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Temporal Bone Findings on Computed Tomography Imaging in Branchio-Oto-Renal Syndrome

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Objectives/Hypothesis: **To describe temporal bone findings using visual inspection and direct measurement on computerized tomography (CT) in individuals with branchio-oto-renal syndrome (BOR). We ask if it is possible for the untrained observer to use a battery of CT observations as a tool in the overall evaluation of the BOR phenotype.** ***Study Design:*** **Retrospective evaluation of CT findings in individuals with a clinical diagnosis of BOR based on criteria derived from genotype-phenotype analyses.** ***Methods:*** **Prospective measurement of temporal bone CT imaging in 21 individuals (42 ears) with BOR and 21 normally hearing controls (21 ears) was performed. Thirty-nine aspects of each temporal bone were evaluated: 17 by direct measurement, 5 computed from direct measurement, and 17 by visual inspection. Thirty-eight recordings from each ear were made on axial section and 1 was made on coronal section.** ***Results:*** **Statistically significant differences were found between BOR and control groups in 30 of 39 categories (76.9%). The most common and easily identifiable characteristics of BOR by visual inspection were 1) hypoplastic apical turn of the cochlea, 2) facial nerve deviated to the medial side of the cochlea, 3) funnel-shaped internal auditory canal, and 4) patulous eustachian tube. The embryological origin of temporal bone anomalies in BOR are described.** ***Conclusions:*** **CT evaluation of the temporal bone, when properly investigated, should be used as an important tool in the overall evaluation of the BOR phenotype.** ***Key Words:*** **Temporal bone, tomography, x-ray computed, CT, branchio-oto-renal syndrome, measure.**

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INTRODUCTION

Branchio-oto-renal (BOR) syndrome is currently difficult to diagnose because of costly genetic testing that is not widely available and because only 40% of people with clinical features of BOR have identifiable mutations in the EYA1 gene.[1] Previous studies relying on visual inspection of the temporal bone on computerized tomography (CT) imaging in BOR have yielded inconsistent findings, making abnormal temporal bone findings a minor criterion in the diagnosis of BOR.[1] The prime objective of this study was to see whether a battery of qualitative and quantitative measures from CT images can be used as a tool in the overall evaluation of the BOR phenotype.

BOR dysplasia was first defined by Melnick et al.[2] in 1975 while describing a family with small, anteverted, cup-shaped ears, prehelical pits, mixed hearing loss (HL), branchial fistulae, and renal anomalies inherited in an apparently autosomal dominant manner. Fraser et al.,[3] in 1980, proposed that BOR dysplasia had a variable expressivity across and within families and estimated its prevalence to be 1:40,000. In 1997, BOR was mapped to the EYA1 gene on chromosome 8q13.3.[4] The EYA1 gene is believed to be expressed in the 4th to 10th week of embryonic life during development of the otic placode and renal anlage.[5] Approximately 40% of persons with clinical criteria for BOR have identifiable mutations in the EYA1 gene.[1]

The few small studies investigating temporal bone findings on CT imaging in BOR have relied solely on visual inspection and have yielded inconsistent findings. Chen et al.[6] described 12 clinically affected individuals with the cochlea hypoplastic (63%) or dysplastic (33%), vestibular aqueduct enlarged (46%), internal auditory canal (IAC) bulbous (25%), or small (8%), vestibule enlarged

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(17%), horizontal semicircular canal hypoplastic (12%), facial nerve having an anomalous course (8%), facial nerve duplication (8%) or overhanging facial nerve (4%), ossicles malpositioned (50%), malformed (33%), laterally fixated (25%), or dislocated (17%), middle ear small (29%) or enlarged (4%), and external auditory canal stenotic (21%), atretic (12%), or tortuous (4%). Kemperman et al.[7] investigated six families using magnetic resonance imaging (MRI) and found temporal bone anomalies in 67% of patients. Ceruti et al.[8] studied a family using CT and MRI and found all had hypoplastic cochleae and lateral semicircular canals, whereas only some had ossicular chain malformations (88%), including absent stapedius muscle and tendon (57%), malleus and incus fused and plump (29%), fixed to the anterior wall of the tympanic cavity (14%) and stapes calcification over the oval window (14%).

Recently, Purcell et al.[9] demonstrated that visual inspection combined with precise measurement of the temporal bone on CT can detect twice as many anomalies as compared with visual inspection alone in individuals with HL versus those without HL. On the basis of this premise, the purposes of this study were to 1) describe temporal bone findings using visual inspection and direct measurement on CT in individuals with BOR and 2) determine whether it is possible for the untrained observer to use a battery of CT observations as a tool in the overall evaluation of the BOR phenotype.

