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OTOPATHOLOGY REPORT

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Otopathology in CHARGE syndrome

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Abstract

Postmortem temporal bone computed tomography (CT) and histopathologic findings in an infant with CHARGE syndrome revealed bilateral cochleovestibular hypoplasia, including cochlear pathology relevant to cochlear implant candidacy. Both ears had absence of the superior semicircular canals (SCCs), severely hypoplastic posterior SCCs, and hypoplastic (right ear) or absent (left ear) lateral SCCs seen on CT and histopathology. Histopathology further revealed the absence of all SCC ampullae except the right lateral SCC ampulla and atrophic vestibular neuroepithelium in the saccule and utricle bilaterally. The right cochlea consisted of a basal turn with patent round window, and malformed middle turn (type IV cochlear hypoplasia), with a small internal auditory canal (IAC) but near normal cochlear nerve aperture (fossette). Quantification of spiral ganglion neurons (SGNs) on histologic sections revealed a reduced SGN population (35% of normal for age), but this ear would still have likely achieved benefit from a cochlear implant based on this population. The left cochlea consisted of only a basal turn with patent round window (type III cochlear hypoplasia) with a small IAC and very small cochlear nerve aperture. Notably, histology revealed that there were no SGNs in the cochlea, and therefore, this ear would not have been a good candidate for cochlear implantation.

Level of evidence: IV.

KEYWORDS

CHARGE syndrome, cochlear implantation, congenital anomalies, otopathology, temporal bone pathology

1 | INTRODUCTION

CHARGE syndrome is a rare genetic disorder that can present with anatomic abnormalities including coloboma, heart defects, choanal atresia, retarded growth, genital abnormalities, and ear malformations. Ear abnormalities are present in over 90% of patients and range from auricular malformations to ossicular dysplasia to inner ear anomalies, including dysplasia of the cochlea or semicircular canals. Over 80% of CHARGE patients have hearing loss as a result.[1] Herein, we present the clinical case, radiologic findings, autopsy, and temporal bone pathology in an infant with CHARGE syndrome and bilateral cochleovestibular hypoplasia. We highlight several computed tomography findings in these temporal bones that correlate with cochlear pathology relevant for cochlear implantation. This emphasizes the importance of radiology

