sensory cells in the cochlea leading to cochlear dysfunction. Estrogen deficiency-associated poor mineralization of the cochlear capsule and its role in hearing impairment has not been well studied.<sup>[37]</sup>

## ADRENAL DISORDERS

Adrenoleukodystrophy is a rare X-linked condition that is caused by mutations in the adenosine triphosphate binding cassette group of transporter genes. The gene encodes the enzyme fatty acylCoA ligase which is responsible for the

peroxisomal transfer of fatty acids. Defective enzymatic activity leads to prevention of transport of fatty acids into the peroxisomes and their accumulation within cells.

Clinical manifestations include behavioral abnormalities, vision and hearing deficits, abnormalities in speech, gait, writing, memory, and adrenal insufficiency. In advanced cases, motor and cognitive dysfunction, dysphagia, and convulsions may occur. Hearing impairment is secondary to deficient auditory processing in the presence of demyelination involving the auditory and other parts of the brain.<sup>[38]</sup>

## DIABETES MELLITUS AND HEARING LOSS

Type 2 diabetes mellitus has been reported to be associated with microvascular complications that may affect hearing. Duration of diabetes and poor glycemic control has been linked to sensorineural hearing loss after adjusting for age.<sup>[39]</sup> Basement membrane thickening of the vascular endothelium is one of the most prevalent morphologic findings in diabetes mellitus. The proposed mechanisms implicated in the causation of hearing loss are as follows:

- i. Diabetic angiopathy causing an interruption in cochlear blood supply and transportation of nutrients
- ii. Vasculopathy that leads to secondary degeneration of the eighth nerve
- iii. Thickening of the capillaries of the stria vascularis
- iv. Atrophy of the spiral ganglion
- v. Demyelination of the eighth nerve
- vi. Perineurial fibrosis
- vii. Decreased nerve fiber density in the spiral lamina
- viii. Reduction in number of cells in the middle and basal turns of the cochlea
- ix. Reduced ganglion cells in the dorsal and ventral cochlear nuclei
- x. Reduced ganglion cells in the superior olivary complex, inferior colliculus, and medial geniculate body.<sup>[40]</sup>

## MISCELLANEOUS CAUSES

### Mitochondrial deafness

Mutations in mitochondrial DNA may result in deafness. As mitochondria are required for oxidative phosphorylation, mitochondrial dysfunction usually results in pleiotropic effects affecting different organ systems.<sup>[41]</sup>

### Kearns–Sayre syndrome

This occurs due to large-scale mitochondrial DNA rearrangements and manifests as chronic progressive external ophthalmoplegia, diabetes, retinitis pigmentosa, cardiac conduction defects, anemia, hypoparathyroidism, and deafness.

### Maternally inherited diabetes and deafness

Maternally inherited diabetes and deafness is a mitochondrial disorder, transmitted in a dominant fashion in which an affected mother transmits the disease to all her offspring. An affected father does not transmit the disease to his progeny as

the mitochondria contained in the sperm are shed before the entry of the sperm nucleus into the egg. Diabetes occurs due to pancreatic beta cell dysfunction and progressive insulinopenia. Sensorineural hearing loss is bilateral, more common in men and is considered to be due to atrophy of cochlear stria vascularis. Rarely other features such as GH and adrenocorticotrophic hormone deficiency, hypothalamic hypogonadism, secondary hypothyroidism, and cardiomyopathy may occur.<sup>[42]</sup>

### Familial paragangliomas and hearing loss

Carotid body paragangliomas are extremely rare tumors that may often be familial; their genetic inheritance is through paternal imprinting. There are families reported to have inherited paragangliomas with sensorineural deafness.<sup>[43]</sup> In addition, paragangliomas of tympanic and vagal origin are known to present with tinnitus and hearing loss as early symptoms.<sup>[44]</sup>

### CONCLUSION

Hearing disorders may be a part of various endocrine and metabolic conditions. Early identification and timely referral to hearing specialists are of utmost importance, especially in children, as hearing loss can have a bearing on language development. Otolaryngologists should also be abreast of the hearing disorders that manifests along with endocrine conditions. A high index of suspicion needs to be maintained to identify hearing loss that occurs as part of syndromes or states of hormone excess or deficiency.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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