MATERIALS AND METHODS

Patients with BOR

Subjects were selected from the patient population of the Department of Otolaryngology, The Hospital for Sick Children, Toronto, Canada. This project was approved by The Hospital for Sick Children Ethics Review Board, which adheres to the "Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans." A database kept by four otolaryngologists from 1975 to 2004 was searched using the key word branchial cleft cyst. One hundred eighty-one patients were identified, and 179 charts were reviewed (2 charts could not be located). Subjects were included in this study if they fulfilled the clinical criteria for BOR defined by Chang et al.[1] based on genotype-phenotype analyses of 40 families. Eleven patients fulfilled these criteria, eight of whom had a petrous temporal bone scan. An additional 5 patients with a clinical diagnosis of BOR were included, for a total of 13 nonrelated individuals. Eight of their family members were also included for a total of 21 individuals from 13 families. Both ears were evaluated in each of these individuals for a total of 42 ears.

Normally Hearing Controls

Normally hearing control subjects were obtained from a database of surgical procedures kept by one otolaryngologist from 1996 to present, searched using the key word cholesteatoma. A retrospective chart review yielded 21 individuals with CT imaging of the temporal bone and a normal audiogram for the unaffected ear. Patients were excluded if they had abnormal clinical findings apart from cholesteatoma.

Temporal Bone Measurements

Prospective measurement of temporal bone CT imaging previously obtained for clinical reasons was performed. CT studies from 19 individuals with a diagnosis of BOR and 21 controls were obtained and stored digitally at The Hospital for Sick Children, Toronto, Canada. CT studies from two individuals with a diagnosis of BOR were only available on hard copy because they were obtained at other institutions. Digitally stored CT images were displayed using the Centricity Picture Archiving Communication System (PACS) by General Electric. Precise measurements were made by an experienced neuroradiologist using the electronic calipers provided by the PACS system. Measurements were recorded in millimeters (rounded to 2 decimal points) in a Microsoft Excel spreadsheet (Redmond, WA). Immeasurable aspects of the temporal bone were categorized by visual inspection and were entered into the same spreadsheet. The same items were measured and categorized for individuals with BOR and for normally hearing controls.

Thirty-nine aspects of each temporal bone CT were recorded (Table I): 17 by direct measurement, 5 computed from direct measurement data, and 17 by visual inspection and categorization. Thirty-eight recordings were made on axial section, and one was made on coronal section. Data were analyzed using SPSS version 11.1 (SPSS Inc., Chicago, IL) using independent samples t tests for continuous data and nonparametric Mann-Whitney tests for categorical data. A subset of 20 ears from both the BOR and control groups were randomized and measured or evaluated for each of the same 39 temporal bone aspects on CT by an otolaryngology–head and neck surgery resident.

RESULTS

Forty-two individuals (63 ears) were included in this study: 21 subjects (42 ears) with a clinical diagnosis of BOR and 21 normally hearing controls (21 ears). The BOR group comprised 21 patients (11 male, 10 female) with a mean age of 12.18 ± 14.10 (range 0.94–42.84) years at the time of imaging. The normally hearing control group comprised 21 patients (16 male, 5 female) with a mean age of 8.98 ± 3.65 (range 1.72–17.32) years at the time of imaging for evaluation of cholesteatoma. There was no statistically significant difference in age across the two groups (t test, $P = .325$).

Prospective evaluation of 39 predetermined aspects of the temporal bone on CT were evaluated for each individual in the BOR and normally hearing control groups using measuring tools provided by the PACS viewing system and by direct visualization and categorization. Measurements from 42 temporal bones of individuals with BOR on CT were compared with measurements from 21 temporal bones of normally hearing controls. Temporal bones of two individuals in the BOR group were available on hard copy only because they were obtained at another institution, and therefore, only categorical data were collected on these subjects. Two subjects in the BOR group had unilateral absence of the ossicles secondary to middle ear surgery, making it impossible to evaluate the ossicular joint space and the anterior ligament. Seven ears in four individuals in the BOR group had fluid or soft tissue in the middle ear, rendering evaluation of the eustachian tube and the presence of the tensor tympani muscle bundle impossible. One enlarged endolymphatic fossa could not be measured because of its abnormal course. The diameter of the basal turn of the cochlea on coronal section could not be measured in three ears in two individuals because no coronal images were obtained and in four ears in two individuals because only hard films were available, prohibiting electronic measurement. Table II outlines the structure of the temporal bone that was evaluated, the number of ears evaluated in the group, the mean measure-

TABLE I.
Summary of Measurements Obtained in Axial and Coronal Planes.