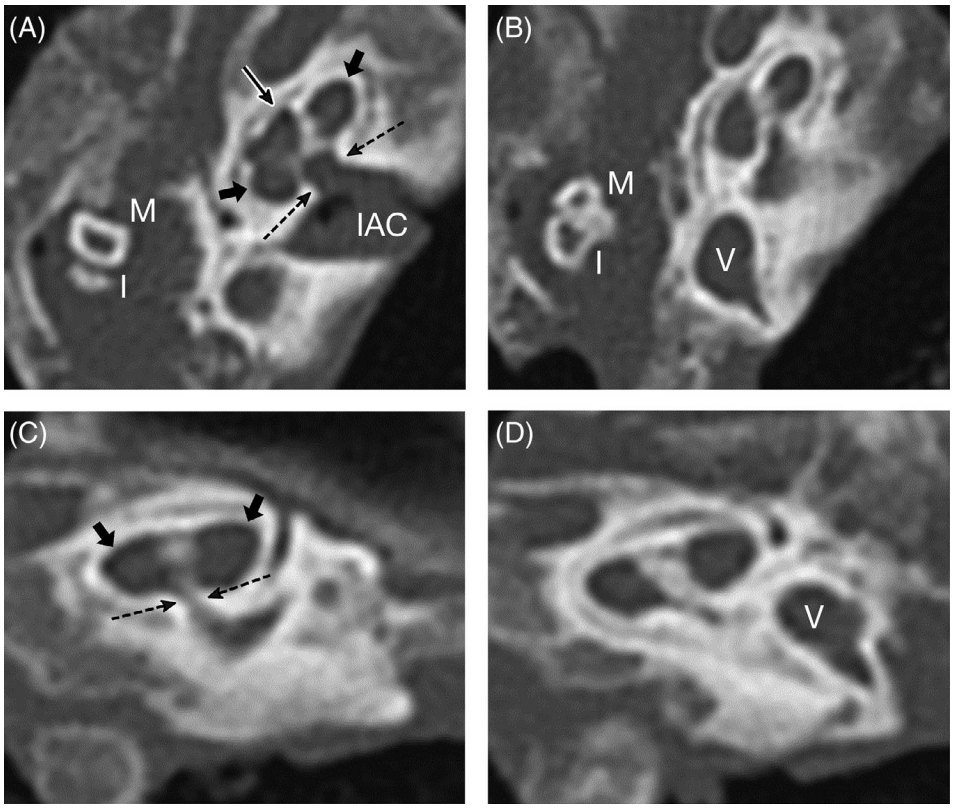

FIGURE 1 Axial CT of the right and left temporal bones. A, Right hypoplastic cochlea with basal turn (thick arrow) and underdeveloped middle turn (thin arrow). The cochlear aperture is near normal caliber (dotted arrows). Malleus (M) and incus (I) present in the middle ear. B, Right vestibule (V) present. Note, the finger-like projection off the vestibule is the take off of the hypoplastic posterior semicircular canal. C, Left hypoplastic cochlea with basal turn (thick arrows) and a very small cochlear nerve aperture (dotted arrows). D, Left vestibule (V) present with hypoplastic posterior semicircular canal

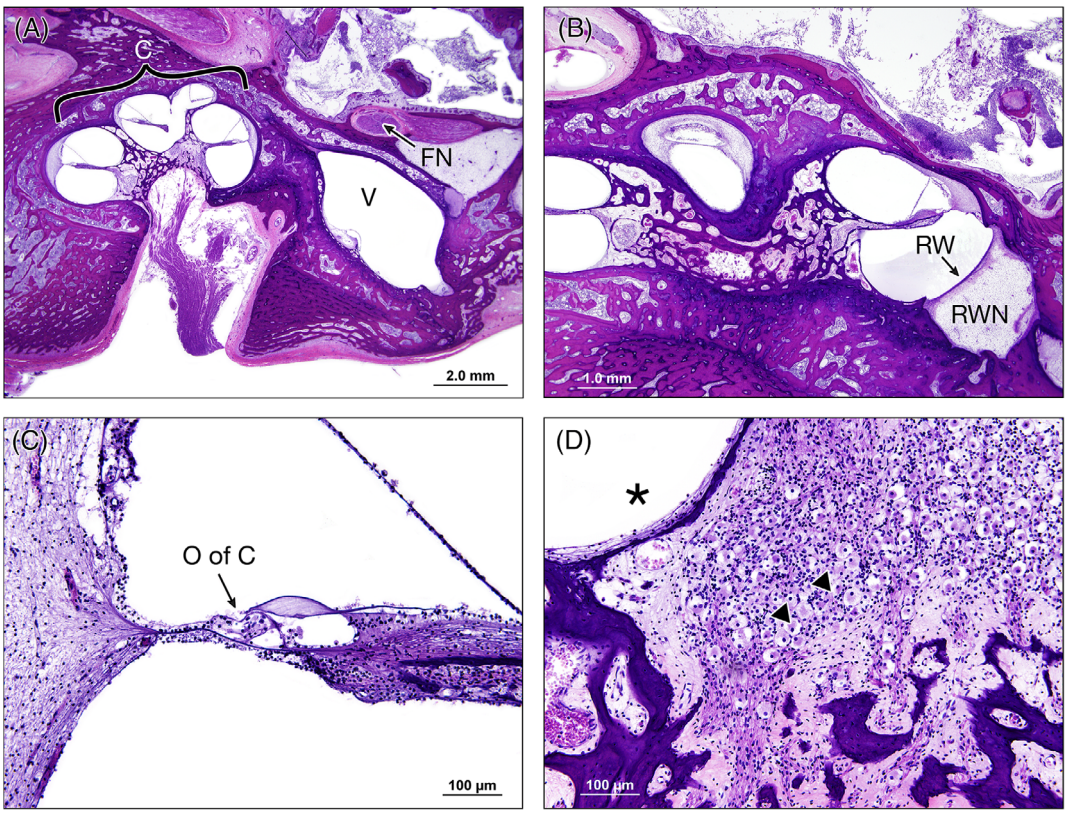

FIGURE 2 Cochlear pathology in the right ear. A, Low magnification near mid-modiolar section showing foreshortened cochlea (C) with two turns. There is no oval window or stapes and thus the facial nerve (FN) crosses directly over the vestibule (V), 1.25×. B, Normally formed round window (RW) and patent round window niche (RWN), 2×. C, Lower basal turn of the cochlea showing normal complement of outer hair cells in the organ of Corti (O of C) and some dendritic fibers of spiral ganglion cells, 10×. D, Mid-modiolar section next to the scala tympani of the middle turn (*) showing significantly reduced numbers of spiral ganglion cells (arrow heads), 10×

in predicting good cochlear implant candidates among those with anomalous inner ears.

