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Hearing Loss in Patients with Spondyloepiphyseal Dysplasia Congenita and Tarda

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Authors' contributions

This work was carried out in collaboration between all authors. Author RA designed the study, wrote the first draft of the manuscript, and managed the literature searches. All authors were involved in the editing and analysis of information provided in the manuscript and approval of the final version.

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ABSTRACT

Aim: To describe hearing loss in patients with spondyloepiphyseal dysplasia congenita and tarda.
Methodology: A literature review of the National Library of Medicine's online database on hearing loss in patients with spondyloepiphyseal dysplasia congenita and tarda was performed.
Results: Four articles were identified that reported hearing loss in subjects with spondyloepiphyseal dysplasia congenita and tarda. Including this study, a total of fourteen patients with hearing loss are reported. Eight patients with sensorineural loss and two patients with mixed hearing loss were identified. The type of hearing loss is unknown in 4 cases.
Conclusion: Serial audiograms are recommended early in life in individuals with spondyloepiphyseal dysplasia congenita and when clinically indicated in patients with spondyloepiphyseal dysplasia tarda.

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1. INTRODUCTION

Spondyloepiphyseal dysplasia congenita and tarda are two major types of spondyloepiphyseal dysplasia (SED). Spranger and Wiedemann first described Spondyloepiphyseal dysplasia congenita in 1966 [1]. It is an autosomal dominant disorder with a prevalence of <10 per million population [2,3]. The true incidence of this rare disease is unknown. Short-trunk dwarfism, noted as early as after birth in some cases, is a hallmark of this type II collagenopathy [4]. Additional clinical manifestations include flat face, hypertelorism, short limbs, genu valgum, pesplanus, and cervical spine subluxation [4]. Myopia is seen in 50% of patients [5]. Cleft palate, micrognathia, and hearing loss are possible otolaryngologic manifestations of this disease [4,5].

Mutation in the COL2A1 gene on chromosome 12 is the underlying etiology for SED congenita [6]. The COL2A1 gene is responsible for formation of type II collagen. Many mutation variants have been reported [6].

Spondyloepiphyseal dysplasia tarda was first described by Jacobson in 1939 as an x-linked disorder, however autosomal dominant and recessive variants have been described [7,8]. It is genetically distinct from the congenita type. Mutations in the SEDL gene responsible for coding sedlin protein have been associated with the X-linked type of this disorder [9-12].

Investigations to elucidate the function of the sedlin protein are being undertaken. This disease manifests itself later in life compared to SED congenita and is mostly a disorder of the skeletal system [9,10]. Short stature, platyspondyly of the lumbar vertebral bodies, and degenerative changes in the spine and hips are its main manifestations [9,10]. Unlike SED congenita, extraskeletal abnormalities are not commonly seen or reported in this disease entity.

Past reports have focused on grossly evident anatomic variations. Identifying different forms of genetic mutations leading to these conditions has also been a main area of focus. The presence or absence of hearing loss is not consistently reported in cases. We provide a literature reference presenting hearing loss in patients with SED congenita and tarda.

1.1 Presentation of Case

Patient is a 63-year-old woman with a history of spondyloepiphyseal dysplasia congenita, who presented with paroxysmal positional vertigo and bilateral hearing loss. Physical exam revealed normal mentation and cognitive ability, short stature, short neck, a normal otoscopic exam, grossly intact cranial nerves, normal upper and lower extremity motor strength, and evidence of posterior canal benign paroxysmal positional vertigo on the dix-hallpike maneuver. Her positional vertigo was treated with an Epley maneuver. Patient's medical comorbidities include glaucoma and rheumatoid arthritis. There is no family history of SED or hearing loss other than presbycusis.

An audiogram revealed asymmetric hearing, excellent word recognition scores, and absent otoacoustic emissions bilaterally. Patient had normal to moderate to severe downsloping sensorineural hearing loss on the right with moderate to severe downsloping mixed hearing loss on the left. Stapedial reflexes were absent on the left side with ipsilateral and contralateral stimulation. Tympanograms were type A bilaterally. Serial audiometry from 2001-2014 revealed progression of the conductive loss on the left (Figs. 1 and 2).

An MRI of the posterior fossa revealed a heterogeneously enhancingclival lesion with no retrocochlear or labyrinthine abnormality (Figs. 3 and 4). The clival lesion had been noted on previous MRIs from over a decade ago and remained stable in size. Computed tomography images of the temporal bone did not reveal any middle or inner ear anomaly.

Treatment options for the hearing loss included explorative tympanotomy with stapedectomy or hearing aid amplification. The patient desired the latter.