Structure	Description of Measurement
Middle ear	
Superior ligament shortened?	On cut demonstrating "ice cream cone" appearance of malleus and incus, judgment if length of ligament attached to incus is short
Superior ligament length	On same cut, measurement of space between incus and closest bone of epitympanum
Superior ligament calcification?	On same cut, judgment if ligament is normal or calcified (white)
Malleoincudal joint space narrow?	On same cut, judgment whether space is normal or narrowed (bone spicules cross joint space)
Eustachian tube patulous? (judgment)	Judgment if gas in eustachian tube extends further anteriorly than expected
Eustachian tube patulous? (criteria)	On cut demonstrating the furthest anterior extension of gas in the eustachian tube, a line is drawn between the medial aspects of the condylar heads; gas extending anterior to this line is a sign of patulosity
Tensor tympani present?	Judgment if present in eustachian tube
Inner ear	
Cochlea apical turn hypoplastic?	On cut of cochlea demonstrating modiolus and eighth nerve canal, judgment if apical turn of cochlea is smaller than expected
Cochlea apical turn anterior-posterior (AP)	On same cut, measurement of AP diameter of apical turn
Cochlea apical turn transverse	On same cut, measurement of transverse diameter of apical turn
Cochlea apical turn ratio AP:transv	Calculated ratio of AP to transverse dimensions of apical turn
Cochlea basal turn AP	On cut of cochlea demonstrating basal turn, measurement of AP diameter
Cochlea basal turn transverse	On same cut, measurement of transverse diameter
Cochlea basal turn ratio AP:transv	Calculated ratio of AP to transverse dimensions of basal turn
Cochlea basal turn height (coronal)	On coronal cut, measurement of largest vertical dimension of basal turn
Modiolus shape	On cut of apical turn of cochlea, judgment if modiolus is normal shape (square), "c"-shaped, or absent
Lamina cribrosa present?	On same cut, judgment if bone plate is present crossing eighth nerve canal
Cochlear nerve canal width	On same cut, measurement between bony edges of eighth nerve canal
Facial nerve	
Courses medial to cochlea?	Judgment if nerve has normal course lateral to cochlea or is medially deviated
Canal width	Measurement of widest dimension of facial nerve canal
Horizontal semicircular canal	
Hypoplastic?	Judgment if canal is of normal size or smaller than expected
Bony island width	Measurement of bony island in dimension perpendicular to long axis of vestibule
Vestibule width	Measurement of vestibule in dimension perpendicular to long axis of vestibule
Vestibule length	Measurement of long axis of vestibule
Vestibule ratio width:length	Calculated ratio of vestibule width to length
Ampulla dilated?	Judgment if ampulla is normal size or dilated
Endolymphatic fossa enlarged?	Judgment if opening into vestibular aqueduct is enlarged
Size if enlarged	Measurement of opening into vestibular aqueduct
Vestibular aqueduct enlarged?	Judgment if vestibular aqueduct is larger than posterior semicircular canal
Size if enlarged	Judgment if aqueduct is normal, large, or extra-large compared with posterior semicircular canal
Shape	Judgment if walls of aqueduct are funnel-shaped or parallel to each other
Internal auditory canal (IAC)	
IAC funnel shaped?	On cut demonstrating apical turn of cochlea, modiolus, and lamina cribrosa, judgment if canal has normal shape or is funnel shaped
IAC angle	On same cut, the cobb angle tool is selected, and a line is drawn along each bony edge of the canal; angle between these lines is recorded
IAC length	On same cut, measurement from the lamina cribrosa to a line drawn across the opening of the porous acousticus
Porous acousticus width	On same cut, measurement across opening of the porous acousticus
IAC ratio porous width:length	Calculated ratio of porous width to IAC length
IAC mid-distance width	On same cut, measurement of the IAC width at a distance midway along the length of the IAC
IAC ratio mid-distance:porous width	Calculated ratio of IAC mid-distance width to porous width
Carotid arteries	
Intercarotid distance	On cut demonstrating full bony circumference of carotid arteries, measurement between medial aspects of these vessels

TABLE II.
Summary of Measurements, Calculated Ratios, and Categorical Evaluations.