2 | METHODS

Temporal bones were removed postmortem. Bones were fixed in formalin for 17 days, then decalcified with ethylenediaminetetraacetic acid for 71 days, and embedded in celloidin prior to being sectioned horizontally at 20 μm intervals. Every 10th section was stained with hematoxylin and eosin and examined under a light microscope. Both cochleae, including Rosenthal's canals, were reconstructed in a two dimensional representation, and then spiral ganglion neurons were counted according to a standard method.[2]

3 | RESULTS

3.1 | Clinical presentation

A female infant, born prematurely at 33 gestational weeks, was diagnosed with CHARGE syndrome due to the presence of right coloboma, bilateral choanal atresia, genital hypoplasia, and auricular abnormalities. A chromosome study showed normal karyotype of 46XX. At 24 days old, she underwent uneventful choanal atresia repair. Nine days later, she was found to have pneumoperitoneum, for which she received an exploratory laparotomy revealing extensive grossly necrotic bowel. She remained in septic shock and respiratory distress and was subsequently placed on comfort measures only. She passed away at 35 days old.

On autopsy, the patient had necrotizing enterocolitis, absent olfactory bulbs, atrial septal defect, absent brachiocephalic trunk, hypoxic/ischemic changes in the white matter of the brain including reactive gliosis with a normal cortex, basal ganglia, brainstem, and cerebellum.

3.2 | Radiology

Temporal bone CT of postmortem temporal bones showed bilateral cochleovestibular hypoplasia. The right temporal bone demonstrated a hypoplastic cochlea with two turns and hypoplastic semicircular canals with an intact vestibule, consistent with cochlear hypoplasia type 3 (Figure 1A,B).[3] The right internal auditory canal was small in size, but the cochlear nerve aperture appeared normal in size. The left temporal bone showed an even more underdeveloped cochlea with only one turn (ie, the basal turn), consistent with cochlear hypoplasia type IV.[3] The left cochlear nerve aperture was markedly stenotic (Figure 1C). The left vestibule was present, and the left ear had extremely hypoplastic semicircular canals, similar to the right side (Figure 1D). The vestibular aqueducts were normal in size bilaterally.