2. MATERIALS AND METHODS

A literature review of the National Library of Medicine's online database with focus on hearing loss in patients with spondyloepiphyseal dysplasia congenita and tarda was performed. Articles with spondyloepiphyseal dysplasia in their title or abstract were searched. A total of 463 articles were identified and reviewed. The

articles were thoroughly reviewed to see if hearing loss was reported. In cases where hearing loss was mentioned, the presence of an audiogram and type and degree of hearing loss was further investigated.

3. RESULTS

Four articles were identified that reported hearing loss in subjects with spondyloepiphyseal dysplasia congenita and tarda [2,13-15]. Including the patient reported in this study, a total of 14 patients were identified with hearing loss. One patient with SED tarda and hearing loss was reported, but the type and degree of hearing loss was not discussed. Thirteen of the patients had SED congenita. Of these 13 patients, 8 reportedly had sensorineural hearing loss, two had mixed hearing loss, and in the other 3, the type of hearing loss was not identified.

Serial audiometry was available in only one patient with SED congenita. This patient had asymmetric hearing with a similar progression of hearing loss as in the patient reported in this study. Audiometry revealed normal to moderate to severe downsloping sensorineural hearing loss on the right with moderate to severe downsloping mixed hearing loss on the left. Carhart's notch was noted at 2000 Hz bilaterally. Word recognition scores degraded over time. The patient was treated with bilateral Behind-the-Ear hearing aids and surgical correction of suspected stapes fixation was deferred (Table 1).

4. DISCUSSION

Spondyloepiphyseal dysplasia congenita and tarda are the two main types of spondyloepiphyseal dysplasias. Short stature dwarfism is the hallmark of these disease entities although other skeletal dyscrasias do exist. SED congenita presents earlier in life and is associated with extraskeletal manifestations. Extraskeletal manifestations are not common in SED tarda. SED tarda involves mutation of the SEDL gene that encodes the sedlin protein. The role of this protein in collagen formation is not fully understood. SED congenita is a type II collagenopathy. Up to 30% of patients with spondyloepiphyseal dysplasia can have hearing loss [13].

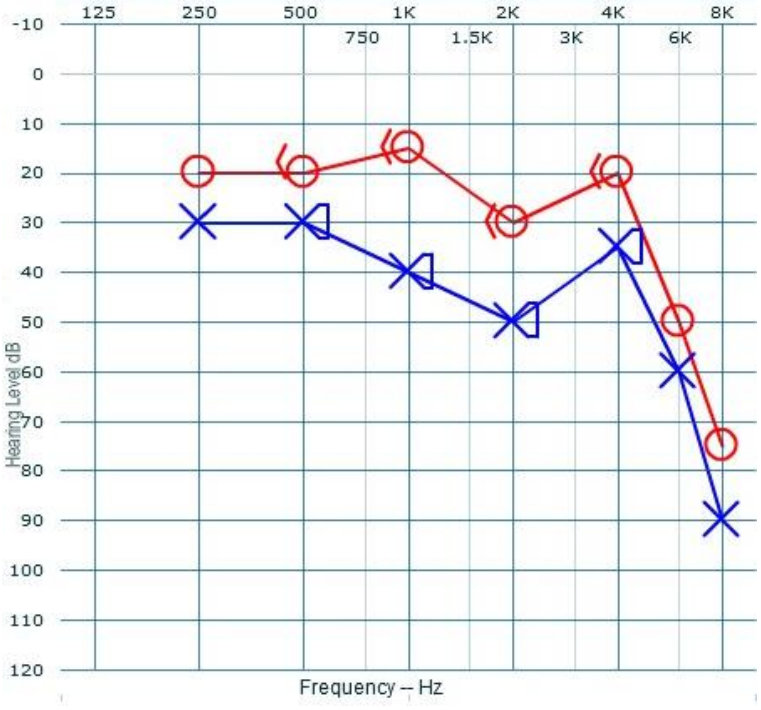

Fig. 1. 2001 audiogram reveals early asymmetric hearing

Table 1. Reported cases of hearing loss in patients with spondyloepiphyseal congenita and tarda

Study	Spondyloepiphyseal dysplasia type	Number of patients with hearing loss	Type of hearing loss
Current study	Congenita	1	Progressive Mixed Hearing Loss
Singhal et al. 2013 [14]	Tarda	1	Not Described
Dahiya et al. 2000 [13]	Congenita	1	Progressive Mixed Hearing loss
Wynne Davies et al. 1982 [2]	Congenita	3 (of 17 cases reported)	Not described: Patients are reported as having "partial deafness"
Fraser et al. 1969 [15]	Congenita	8 (of 9 cases reported)	Sensorineural Hearing Loss (perceptive deafness) • 2 with mild loss • 6 with moderate to severe loss • 4 of the 8 had worse hearing in the higher frequencies • 1 patient had early conductive loss from effusion that resolved after drainage