Structure	BOR			Control			Difference
	n	Mean/Mode	SD	n	Mean/Mode	SD	*P* Value
Middle ear							
Superior ligament shortened?	40	Yes		21	No		.000***
Superior ligament length	36	0.19	0.22	21	1.20	0.51	.000***
Superior ligament calcification?	40	Yes		21	No		.000***
Malleoincudal joint space narrow?	40	No		21	No		.000***
Eustachian tube patulous? (judgment)	35	Yes		21	No		.003**
Eustachian tube patulous? (criteria)	35	Yes		21	No		.632
Tensor tympani present?	35	Yes		21	Yes		1.000
Inner ear							
Cochlea apical turn hypoplastic?	42	Yes		21	No		.000***
Cochlea apical turn anterior-posterior (AP)	38	2.42	0.36	21	3.38	0.42	.000***
Cochlea apical turn transverse	38	3.44	0.42	21	5.68	0.36	.000***
Cochlea apical turn ratio AP:transv	38	0.72	0.17	21	0.60	0.07	.000***
Cochlea basal turn AP	38	1.78	0.27	21	2.15	0.30	.000***
Cochlea basal turn transverse	38	6.56	0.84	21	8.26	0.74	.000***
Cochlea basal turn ratio AP:transv	38	0.28	0.06	21	0.26	0.03	.292
Cochlea basal turn height (coronal)	36	1.07	0.20	20	1.99	0.25	.000***
Modiolus shape	42	“c”		21	Normal		.000***
Lamina cribrosa present?	42	Full		21	Full		.000***
Cochlear nerve canal width	38	1.42	0.37	21	2.05	0.24	.000***
Facial nerve							
Courses medial to cochlea?	42	Yes		21	No		.000***
Canal width	38	1.35	0.44	21	0.86	0.28	.000***
Horizontal semicircular canal							
Hypoplastic?	42	Yes		21	No		.000***
Bony island width	38	3.01	0.63	21	4.04	0.49	.000***
Vestibule width	38	2.68	0.34	21	3.01	0.36	.001**
Vestibule length	38	5.08	0.47	21	5.66	0.39	.000***
Vestibule ratio width:length	38	0.53	0.07	21	0.53	0.06	.864
Ampulla dilated?	42	No		21	No		.007*
Endolymphatic fossa enlarged?	42	No		21	No		.151
Size if enlarged	19	3.38	2.02	6	2.3	0.58	.050*
Vestibular aqueduct enlarged?	42	No		21	No		.063
Size if enlarged	10	L/XL		1	Large		.545
Shape	10	Funnel		1	Funnel		1.000
Internal auditory canal (IAC)							
IAC funnel shaped?	42	Yes		21	No		.000***
IAC angle	38	43.53	11.80	21	10.72	8.24	.000***
IAC length	38	7.76	1.70	21	8.85	1.38	.015*
Porous acousticus width	38	8.02	1.77	21	6.14	2.02	.000***
IAC ratio porous width:length	38	1.06	0.23	21	0.71	0.22	.000***
IAC mid-distance width	38	5.87	0.98	21	5.59	1.22	.340
IAC ratio mid-distance:porous width	38	0.81	0.26	21	0.97	0.30	.036*
Carotid arteries							
Intercarotid distance	19	11.67	3.18	21	18.41	2.15	.000***

BOR = branchio-oto-renal syndrome. *P = .05, **P = .005, ***P = .0005.

ment (for items directly measured or calculated from direct measurements) or mode (for categorical data), SD, and whether the difference between groups for each measure attained statistical significance. Asterisks next to significance values indicate the degree of significance: *P = .05, **P = .005, ***P = .0005.

Statistically significant differences ($P \leq .05$) between individuals with BOR and those with normal hearing were found in 30 of 39 (76.9%) categories: 24 (61.5%) attained a significance of $P \leq .0005$, 2 (5.1%) attained a significance of $P \leq .005$, and 4 (10.3%) attained a significance of $P \leq .05$. The most common and easily identifiable characteristics of BOR by visual inspection were 1) hypoplastic apical turn of the cochlea (present in all individuals with BOR and none of normally hearing individuals), 2) facial nerve deviated to medial side of cochlea (present in 38 of 42 [90.5%] BOR ears and none of normally hearing individuals), 3) funnel shaped IAC (present in 36 of 42 [85.7%] BOR ears and 1 of 21 [4.8%] of normally hearing individuals), and 4) patulous eustachian tube (present in 21 of 35 [60%] BOR ears and only 4 of 21 [19%] of normally hearing individuals).

Measurements made by the neuroradiologist were correlated with those made by the otolaryngology–head and neck surgery resident. Measurements of all continuous variables were pooled and yielded a Pearson correlation of 0.950 ($P < .01$). Spearman rank correlation for pooled categorical data was 0.820 ($P < .01$). Interrater reliability using Cohen's Kappa for pooled categorical data was 0.708 ($P < .01$).