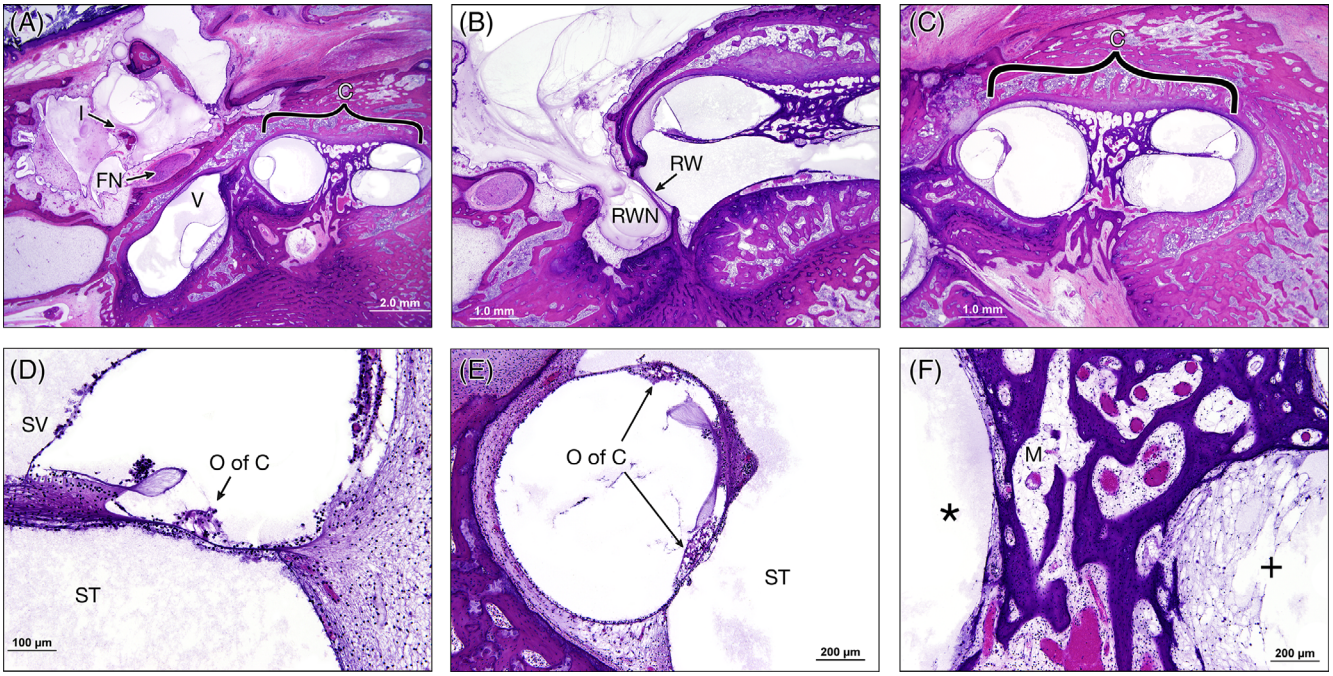

FIGURE 3 Cochlear pathology in the left ear. A, Low magnification view of the middle ear with the lenticular process of the incus (I) as well as the facial nerve (FN) coursing over the vestibule (V), 1.25×. Basal turn of the cochlea (c). B, The round window (RW) and round window niche (RWN) are normally formed. C, The cochlea (c) is hypoplastic with missing turns, a very small fundus and cochlear nerve aperture, 2×. D, The lower basal turn of the cochlea with proteinaceous debris in the scala vestibule (SV) and scala tympani (ST). The osseous spiral lamina appears empty. The organ of corti appears fully formed. E, In the upper basal turn, there is greater deformity of the cochlea as shown by the development of two organ of Corti (O of C) and tectorial membranes, 10×. F, Modiolus (M) between the scala tympani of the upper (*) and lower (+) basal turns with no spiral ganglion cells, 10×

