Anatomical and audiological considerations in branchiootorenal syndrome: A systematic review

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Abstract

Objective: Establish anatomical considerations, audiological outcomes, and optimal management in patients with branchiootic/branchiootorenal syndrome (BO/BOR).

Methods: Databases reviewed: Medline, Pubmed, Embase, Web of Science, Cochrane Collection, and ClinicalTrials.gov. Clinical or radiological studies of patients with BOR syndrome describing either the audiological profile or anatomical changes were included. Articles in which BOR syndrome was associated with other syndromes, and those that were focused only on general and genetic aspects of BOR syndrome were excluded. Articles were assessed using Oxford Centre for Evidence-Based Medicine (OCEBM) grading system and the Brazzelli risk of bias tool for nonrandomized studies.

Results: Searches identified 379 articles. Of these, 64 studies met the inclusion criteria, reporting outcomes in 482 patients from at least 95 families. In 308 patients, hearing loss was categorized as sensorineural (29%), conductive (20%), and mixed (51%). Hearing outcomes were variable in terms of onset, pattern, and severity; ranging from mild to profound deafness. One hundred sixty-nine patients presented with inner ear anomalies, 145 had middle, and 151 had external ear abnormalities. In 44 studies, 58 ear operations were described. Mixed outcomes were reported in patients managed with hearing aids or middle ear surgery; however, successful cochlear implantation was described in all five cases.

Conclusion: The anatomical and audiological profiles of patients with BO/BOR are variable. A range of surgical procedures were described, however lacked objective outcome measures. Given the range of anatomical variants, management decisions should be made on an individual basis including full audiological and radiological assessment.

Level of evidence: NA.
1 | INTRODUCTION

Branchio-oto-renal (BOR) syndrome is a rare autosomal dominant condition, first described by Melnick et al. in 1975. BOR is also referred to as Melnick-Fraser syndrome and branchio-otic syndrome (BO). It accounts for 2% of childhood inner-ear deafness, affecting one in 40,000. The clinical features of BOR are variable. Chang et al. developed diagnostic criteria to include major and minor phenotypic features (Table 1). Major criteria included branchial anomalies, deafness, preauricular pits, or renal anomalies and minor criteria included inner, middle, and external ear anomalies, preauricular tags, facial asymmetry, and palatine abnormalities. Chen et al. considered anomalies affecting over 20% of patients to be common; these included hearing loss, preauricular pits or tags, renal anomalies, branchial fistulae, pinnae deformities, and external auditory canal stenoses. Other clinical features described in BOR include otitis media, facial abnormalities, lacrimal dysfunction, and abnormalities of the bladder and ureters and gastrointestinal system. Fraser et al. reported a range of hearing impairments, including conductive, sensorineural, and mixed loss from a young age. An audiological literature review by Lindau et al., determined mixed loss to be the most common type of hearing impairment with variability in type, degree and progression of hearing loss. Stenosis and atresia of the external auditory canal, and pinnae deformities are the most common external ear anomalies. Malformations of the ossicles and middle ear cavity have been described, alongside inner ear abnormalities, including cochlear hypoplasia and an enlarged vestibular aqueduct. CT scanning has proven to be particularly useful at identifying temporal bone abnormalities. Propst et al. reported the most common characteristics identified on CT as, hypoplastic apical turn of the cochlea (incomplete partition type II or “Mondini dysplasia”), a facial nerve medial to the cochlea, funnel-shaped internal auditory canal, and a patulous eustachian tube. The presence of an “unwound cochlea” on CT has also been reported specifically in patients with BOR; typically featuring hypoplastic middle and apical turns anteriorly offset away from a tapered basal turn. When compared to controls, patients with BOR had significant anatomical differences including an underdeveloped mastoid tip, low tegmen, and a higher frequency of nonpneumatization in the mastoid cortex and facial recess.

The EYA1 gene (homolog of the Drosophila eyes absent gene) was first identified to underlie BOR syndrome in 1997. It is located in the chromosomal region 8q13.3 and accounts for approximately 40% of cases. Over 80 different EYA1 mutations are reported; however, no correlation with phenotypic presentation has been identified. Less commonly, SIX1, SIX5, and SALL1 genes have been implicated, with an unidentified genotype in approximately half of all BOR cases. Given the clinical and genetic heterogeneity, diagnosis of BOR is challenging and it has been referred to as “spectrum disorder”. Chang et al. proposed phenotypic criteria to determine which patients should undergo genetic investigation (Table 1). Patients qualified for EYA1 genetic analysis if they had either; three of the four major criteria (branchial anomalies, deafness, preauricular pits, or renal anomalies), two major and two minor characteristics, or one major if their first-degree relative was also affected. Hsu et al. suggest radiologic criteria, such as the “unwound cochlea” and medialized facial nerve are specific for BOR, and could be used to stratify for genetic studies in sensorineural hearing loss.