DISCUSSION

Prospective evaluation of 39 predetermined aspects of the temporal bone on CT were evaluated for 21 individuals (42 ears) with a clinical diagnosis of BOR and 21 normally hearing controls (21 ears) using measuring tools provided by the PACS viewing system and by direct visualization and categorization. Statistically significant differences ($P \leq .05$) between these groups were found in 30 of 39 (76.9%) aspects of the temporal bone.

In the middle ear, individuals with BOR were significantly more likely than normally hearing individuals to have a shortened and calcified anterior ligament (Fig. 1). Even though the majority of individuals with BOR and with normal hearing did not show evidence of a narrow malleoincudal joint space, significantly more individuals with BOR had this finding (Fig. 1). Ossicular displacement in a small middle ear in BOR has previously been described.[6] Embryologically, in normally hearing individuals, the tympanic ossicles develop in the mesenchyme of the first two pharyngeal arches.[10] The malleus and incus start as a single mass and separate at 8.5 weeks, forming the incudostapedial joint.[10] When the mesenchyme of the second branchial arch resorbs and the ossicles are free, the endodermal epithelium of the tympanic cavity connects the ossicles to the cavity and allows for development of the ossicular ligaments. In individuals with BOR, this process beginning at 8.5 weeks appears to be affected because the ossicles are neither completely separated nor completely free from the cavity wall.

Significantly more individuals with BOR had a patulous eustachian tube by judgmental criteria as compared with normally hearing individuals (Fig. 1). Surprisingly, the patulous eustachian tube in BOR has not been previously described to the authors' knowledge. Despite the nonsignificant difference between the groups in the degree of dilatation of the eustachian tube (as determined by presence of air anterior to a line drawn between the medial aspects of the ascending rami of the mandible), a greater percentage of individuals with BOR had air anterior to this line as compared with normally hearing individuals. Awareness of the patulous eustachian tube is important for the otolaryngologist planning surgical adenoidectomy in an individual with BOR because removal of adenoid tissue can lead to chronic otitis media and mastoiditis secondary to reflux of food from the nasopharynx to the middle ear. The authors' postulate that the eustachian tube appeared patulous because the tensor tympani muscle belly was absent was false, because the tensor tympani was present in almost all individuals in both groups.

In the inner ear, individuals with BOR had a significantly higher incidence than normally hearing individuals of a hypoplastic apical turn of the cochlea in both anterior-posterior (AP) and transverse dimensions (Fig. 2). Moreover, the apical turn of the cochlea in BOR was significantly more square shaped with an AP to transverse ratio closer to 1 as compared with normally hearing individuals. Individuals with BOR also had significantly more instances of hypoplasia of the basal turn of the cochlea in both AP and transverse dimensions on axial section and in the vertical dimension on coronal section (Fig. 3). The finding that the ratio of AP to transverse measurements in the basal turn of the cochlea was not statistically significant across groups suggests that although the basal turn of the cochlea is hypoplastic in BOR, it likely develops in the same proportions as in normally hearing individuals. Although cochlear findings in BOR have been described as being of the Mondini type,[2] the present study has disproven this theory. Mondini malformations comprise a normal basal turn and fusion of the second and apical turn,[11] whereas individuals with BOR appear to also have hypoplasia of the basal turn of the cochlea. The shape of the modiolus in individuals with BOR was significantly more hypoplastic with a "c"-shape configuration as opposed to the rectangular or square shape present in normally hearing individuals. Modiolar shapes in individuals with BOR ranged from square but hypoplastic to completely absent (Fig. 2). Approximately one half of the individuals with BOR had a lamina cribrosa that was either partial or absent (Fig. 2), as compared with normally hearing individuals who all demonstrated a full lamina cribrosa. Individuals with BOR also had significantly smaller cochlear nerve canal widths than normally hearing controls (Fig. 2). Embryologically, in normally hearing individuals, labyrinthine development begins at 3 weeks' gestation with the formation of the otic placode.[12] The first turn of the cochlea is formed at week 7, and the entire 2.5 to 2.75 turns have been completed by week 8.[13] The hypoplastic cochlea in individuals with BOR provides evidence for disruption of this process.

The facial nerve coursed medial to the cochlea in 90.5% of ears in individuals with BOR and lateral to the cochlea in all normally hearing controls (Fig. 4). Even though an anomalous course of the facial nerve in BOR has been described in a small percentage of patients,[6] this finding has not been consistently associated with BOR. Medial deviation of the facial nerve has been described in

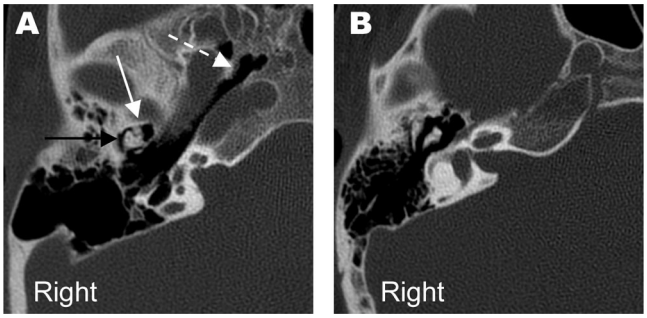

Fig. 1. Middle ear, axial section. Note the short, calcified superior ligament (white arrow), absent malleoincudal joint space (black arrow), and patulous eustachian tube (dashed white arrow) in branchio-oto-renal syndrome (**A**) as compared with normally hearing control (**B**).