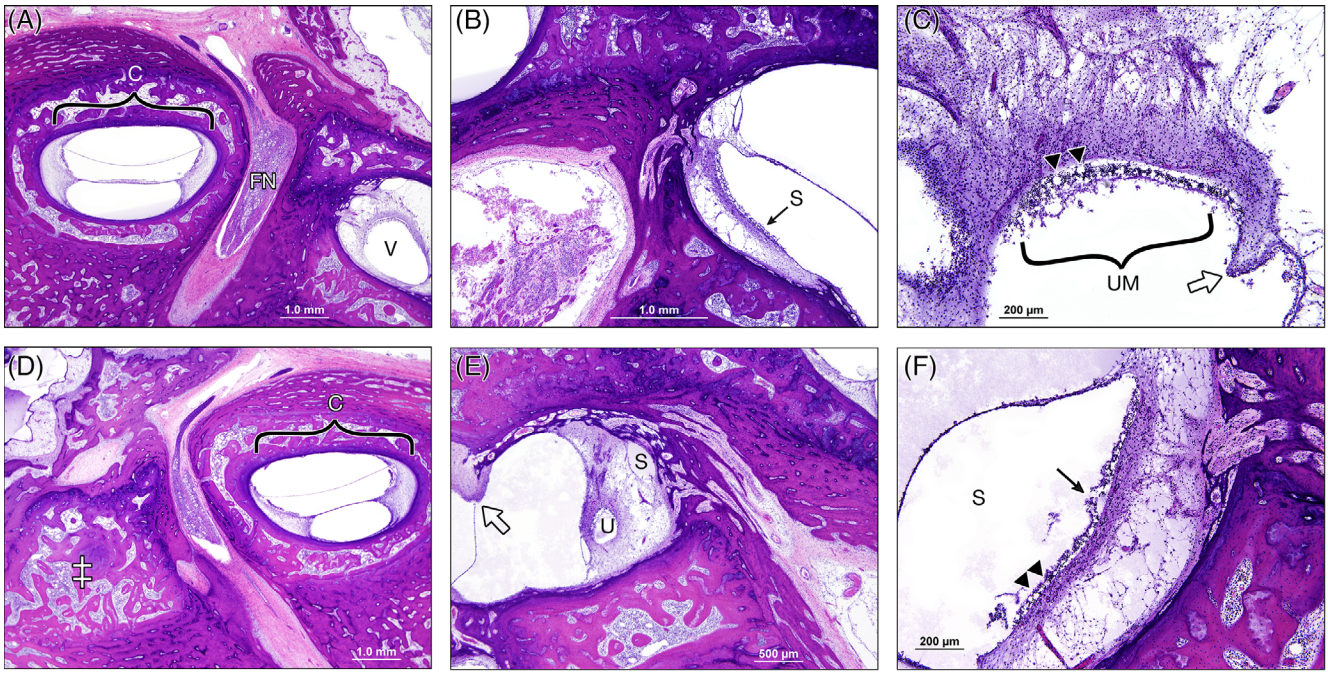

FIGURE 4 Vestibular findings. Right ear: A, Abnormal position of the geniculate ganglion cells located within the labyrinthine facial nerve (FN), 2×. Vestibule (V) is present but there is no superior SCC. Basal turn of hypoplastic cochlea (c). B, Small saccule (S) with vestibular neuroepithelium (arrow). C, Utricular macula (UM) with vacuolated spaces consistent with the presence of type 1 vestibular hair cells (arrow heads). The vestigial ampulla of the lateral SCC (open arrow) with limited true neuroepithelium, 10×. Left ear: D, Significant vestibular hypoplasia notable for lack of superior SCC typically in the area marked (‡), 2×. E, The beginning of the lateral SCCa ampulla (open arrow), with underdeveloped utricle (U) and saccule (S), 4×. F, Saccule (S) with neuroepithelium present (arrow) and vacuolated spaces consistent with the presence of type 1 vestibular hair cells (arrow heads), 10×

3.3 | Histopathology

3.3.1 | Right ear

The right middle ear had an intact malleus and incus, but there was no stapes (Figure 2A). The oval window was absent, and the tympanic segment of the facial nerve coursed directly over the vestibule (where the oval window would normally have been located). The round window was normal with a patent round window niche (Figure 2B). The right cochlea had two complete turns (cochlear hypoplasia type IV).[3] The lower basal turn demonstrated the full complement of outer and inner hair cells with a normal appearing organ of Corti (Figure 2C). The stria vascularis was present, and the modiolus had 12 357 spiral ganglion neurons (SGNs). This represents 35% of the normal spiral ganglion cell population for age, as normal neonates have 35 500 SGN on average (Figure 2D).[2] The geniculate ganglion cells were found within the labyrinthine segment of the facial nerve at the level of the cochlea, rather than forming a true geniculate ganglion in the normal location superior to the cochlea. The internal auditory canal was small with a present cochlear nerve.

3.3.2 | Left ear

The middle ear had an intact malleus and incus, and the stapes superstructure was malformed (Figure 3A). The round window and round window niche were normal and patent (Figure 3B). The cochlea was very hypoplastic (cochlear hypoplasia type III, Figure 3C),[3] with only one turn (ie, the basal turn). The lower basal turn showed a fully formed organ of Corti and an empty osseous spiral lamina, whereas the upper basal turn demonstrated vestigial development of a middle/second turn with duplicated organs of Corti and tectorial membranes (Figure 3D,E). There was evidence of mild endolymphatic hydrops in the basal turn. The stria vascularis was normal. The cochlear nerve aperture was very small, and the internal auditory canal was also small. Notably, on review of all H&E stained sections through the modiolus, we found no spiral ganglion cells in this ear and Rosenthal's canal was absent (Figure 3F).

3.3.3 | Vestibular systems

The vestibule, utricle, and saccule were present but hypoplastic bilaterally. The vestibular aqueducts were normal in caliber bilaterally. In both ears, the facial nerve crossed directly over the vestibule. In the right ear, the posterior ampullary nerve was visible in a rudimentary singular canal, although the posterior semicircular canal (SCC) and posterior SCC ampulla were notably absent (Figure 4A). The vestibule was present, but there was no superior SCC. The saccule was present but small, with some intact vestibular neuroepithelium (Figure 4B). The vestigial ampulla of the lateral

semicircular canal had very limited true neuroepithelium (Figure 4C). The right utricular macula demonstrated some postmortem autolysis with vacuolated spaces consistent with the presence of type 1 vestibular hair cells. In the left ear, there was again a small vestibule with endochondral bone present in the area that would have formed the superior SCC, and there was no real extension of the lateral semicircular canal (Figure 4D,E). The hypoplastic saccule was filled with proteinaceous debris (Figure 4F).