This systematic review and narrative synthesis aims to establish anatomical considerations, audiological outcomes and optimal management in patients BO/BOR.

Population: Adults or children with BO/BOR.

Intervention: Surgical procedures of the internal, middle, or external ear, including cochlear implantation (CI).

Comparison: Other method of hearing rehabilitation or repeated measures within the same patients.

Outcomes: Audiometric outcomes, whether objective or subjective.

2 | METHODS

This study is a systematic review and narrative synthesis conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA guidelines). A protocol was written however it was not formally registered with PROSPERO.

2.1 | Inclusion and exclusion criteria

Clinical or radiological studies of patients with BOR syndrome describing either the audiological profile or anatomical changes in patients with BOR syndrome were included. Exclusion criteria was based on the methods described by Lindau et al. in their audiological

| TABLE 1 | Diagnostic criteria |
|---------------------------------|-------------------|
| **Diagnostic criteria for BOR syndrome**<sup>a</sup> | **(Chang et al.)** |
| **Major criteria** | **Minor criteria** |
| Branchial anomalies | External ear anomalies |
| Deafness | Middle ear anomalies |
| Preauricular pits | Inner ear anomalies |
| Renal anomalies | Preauricular tags |
| Other: facial asymmetry, palate abnormalities |

<sup>a</sup>All affected individual must have at least three major criteria; two major criteria and at least two minor criteria, or one major and an affected first-degree relative meeting criteria for BOR.
review of BOR syndrome. This review used the following criteria for
the exclusion of articles: the title and summary were not related to
the purpose of the review, duplicated articles, animal studies, articles
written in languages other than English, editorial letters, conference
abstracts, book chapters, review articles, articles in which BOR syn-
drome was associated with other syndromes, articles that cited BOR
syndrome as a cause of loss of hearing, and those that were focused
only on general and genetic aspects of BOR syndrome.

2.2 | Search strategy

Two reviewers (KB/GC) independently performed the searches and
screened the abstracts. The following databases were searched:
MEDLINE, PubMed, EMBASE, Web of Science, Cochrane Collection,
and ClinicalTrials.gov (via Cochrane).

The search terms used were as follows:

1. “Branchio-Oto-Renal”
2. “Branchio-Otic”
3. BOR
4. Melnick-Fraser
5. 1 OR 2 OR 3 OR 4
6. “Hearing loss”
7. “hearing disorders”
8. Audiolog*
9. 6 OR 7 OR 8
10. 5 AND 9

2.2.1 | No limit was placed on year or language of
publication

2.3 | Selection of studies

Searches were performed by an Information Specialist Librarian
(Matthew Stone). The two reviewers (KB/GC) independently screened
all the records by title and abstract identified from the database
searches. Studies describing audiological findings or ear anatomy in
patients with BOR syndrome were assessed against the inclusion and
exclusion criteria, with any disagreement resolved by discussion with
a third reviewer (CM/JM). Studies without accessible abstract or full
text after the title/abstract screening were followed up by attempting
to contact the respective study authors. If they remained unavailable,
the study was excluded.

Studies that described either audiological or anatomical features
of BO/BOR were included. Most studies (case series) were only
descriptive, with no detail provided on clinical intervention. In studies
including surgical or hearing rehabilitation, all described audiological
outcomes were recorded. Some noninterventional studies, focused on
temporal bone imaging, presented anatomical findings only.

2.4 | Data extraction

Data were extracted by the first reviewer (KB) and then checked by a
second reviewer (GC). Data was extracted on patient age and sex, the
type, degree, onset and pattern of their hearing loss, features of BOR
syndrome, genetics, ear anatomy, hearing interventions and the out-
comes of the intervention. Extracted data were arranged and percent-
ages were calculated in a spreadsheet (Excel, Microsoft Corp.).

2.5 | Risk of bias quality scoring

The two reviewers independently assessed the risk of bias using the
Brazzelli risk of bias tool for nonrandomized studies.21 Studies were
also graded according to the Oxford Centre for Evidence-Based Medi-
cine (OCEBM) grading system.22 Discrepancies between the
reviewers were resolved by discussion.

RESULTS

Searches were initially performed on August 25, 2020, and rechecked
on October 11, 2020. A flowsheet detailing the study selection
according to the PRISMA20 is included in Figure 1.