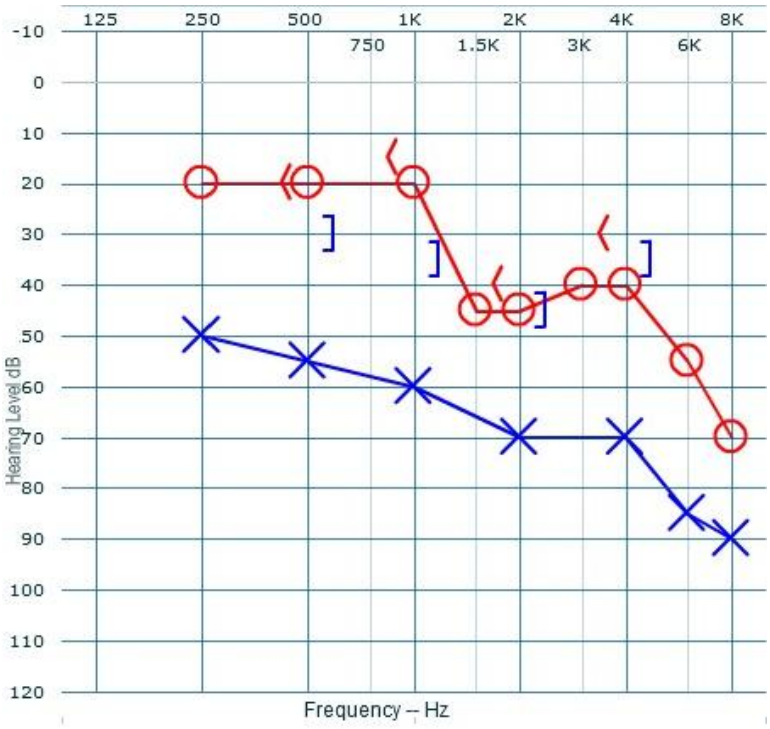

Fig. 2. 2014 audiogram with mixed loss on the left with a 25-30 dB air-bone gap and purely sensorineural loss on the right

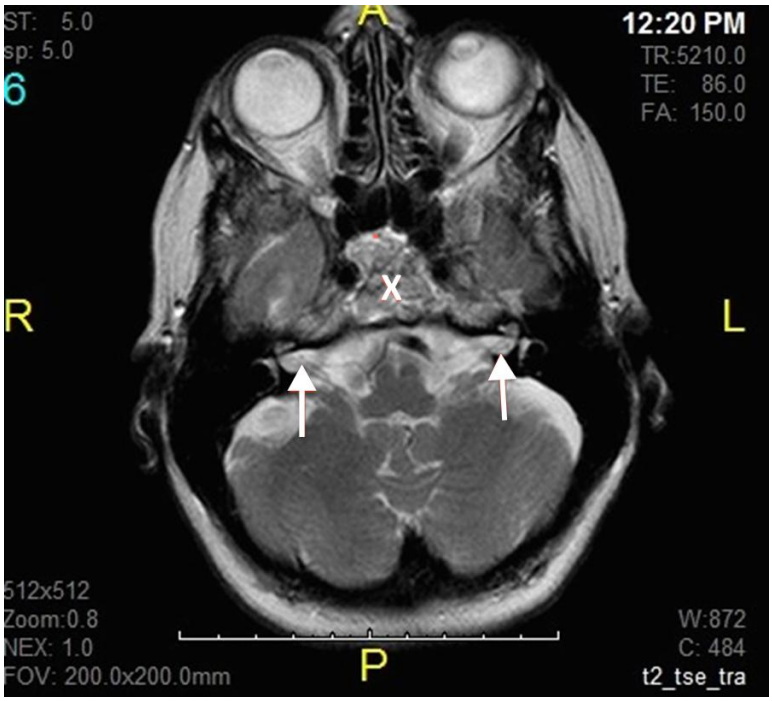

Fig. 3. T2 weighted axial magnetic resonance image of the internal auditory canal and posterior fossa. X labels the abnormal clivus. Arrows point to the normal internal auditory canal structures