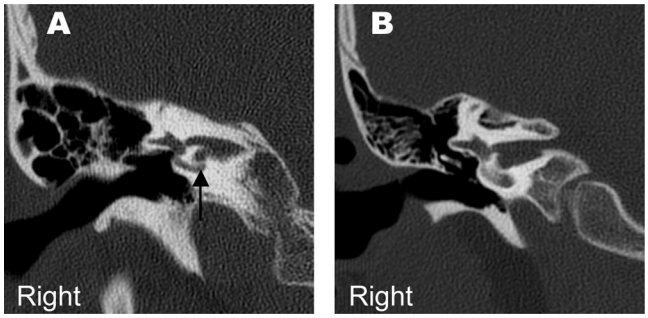

Fig. 3. Inner ear, coronal section. Note the hypoplastic basal turn (black arrow) in branchio-oto-renal syndrome (**A**) as compared with normally hearing control (**B**).

association with hypoplasia of the cochlea but was not ascribed to BOR.[14] The facial nerve canal width in individuals with BOR was also significantly wider as compared with normally hearing individuals (Fig. 4). To the authors' knowledge, this finding has not previously been described. Embryologically, two theories exist to describe the abnormal course of the facial nerve. The first postulates that because the normal facial nerve is located posterior to the structures formed by Reichert's cartilage (anlage of the second branchial arch), abnormal development of structures derived from Reichert's cartilage, such as the stapes crura, allows the facial nerve to take a more direct route to the muscles of facial expression.[15] Malformations of the stapes such as hypoplasia and a calcified plate over the oval window have been described in the BOR syndrome.[8] The second theory postulates that the course of the facial nerve is determined by otic vesicle cartilage formation, which occurs at 7 weeks' gestation after condensation of mesenchyme around the developing membranous labyrinth.[13] On the basis of this theory, the medially deviated facial nerve in BOR would directly result from the abnormal development of the cochlea.

The horizontal semicircular canal in individuals with BOR was significantly more hypoplastic as compared with normally hearing individuals, with a decreased width of the bony island and decreased dimensions of the vestibule (Fig. 5). A hypoplastic lateral semicircular canal has been previously described in BOR,[6,8] albeit inconsistently. Even though previous authors described an enlarged vestibule in BOR,[6] this error was likely caused by the fact that the vestibule appears large in relation to a hypoplastic bony island. The preserved ratio of vestibule width to length in individuals with BOR as compared with normally hearing individuals suggests that the vestibule is uniformly underdeveloped. Twelve of 42 (28.6%) ears in individuals with BOR had dilated ampullae as compared with none of the normally hearing controls (Fig. 5). Twenty of 42 (47.6%) ears in individuals with BOR had dilated endolymphatic fossae as compared with 6 of 21 ears (28.6%) in normally hearing individuals (Fig. 6). Moreover, dilated endolymphatic fossae in individuals with BOR were on average 1 mm larger than dilated fossae in normally hearing individuals. In the BOR group, 10 of 42 (23.8%) ears demonstrated vestibular aqueduct enlargement as compared with 1 of 21 (4.8%) in normally hearing individuals (Fig. 6). When enlarged, 5 of 10 (50%) vestibular aqueducts in individuals with BOR were large (larger diameter than the posterior limb of the lateral semicircular canal on the same slice), and 5 of 10 (50%) were extra-large (funnel shaped), as compared with normally hearing individuals in whom large vestibular aqueducts were all categorized as large. Enlarged vestibular aqueducts in both groups of individuals were funnel shaped. Embryologically, abnormal condensation of mesenchyme around the developing membranous labyrinth at weeks 4 to 6 of gestation likely contributes to malformation of the horizontal semicircular canal and endolymphatic duct.[13] The lateral semicircular