3.1 | Description of Studies

A total of 64 studies met the inclusion criteria with a total of
482 patients from at least 95 different family groups. There were
39 case series, 21 single-case studies, 3 case–control studies, and
1 cross-sectional study. All studies were published between 1976 and
2020. A total of 17 studies included pediatric patients only, 29 studies
included both adults and children, 11 studies included adults only, and
data were missing in 7 studies. The age of subjects ranged from 0 to
79 years, and 53% (175/331) of subjects were female. Data on
patients’ sex were missing for 151 cases. Genetic testing demon-
strated 190 (39%) patients to be positive for EYA1 mutations or link-
age, 21 (4%) patients with SIX1 mutations,23–26 two patients (<1%)
with a SALL1 mutation and one 22q partial tetrasomy.23 Study char-
acteristics are summarized in Table 2.

3.2 | BOR spectrum

A range of BOR symptoms were described, with 42 studies (66%)
involving patients with renal manifestations4,13,16,23,24,27–63
including renal hypoplasia16,27,42,43,46,52,58–60 or
agenesis,16,29,33,35,41,55,57,61 hydronephrosis,16,31,32,53,54
secondary arterial hypertension,58 mesangial cell glomerulitis,64 and
renal failure of varying degrees,28,36,37,42,47,50,52,54,58 In 53 of the
64 studies, authors reported patients with preauricular pits, tags,
clefts, or sinuses4,13,16,23–35,37–47,49–53,55–62,64–74 and in 47 studies,
patients with branchial cleft abnormalities were described. Facial anomalies were described in several studies including dysmorphic features, lacrimal anomalies, palatine malformations, hemifacial microsomia, facial nerve paresis, prominent epicanthic folds, jaw anomalies, iris atrophy, and microdontia. Other clinical manifestations described included cardiac malformations, developmental delay, mental retardation, hip dysplasia, osteosclerosis, imperforate anus, intracranial hemorrhage, sloping shoulder deformity, diabetes mellitus, and epilepsy.

### 3.3 Anatomical and audiological findings

The key anatomical and audiological findings are summarized in Table 2. Inner ear malformations were described in 169 patients, 70 (41%) of which were detected to have linkage or mutations of the EYA1 gene. Middle ear anomalies were reported in 145 cases, including 48 (33%) patients with EYA1 linkage/mutations. External ear abnormalities were described in 151 patients, 87 (58%) of which had EYA1 mutations or linkage to the gene. The anatomical findings according to genetic status can be found in Figure 2.

### Table 2

| Anatomical and Audiological Findings | EYA1 Mutations or Linkage |
|-------------------------------------|---------------------------|
| Inner Ear Malformations             | 70 (41%)                  |
| Middle Ear Anomalies                | 48 (33%)                  |
| External Ear Anomalies              | 87 (58%)                  |