4 | DISCUSSION

In this case, we present the radiological and temporal bone pathology findings in a female newborn with CHARGE syndrome. Both radiologic imaging and histopathology revealed bilateral underdeveloped cochlea with rudimentary or absent apical turns and hypoplastic semicircular canals. Although both ears had cochlear hypoplasia with fully developed basal turns, the left ear was consistent with type III cochlear hypoplasia with less than two turns, while the right ear represented type IV cochlear hypoplasia (a relatively new classification that was described in the past decade).[3] Both ears had normal round windows that could accommodate a cochlear implant electrode; however, while the right ear had a diminished number of spiral ganglion cells, the left ear had no spiral ganglion cells. This may have been predicted by the temporal bone CT finding of severe cochlear nerve aperture stenosis on the left.

Only one other paper in the recent literature has described temporal bone histopathology in CHARGE syndrome. In Haginomori et al.'s 2002 report of two infants with CHARGE syndrome, one patient also had partial DiGeorge syndrome and presented with coloboma, heart defects, and cleft lip and palate.[4] This patient had bilateral mildly hypoplastic cochleae with missing third turns and absent semicircular canals and their ampullae. The left inner ear was missing the cochlear nerve and spiral ganglion cells. In comparison, the second patient who was born with congenital heart defects, choanal atresia, tracheo-esophageal fistula, and vertebral anomalies without coloboma, had almost normal structures in the inner ear, middle ear, and eustachian tube. The current paper's case presented with a constellation of otologic findings placing her closer to the more severe of the two presentations described by Haginomori et al as this infant had modestly better developed vestibular systems with worse cochlear hypoplasia.

In the literature, the radiographic findings of otologic abnormalities in CHARGE syndrome underscore this wide range of cochlear and vestibular abnormalities. In a recent series of 42 patients with CHARGE syndrome, CT scans revealed abnormalities of the cochlea, semicircular canals, middle ear, and internal auditory canal.[1] Common findings included underdeveloped or absent semicircular canals (77%), hypoplastic cochleas (38%), stenotic cochlear apertures (37%), and abnormal course of the facial nerves (19%).

Successful cochlear implantation relies on an understanding of the wide spectrum of temporal bone and otologic abnormalities in CHARGE syndrome. Loss or malpositioning of landmarks, such as the lateral semicircular canal, oval window, and tympanic segment of the facial nerve can make identifying the round window more difficult. Furthermore, the abnormal course of the facial nerve can significantly increase the likelihood of facial nerve palsy. Alternative surgical techniques may be required to avoid an aberrant facial nerve or venous abnormalities in the mastoid, such as a suprameatal approach or a modified Rambo transcanal approach. Note that in the case presented, the patient had patent round windows and basal turns of the cochlea bilaterally that would have been amenable to a round window insertion of a cochlear implant electrode.

Despite the variety of techniques proposed for cochlear implantation in CHARGE syndrome, considerable variability in outcomes exists. One recent study found that after cochlear implantation in 12 children with CHARGE, two saw minimal benefit, four demonstrated improved sound detection, three developed closed set speech perception, and three had open set speech perception.[5] This variability likely reflects the large range of otologic abnormalities that can exist in CHARGE syndrome, such as the degree of cochlear hypoplasia, the diameter of the internal auditory canal to accommodate varying numbers of cochlear neurons, and presence of SGNs. A complete evaluation using all available imaging (CT temporal bone, MRI) is necessary to identify which patients and which ears may be the best candidates for cochlear implantation. In this study, temporal bone CT would have predicted a better outcome in implanting the right ear compared with the left, and otopathology affirms this prediction in the dramatically different spiral ganglion cell counts.

5 | CONCLUSIONS

Radiologic and histopathologic findings in a patient with CHARGE syndrome revealed bilateral cochlear and semicircular hypoplasia with intact round windows and abnormalities in SGN populations. In this case, the left ear would have been a poor implant candidate with no spiral ganglion cells, correlating with postmortem temporal bone CT findings of severe stenosis of the cochlear aperture. In contrast, the right ear may have been a viable candidate for cochlear implantation. This case contributes to a richer understanding of the spectrum of otologic manifestations of CHARGE syndrome and emphasizes the need to carefully select the best candidates and surgical approaches for cochlear implantation based on the temporal bone abnormalities.

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CONFLICT OF INTEREST

None.

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