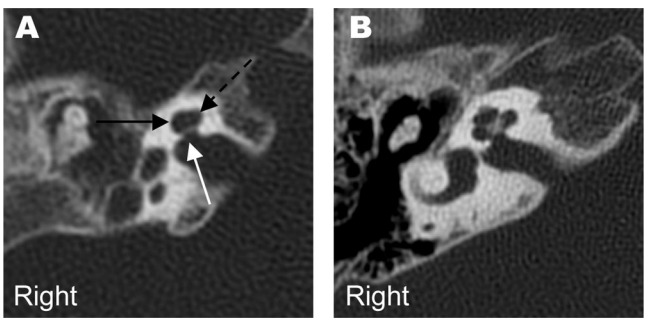

Fig. 2. Inner ear, axial section. Note the hypoplastic cochlea (black arrow) with absent modiolus (dashed black arrow) and only a lamina cribrosa present across the cochlear nerve canal (white arrow) in branchio-oto-renal syndrome (**A**) as compared with normally hearing control (**B**).

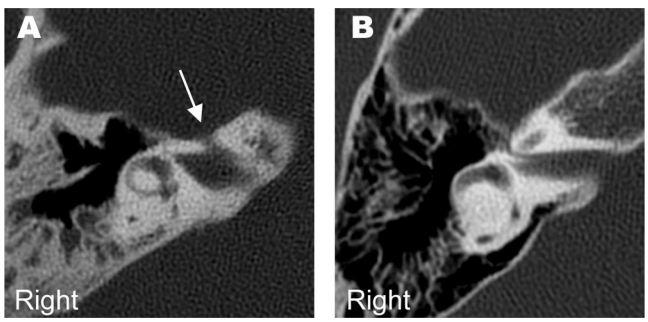

Fig. 4. Facial nerve, axial section. Note the medial deviation and wide canal width (white arrow) of the facial nerve in branchio-oto-renal syndrome (**A**) as compared with normally hearing control (**B**).

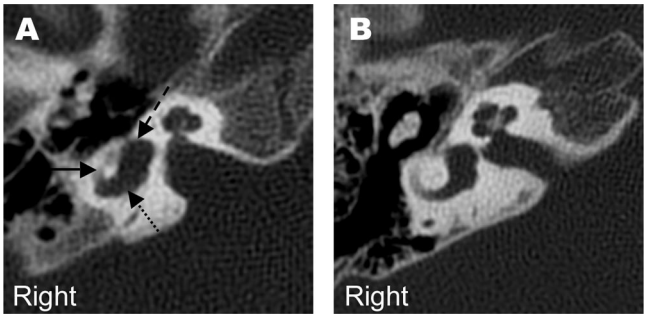

Fig. 5. Horizontal semicircular canal, axial section. Note the hypoplastic bony island (black arrow), small vestibule (dashed black arrow), and dilated ampulla (dotted black arrow) in branchio-oto-renal syndrome (**A**) as compared with normally hearing control (**B**).

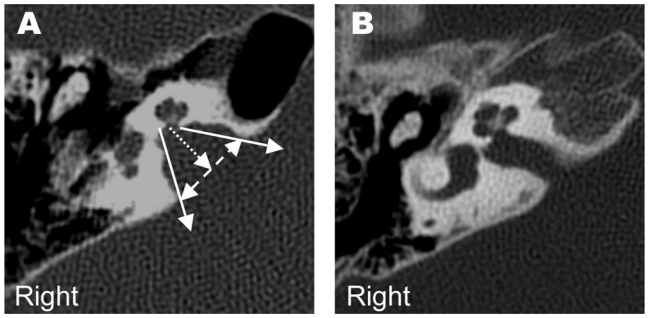

Fig. 7. Internal auditory canal (IAC), axial section. Note the funnel-shaped IAC with a large angle (white arrows), short length (dotted white arrow), and large porous width (dashed white double-headed arrow) in branchio-oto-renal syndrome (**A**) as compared with normally hearing control (**B**).

canal is more often affected than other canals because it forms later.[13] The internal aperture of the vestibular aqueduct begins to form at 4 to 6 weeks' gestation[13] and continues to grow postnatally until the age of 3 or 4 years.[16] Therefore, the large vestibular aqueduct may result from the abnormal development of the semicircular canal and vestibule.