In the inner ear, a variety of anomalies have been observed including cochlear hypoplasia or dysplasia, Mondini deformity, hypoplastic, malformed, or displaced ossicles. In one study, three patients were found to have a massive ossicular chain with reduced middle ear space. An underdeveloped tympanic cavity was also described in two further studies, one of which was associated with an absent, oval window. Other anomalies included cholesteatoma, otitis media with effusion, patulous Eustachian tube, and a middle ear dermoid cyst. Tympanic membrane perforations were reported by Bisanna et al.; however, Castiglione et al. and Millman et al. reported normal otoscopic examinations. In three studies, there was poor or absent pneumatization of the mastoid with increased bilateral pneumatisation reported in one study. Other abnormalities included an absent Koerner’s septum, hypoplastic, enlarged or absent antrum, tympanic plate defects, and displaced ossicles.
| Author          | Sample          | Type of hearing loss | Age                          | Degree          | Pattern | Ear anatomy                                             | Intervention                                                                 | Outcomes                                                                 |
|-----------------|-----------------|----------------------|------------------------------|-----------------|---------|---------------------------------------------------------|----------------------------------------------------------------------------|--------------------------------------------------------------------------|
| 1 Melnick et al | n = 4 (two     | Mixed               | Father = 44 years,           | Variable        | x       | MD, stapes fixation, cup-shaped pinnae                  | 1 = HA, auricular surgery                                                  | Difficulty in communicating despite HA (n = 1)                           |
|                 | generations)    |                      | children unknown             |                 |         |                                                         |                                                                            |                                                                          |
| 2 Fraser et al  | n = 8 (three    | Mixed, conductive, SN| 11 months–40 years          | Mild–severe     | Progressive | ME fluid, otosclerosis, ossicle hypoplasia and OC displacement, OM, protuberant auricles, cochlear hypoplasia | Case 1: myringotomies (B/L) for recurrent OM, HA and rehabilitation. Case 2: repeated stapedectomies | 4x unsuccessful stapedectomies (n = 1), hearing aids unsuccessful (n = 1) |
|                 | generations)    |                      |                             |                 |         |                                                         |                                                                            |                                                                          |
| 3 Cremers et al | n = 19 (four    | Mixed, conductive    | x                           | x              | x       | Cochlear hypoplasia/ dysplasia, narrow or wide IAC, OC anomalies (not specified), SC (horizontal) hypoplasia, anomalous pinna | Exploratory tympanotomy in 6 patients (7 ears), Teflon interposition attempted in 3 patients | Middle ear surgery feasibly impractical to attempt (n = 4), Teflon interposition unsuccessful (n = 3) |
|                 | families)       |                      |                             |                 |         |                                                         |                                                                            |                                                                          |
| 4 Smith et al   | n = 3 (two      | Mixed, conductive    | 4–26 years                   | Mild–severe     | Progressive, stable | Recurrent OM, fused incudomalleolar complex, absence of stapes and long process of the incus, cup-shaped pinnae | Case 1: myringotomies with grommet insertion (B/L), exploratory tympanotomy and ossicular reconstruction with total ossicular replacement prosthesis. Case 2: myringotomies with grommet insertion (B/L) | Case 1: Persistent conductive loss after myringotomies, postossicular reconstruction: mild–moderate conductive loss on PTA, speech reception threshold: Right 88%, 35 dB; Left 88%, 30 dB. Case 2: interval PTA: mild low-frequency conductive loss, speech reception threshold: Right, 88%, 10 dB; Left, 88%, 20 dB, being evaluated for HA |
|                 | generations)    |                      |                             |                 |         |                                                         |                                                                            |                                                                          |
TABLE 2 (Continued)