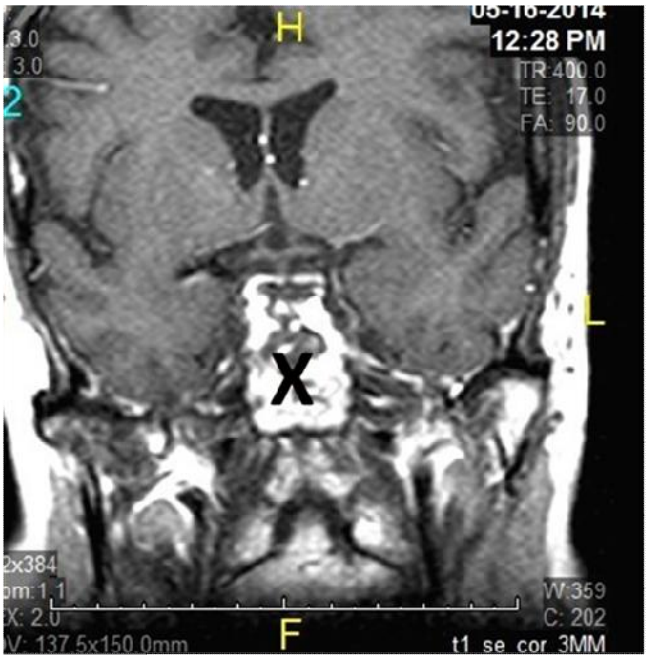

Fig. 4. T1 weighted post-contrast coronal magnetic resonance image. X depicts the heterogeneously enhancing clival lesion

Type II collagen is associated with cartilage, however it is also found in other connective tissue structures. In 1990 Ishibe and Yoo performed an extensive study of type II collagen within the temporal bone [16]. The authors report type II collagen in the cartilage plates of the auricle and external auditory meatus, tympanic annulus, pars tensa of the tympanic membrane, incudo-mallear and incudo-stapedial joints, stapes footplate, cartilage of the eustachian tube, cartilage layer and globuli interossei of the otic capsule, Rosenthal's canal, osseous spiral lamina, spiral ligament, limbus, tectorial membrane, semicircular canal membrane and ampullary cristae, utricular and saccular maculae, and endolymphatic duct and proximal part of the endolymphatic sac. Based on the extensive areas of presence of type II collagen within the normal temporal bone, type II collagenopathy, can potentially lead to sensorineural hearing loss, conductive hearing loss, mixed hearing loss, and even vestibular symptoms.

Including our case, a total of 2 patients with SED congenita are reported with asymmetric hearing loss in the literature. In both cases there is mixed hearing loss on one side and mostly high frequency sensorineural loss on the other. Other than the case of mixed hearing loss reported by Dahiya et al. [13], asymmetry in hearing is not mentioned and audiometric evidence is not provided by the other references.

Autoimmune response to type II collagen has been associated with otospongiosis and otosclerosis [17-19]. Mutant type II collagen may also elicit a similar immune response and lead to stapes fixation. Collagenopathy within the incudo-mallear and incudo-stapedial joints may also contribute to conductive hearing loss. The connective tissue changes from the level of the tympanic membrane to footplate and the inner ear changes involving the spiral lamina, tectorial membrane, spiral ligament, otic capsule, and other areas, may account for mixed hearing loss in these patients.

Animal models for studying SED are limited. A missense mutation of the CoL2a1 gene in the mouse model led to a phenotype resembling human SED [20]. SED patients have a similar molecular mutation in the COL2A1 gene encoding type II collagen. All 12 mice homozygous for the aforementioned mutation had hearing loss demonstrated on auditory evoked brainstem response testing. One mouse had profound deafness and the other 11 had 35-50dB higher thresholds compared to the control group. Head bobbing and circular motion, indicative of vestibular dysfunction, was also seen in mutant mice.

We recommend serial audiometry for patients with spondyloepiphyseal dysplasia congenita for early detection of hearing loss when present and to monitor progression. Beyond the newborn screening test, initial audiometry should be before school age or sooner if clinical concern exists. Hearing aids are recommended for treatment of hearing loss. Surgical management of suspected stapes fixation and otosclerosis may be considered but should be conducted cautiously as literature on this matter does not exist. Because extra-skeletal manifestations are uncommon in individuals with spondyloepiphyseal dysplasia tarda and only one case of hearing loss was identified in the literature, we recommend audiometric testing only when clinically necessary. Further study of hearing loss in patients with SED is necessary. We recommend future reports of patients with SED to include details on the presence, type, and degree of hearing loss. Structural variations noted at the time of otologic surgery in these patients should also be reported.

5. CONCLUSION

Spondyloepiphyseal dysplasia congenita is a result of a type II collagenopathy. The presence of type II collagen in the middle and inner ear may explain hearing loss in these patients. Serial audiograms are recommended early in life in individuals with SED congenita. Audiometric testing is recommended only when clinically necessary in individuals with SED tarda. Further study of hearing loss in patients with spondyloepiphyseal dysplasia is necessary.

CONSENT

All authors declare that informed consent was obtained from the patient for publication of this case report.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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