The IAC in individuals with BOR was significantly more funnel shaped on axial images, with the walls of the canal at a larger angle to each other and having a shorter length and wider porous width, as compared with normally hearing individuals (Fig. 7). A bulbous IAC has been previously described in BOR, albeit inconsistently and not in detail.[6–8] The ratio of the porous width to the IAC length was significantly closer to 1 in individuals with BOR as compared with normally hearing individuals, suggesting that the IAC is more squarely shaped than normal. Interestingly, the width of the IAC midway from the cochlea to the porous acousticus was not significantly different across both groups, suggesting that the canal flares from the mid-fundus to the porous in individuals with BOR. This was supported by the calculated ratio of mid-distance to porous width. Embryologically, the otic vesicle produces a growth factor that promotes and aids continued survival of the vestibulocochlear nerve, which in turn inhibits cartilage formation and leads to creation of the IAC.[17] Even though the cochlea and vestibulocochlear nerve canal are hypoplastic in individuals with BOR, there appears to be increased inhibition of cartilage formation evidenced by an enlarged IAC. Perhaps the effect of the small vestibulocochlear nerve and its purportedly decreased growth factors is manifested more distally as evidenced by an overall decreased length of the IAC in individuals with BOR as compared with normally hearing individuals.

The distance between the medial aspects of the carotid arteries was significantly decreased in individuals with BOR as compared with normally hearing individuals (Fig. 8). To the authors' knowledge, this finding has not been previously related to the BOR syndrome. Embryologically, the carotid arteries develop from the third aortic arches. At approximately 40 days of gestation, the rapid descent of the heart causes the origin of the external carotid artery to migrate downward and move toward the midline.[18] In BOR, the medially deviated carotid arteries may result from a larger than normal descent of the heart. Alternatively, the medially deviated carotid arteries in BOR may result from underdevelopment of the clivus.

Measurements made by the neuroradiologist correlated highly with those made by the otolaryngology–head and neck surgery resident, suggesting that the method of temporal bone evaluation described in this study can be used by naïve evaluators to assist in the diagnosis of BOR. The higher correlation among evaluators for continuous, measured data as compared with categorical data was

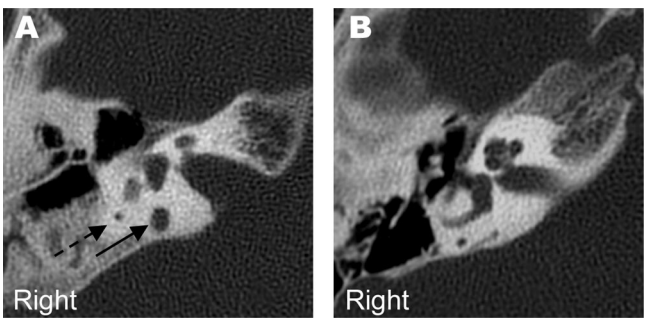

Fig. 6. Vestibular aqueduct, axial section. Note the funnel-shaped vestibular aqueduct (black arrow) that is larger than the posterior limb of the posterior semicircular canal (dashed black arrow) in branchio-oto-renal syndrome (**A**) as compared with normally hearing control (**B**).

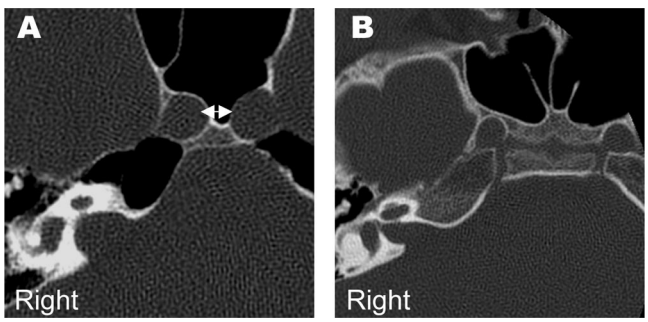

Fig. 8. Carotid arteries, axial section. Note the decreased intercarotid distance (white double-headed arrow) in branchio-oto-renal syndrome (**A**) as compared with normally hearing control (**B**).

likely caused by the fact that judgment and experience are more critical when categorizing information on CT imaging as compared with direct measurement tasks.

CONCLUSION

BOR is generally difficult to accurately diagnose. Genetic testing is costly and is not widely available, and, in any case, only 40% of people with clinical features of BOR have identifiable mutations in the EYA1 gene.[1] Previous studies relying on visual inspection of the temporal bone on CT imaging in BOR have yielded inconsistent findings, making abnormal temporal bone findings a minor criterion in the diagnosis of BOR.[1] Results from this prospective evaluation identified 30 different temporal bone findings that were significantly different across individuals with BOR and normally hearing individuals, the most common and easily identifiable being 1) hypoplastic apical turn of the cochlea, 2) medial deviation of the facial nerve, 3) funnel-shaped IAC, and 4) patulous eustachian tube. These findings suggest that temporal bone evaluation should be used as an important tool in the overall evaluation of the BOR phenotype. The high correlation between measurements made by a neuroradiologist and an otolaryngology–head and neck surgery resident suggests that the method of temporal bone evaluation described in this study can be used by naïve evaluators to assist in the diagnosis of BOR.

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