| Author       | Sample | Type of hearing loss | Age          | Degree       | Pattern      | Ear anatomy                                                                 | Intervention                                                                 | Outcomes                                                                 |
|--------------|--------|----------------------|--------------|--------------|--------------|----------------------------------------------------------------------------|----------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Slack et al  | n = 12 (four families) | Mixed, SN | 6 months–26 years | Severe       | Stable       | Monopodal stapes, abnormal malleus and incus, IAC bulbous, cochlear hypoplasia with reduced turns, short and wide SC (lateral), lop ears | Exploratory tympanotomies in 2 cases, stapes reconstruction with interposed homograft incus between malleus handle and oval window | No improvement in hearing (numbers not included in paper)                |
| Gimsing et al| n = 17 (three families) | Mixed, conductive, SN | 7–48 years | Mild–severe  | Productive, stable | Malformed incus, absent stapes and oval window, under developed middle cavity, cochlear hypoplasia, cup-shaped pinnae, microtia | Case 1: malformed incus replaced with homograft prosthesis. Case 2: non-specified middle ear surgery (severely malformed) | Case 1: postoperative improvement in air bone gap below 2000 Hz, unchanged at higher frequencies. Case 2: air conduction threshold improved only 20 dB. |
| Lipkin et al | n = 2 (two generations) | SN | 5 and 31 years | Mild–severe  | Stable       | Congenital cholesteatoma filling the sinus tympani, facial recess and ME, displaced ossicles | First procedure: ME exploration and removal of a cholesteatoma, second procedure (1 year later): ossicular reconstruction with ceramic total ossicular replacement prosthesis. | No recurrence of cholesteatoma seen at second surgery                    |
| Martini et al | n = 8 | Mixed, conductive, SN | 4-year-adult | Mild–severe  | x            | Displaced OC, abnormal SC, labyrinth and cochlear hypoplasia with absent basal turn, cup-shaped pinnae | Exploratory tympanotomy | x                                                                 |
| Ostri et al  | n = 19 (four generations) | Mixed | x | Moderate–severe | Stable       | Cochlear and SC hypoplasia, massive OC and reduced size of ME, auricular anomalies | HA in 16 cases | x                                                                 |
| Daggias et al | n = 1 | X | 2.5 years | Severe      | x            | EAC stenosis, bilateral ossicular mass fixation, malformed incus, HA | Normal speech |                                                                 |
| Author          | Sample          | Type of hearing loss | Age     | Degree    | Pattern | Ear anatomy                                                                 | Intervention                                                                 | Outcomes                                                                 |
|-----------------|-----------------|----------------------|---------|-----------|---------|----------------------------------------------------------------------------|----------------------------------------------------------------------------|--------------------------------------------------------------------------|
| 11 Cremers et al| n = 3 (one family) | Mixed, conductive | 16 years | Mild–severe | x       | Curved EAC, no pneumatization of mastoid, absent stapes footplate and long process incus, nonmobile malleus, pinna dysplasia | Two operations: auricle reconstruction, and exploratory tympanotomy and mastoidectomy with creation of neo-oval window | Significant hearing improvement at 2 yr follow-up (55 dB to 15 dB PTA air bone gap closure), no complications |
| 12 König et al  | n = 3           | Mixed               | x       | Severe    | x       | Small incus and a very x large antrum                                       | x                                                                         | x                                                                        |
| 13 Chen et al   | n = 32          | Mixed, conductive, SN | x       | Mild–profound | Productive, stable | Stenosis of the EAC, malformation of OC, cochlear hypoplasia/dysplasia, EED, lop ear deformity | x                                                                         | x                                                                        |
| 14 Millman et al| n = 1           | x                   | 6 months | Severe    | x       | Normal otoscopy                                                             | x                                                                         | x                                                                        |
| 15 Misra et al  | n = 1           | Mixed               | 44 years | Moderate–severe | x       | Displaced and misshapen ossicles, facial nerve anomaly                       | HA (B/L) from childhood, 2 surgeries to left ear (age 27 and 33), followed by radical tympanomastoidectomy with facial nerve decompression | x                                                                        |
| 16 Graham et al | n = 2 (one family) | Mixed, conductive | 14 months, 36 years | Moderate | Stable | Cholesteatoma, absence/abnormality of the ossicles and oval window, lateralization of the malleus-incus complex and the absence of contact with the stapes, facial nerve anomalies | Mother: HA + left exploratory tympanotomy age 16, infant: HA + surgical removal cholesteatoma at 10 months | Infant: inadequate postoperative healing and infection of mastoid process (requiring IV antibiotics) after successful cholesteatoma removal, with 3× OM episodes |
| Author            | Sample | Type of hearing loss | Age          | Degree          | Pattern | Ear anatomy                          | Intervention                                      | Outcomes                                                                 |
|------------------|--------|----------------------|--------------|-----------------|---------|--------------------------------------|--------------------------------------------------|--------------------------------------------------------------------------|
| 17 Weber et al   | n = 6  | Conductive, SN       | newborn to 33 years | Mild–moderate  | x       | Cup-shaped pinna                      | x                                                | x                                                                        |
| 18 Worley et al  | n = 1  | Mixed                | 3 years       | Moderate        | Stable  | Cholesteatoma (B/L)                  | OME and loss of ventilation tubes, deformed ME cavity (B/L), malformed ossicles with fused malleus and incus, SC and cochlear hypoplasia, microtia | Grommets inserted, HA (B/L), radical mastoidectomy w/o reconstruction, stenting of stenosed meatus required |
|                  |        |                      |              |                 |         |                                      | Facial nerve function preserved postoperatively, manages well with HA (B/L). She attends a mainstream school with input from a teacher for the deaf |
| 19 Prabhu et al | n = 1  | Mixed                | 12 years      | x               | x       | Pinna dysplasia (unilateral)         | x                                                | x                                                                        |
| 20 Usami et al  | n = 3  | Mixed, conductive    | x            | Mild–severe     | Stable  | Cochlear and SC (lateral and posterior) hypoplasia (B/L), displaced OC, congenital cholesteatoma, cup-shaped pinnae | Exploratory tympanotomy                             | x                                                                        |
| 21 Bamiou et al | n = 3  | SN                   | x            |                 |         |                                      | MD                                               | x                                                                        |
| 22 Kemperman et al | n = 2 | Mixed, SN            | 55 and 30 years | Profound        | Progressive, fluctuant | Son: Abnormal configuration of OC, dysplastic long process of incus, incomplete stapedia crura, MD, wide IAC, plump vestibule, EVA, recurrent OME, Father: cochlear and vestibular hypoplasia, EVA, cup-shaped pinnae | Son: HA, Grommets inserted for OME, myringoplasty to repair perforation, exploratory tympanotomy w/o reconstruction | Recurrent OE from HA. Progressive loss over 23 years (29 audiograms), regression analysis was performed for air conduction and showed that progression was generally significant at all frequencies. However (after exclusion of the first audiogram), progression may have been nonlinear; the |
| Author          | Sample | Type of hearing loss | Age          | Degree | Pattern | Ear anatomy | Intervention | Outcomes |
|-----------------|--------|----------------------|--------------|--------|---------|-------------|--------------|----------|
| 23 Bellini et al| n = 10 (nine families) | Mixed, conductive, SN | <1 months | x      | x       | Lop-ear deformity | x          | x        |
| 24 Stinckens et al | n = 12 (two generations) | SN | 1–35 years | x      | Progressive, stable | EVA, cochlear hypoplasia | x        | x        |
| 25 Klingebiel et al | n = 2 | SN | x          | x      | x       | SC (superior) dysplasia, cochlear hypoplasia, EVA, | x        | x        |
| 26 Fukuda et al  | n = 5 (two generations) | Mixed, SN | x          | Mild-profound | x       | OME | Tympanotomy for effusion | x        |
| 27 Kemperman et al | n = 35 (six families) | Mixed, SN | x          | x      | Progressive, fluctuant | EES/D, cochlea and labyrinth hypoplasia, malformed auricles, | B/L correction of malformed auricles (n = 3), myringoplasty (n = 1), Reconstruction of EAC atresia (n = 1) | x        |

Runs test was significant at 0.25 to 2 kHz in the left ear and at 0.25 kHz in the right ear. Progression in bone conduction thresholds was significant at 0.5 and 1 kHz in both ears and at 2 kHz in the left ear. Independently of age, the air-bone gap in both ears was 30 to 60 dB at 0.5 to 1 kHz and under 40 dB at the higher frequencies. Thus, the air-bone gap did not show any substantial progression, but it did show considerable fluctuation.
| Author         | Sample                  | Type of hearing loss | Age          | Degree          | Pattern       | Ear anatomy                                                                 | Intervention                                                                 | Outcomes |
|---------------|-------------------------|----------------------|--------------|-----------------|---------------|-------------------------------------------------------------------------------|--------------------------------------------------------------------------------|----------|
| Pierides et al | n = 10 (two generations) | x                    | x            | Variable        | Progressive   | Fluid in ME, EAC atresia                                                      | x                                                                | x        |
| Ceruti et al   | n = 8 (two generations) | SN                   | 5–39 years   | Variable        | Progressive   | Cochlear hypoplasia/dysplasia, B/L, cochlear nerve hypoplasia, SC and OC malformations, EVA, EES/D | x                                                                | x        |
| Yashima et al  | n = 3 (two families)    | Mixed, SN            | 18–53 years  | Mild-moderate   | x             | Mild stapes deformity, EVA, common cavity of vestibule (B/L), cup shaped pinnae | x                                                                | x        |
| Kemperman et al| n = 32 (six families)   | X                    | 16–79 years  | x               | Progressive, fluctuant | EVA, cochlear hypoplasia                                                        | x                                                                | x        |
| Propst et al   | n = 21                  | X                    | 0.9–42.8 years| x               | x             | Cochlea hypoplasia (apical turn), mediadly deviated facial nerve, funnel-shaped IAC, patulous eustachian tube, abnormal incus ligaments, malleoincudal anomalies | x                                                                | x        |
| Rana et al     | n = 1                   | X                    | 6 years      | x               | x             | Poorly pneumatized mastoids, partial agenesis of EAC (B/L), malformed (cupped) auricles (B/L) | x                                                                | x        |
| Kim et al      | n = 2 (two generations) | Mixed                | 3 and 30 years| Moderate profound| x             | EAC stenosis, poor pneumatization and dense mass in the mastoid and ME cavity, cochlear hypoplasia, EVA, OC malformation, HA and auditory rehabilitation | x                                                                | x        |
| Author          | Sample       | Type of hearing loss | Age   | Degree   | Pattern | Ear anatomy                                                                 | Intervention                                                                 | Outcomes                                                                 |
|-----------------|--------------|----------------------|-------|----------|---------|----------------------------------------------------------------------------|-------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| 35 Ito et al    | $n = 1$      | Mixed                | 18 years | Moderate | Progressive | OM, bilateral cup-shaped antverted microtia | EVA, enlarged vestibule, middle and inner ear malformations | x                                                                           |
| 36 Kameswaran et al | $n = 1$ | SN                     | 3 years | Profound | x                               | Severe vestibular dysplasia, dilated SC and malformed ossicles (B/L), cup-shaped ears, contracted mastoid antrum | HA at 1 year, At 3 years CI: Nucleus 24 channel straight array was inserted and 19 electrodes, cochleostomy was sited more antero-superior to the round window | No intraoperative complications, good improvement with closed-set speech recognition |
| 37 Dogru et al  | $n = 1$      | Mixed                | 20 years | Moderate | x                               | Increased mastoid pneumatization (B/L) |                                                                                  |                                                                              |
| 38 Matsunaga et al | $n = 4$ (three generations) | Mixed                | 31–65 years | Mild–severe | Stable | EVA, cochlear hypoplasia, abnormal ossicles, enlarged vestibule, lop-ear deformity | HA from infancy, ossicular reconstruction | Manipulation within the tympanic cavity was suspended after difficulties, with failed improvement of hearing |
| 39 Sanggaard et al | $n = 17$ (two families) | SN | x | Mild–profound | Progressive | External, middle and inner ear anomalies (nonspecified) |                                                                                  |                                                                              |
| 40 Garg et al   | $n = 1$      | x                     | 19 years | Profound | x                               | Low set, lop-ears | HA | Good response                                                                 |
| 41 Senel et al  | $n = 2$ (two generations) | Mixed, conductive | 6 and 44 years | Mild–moderate | x                               | Cochlear and SC hypoplasia, OC malformation, enlarged IAC (B/L), unilateral malleus and incus hypoplasia | Operations for hearing loss scheduled for both patients | x                                                                           |
| 42 Ayçiçek et al | $n = 7$ (three generations) | Mixed, conductive, SN | 18–75 years | x | x | Prominent ear deformity |                                                                                  |                                                                              |
| 43 Johnston et al | $n = 1$     | Mixed                | 12 months | Moderate–severe | x                               | ME dermoid cyst, displaced malleus, malformed ossicles, medially located | HA (B/L), Myringotomy with grommet insertion for bilateral OME, transmastoid and | At 6 months, good healing and audiogram was unchanged (PTA                  |
| Author         | Sample | Type of hearing loss | Age     | Degree          | Pattern   | Ear anatomy                                                                                     | Intervention                                                                                     | Outcomes                                                                                     |
|---------------|--------|----------------------|---------|-----------------|-----------|-----------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| 44 Bisanna et al | n = 1  | SN                   | 16 years| Moderate-severe | Progressive| Cholesteatoma, partially destroyed malleus and incus, sclerotic mastoid, perforated TM, cup-shaped pinnae, low set ear | Cholesteatoma removed with radical mastoidectomy                                           | showed R moderately to mild mixed loss, L profound-severe loss. The patient was wearing binaural aids and participated in mixed signing and spoken English |
| 45 Noguchi et al | n = 1  | Mixed                | 21 years| Moderate        | Stable    | EVA (B/L)                                                                                       | HA                                                                                            | x                                                                                          |
| 46 Song et al  | n = 10  | Mixed                | 1-43 years| Moderate-severe | Progressive| Cochlear hypoplasia, EVA, dilated vestibule, facial nerve anomaly, malformed/ misaligned/fused ossicles, IAC bulbous/funnel | HA (n = 10), 3 ossiculoplasties, 2 stapedotomies, 1 cholesteatoma removal with incus interposition, 2 CI | All ME surgeries were unsuccessful, 8/10 benefitted from HA, 2 who did not benefit went on to have successful outcomes with CI (hearing and language ability) |
| 47 Jankauskienè et al | n = 1  | x                    | 4 days  | x                | x         | x                                                                                               | x                                                                                            | x                                                                                          |
| 48 Lapeña et al | n = 1  | x                    | 6 years | Moderate-severe | x         | x                                                                                               | HA (B/L) at age 3 years                                                                   | x                                                                                          |
| 49 Castiglione et al | n = 2  | Conductive           | 9 and 30 years| Mild          | Progressive| Mild auricular anomalies, normal otoscopy, hypoplastic/ dysplastic SC, dilated/bulbous IAC, FN deviation, large mastoid emissary vein, dysplastic incus | No intervention required                                                               | x                                                                                          |
| Author          | Sample | Type of hearing loss | Age  | Degree | Pattern | Ear anatomy                                                                 | Intervention                                                                 | Outcomes                                                                 |
|-----------------|--------|----------------------|------|--------|---------|----------------------------------------------------------------------------|----------------------------------------------------------------------------|--------------------------------------------------------------------------|
| 50 Jalil et al  | n = 1  | Conductive           | 8    | x      | Progressive | OME and hypoplastic long process, patulous Eustachian tube, hypoplastic/dysplastic cochlea | Grommets, HA and rehabilitation | No improvement with grommets                                           |
| 51 Morisada et al | n = 45 | Mixed, conductive, SN | x    | x      | x           | EAC stenosis, pinnae deformities HA (n = ?), surgical management including tympanoplasty, grommet insertion and CI (n = 11) | HA, 80% success with HA, 64% (7/11) success with surgery                  |
| 52 Schmidt et al | n = 1  | SN                   | 43   | x      | Progressive | Enlarged Eustachian tubes, absent mastoid cells HA at age 3 years | x                                                                                        |
| 53 Ječmenica et al | n = 1  | Conductive           | 4    | Severe | x         | HA for air conduction | Subjective speech improvements, but intelligibility is still not satisfying |
| 54 Ginat et al  | n = 1  | Mixed                | 50   | Profound | Progressive | Extensive ossicular anomalies (B/L), ectopic and dysmorphic right incudo-malleal complex projecting into the middle cranial fossa, cochlear hypoplasia (B/L), malformed vestibules and SC (lateral and posterior), ICA canal hypoplasia, high-riding jugular bulb up to the round window, dysmorphic IAC, anomalous positioning of the facial nerve canals | HA (B/L) from childhood, unilateral CI at 50 years, CI with compressed array of electrodes (round window approach) | HA not sufficient, excellent subjective improvement with CI, no complications. Initial postoperative sound detection thresholds at 40 dB or less 250–2000 Hz and 50 dB or less for 4000–6000 Hz |
| Author          | Sample                  | Type of hearing loss | Age          | Degree | Pattern | Ear anatomy                                                                 | Intervention         | Outcomes |
|-----------------|-------------------------|----------------------|--------------|--------|---------|------------------------------------------------------------------------------|----------------------|----------|
| Unzaki et al    | $n = 44$                | Mixed, conductive, SN| 0–60 years   | $x$    | $x$     | Inner, middle, external, and EAC anomalies (nonspecified)                     | xx                   | xx       |
| Nasir et al     | $n = 1$                 | Mixed                | 4 years      | Severe | $x$     | HA (B/L)                                                                     | xx                   | xx       |
| Hsu et al       | $n = 9$                 | Mixed, conductive, SN| 1–14 years   | $x$    | $x$     | Unwound cochlear dysmorphology, funnel IAC, EVA, medialized facial nerve    | xx                   | xx       |
| Parkes et al    | $n = 30$                |                      | 0.5–42.8 years| $x$    | $x$     | Abnormally located/absent Koerner's septum (45%), severely hypoplastic/absent antrum (50%), dysplastic short process of incus (62%), dysplastic SC (73%) | xx                   | xx       |
| Wang et al      | $n = 3$ (one family)    | Mixed, conductive    |              | $x$    | $x$     | ME malformation (B/L), cochlear and SC (posterior) hypoplasia, OM (B/L), microtia | xx                   | xx       |
| Chen et al      | $n = 7$ (two families, three generations) | Mixed |              | Profound | Progressive | Cochlear hypoplasia, stenosis of cochlear nerve canal orifice, displaced and deformed ossicles, mastoid cells hypoplasia | xx                   | xx       |
| Mironovich et al| $n = 8$ (four families) | Conductive, SN       | 3–38 years   | Mild–severe | $x$     | EVA + EES, cochlear hypoplasia, dysplastic SC, dilated IAC, ossicle malformations, protruding ears | xx                   | xx       |
| Men et al       | $n = 3$ (one family)    |                      |              | $x$    | $x$     | EVA, EES, MD, cochlear fusion, ME anomalies, cup 1 CI                       | Easy electrode implantation, no complications, Preoperatively, | xx       |
| Author   | Sample | Type of hearing loss | Age   | Degree  | Pattern | Ear anatomy                                                                 | Intervention                        | Outcomes                                                                 |
|----------|--------|----------------------|-------|---------|---------|-----------------------------------------------------------------------------|-------------------------------------|--------------------------------------------------------------------------|
| Li et al | n = 1  | Mixed                | 7 years | Moderate | x       | Auricular anomalies (dysplasia, anterior auricular fistulas, auricular appendix), EAC stenosis, OM papillae, microtia, pinnæ deformity, ankytolia | EAC formation, and tympanoplasty    | Significant improvement in hearing 1-year postoperative. Preoperative hearing threshold: 56.25 (right) and 62.5 dB (left) hearing level in air conduction. Postoperative: 52.5 (right) and 25 dB (left) |
| Xing et al | n = 4 (three generations) | Mixed | 1.5–51 years | x       | Stable  | Cochlear hypoplasia (B/L), narrow EAC, ossicular dysplasia, microtia, auricular malformation | BAHA for 2 cases                   | Good response                                                            |

*Study reports six families, four of which are already included by Ostri and Gimsing. Abbreviations: EAC, external auditory canal; EED, external ear deformity; EVA, enlarged ventricular aqueduct; IAC, internal auditory canal; MD, Meniere’s disease; ME, middle ear; OC, ossicular chain; OME, otitis media with effusion; PTA, pure tone audiogram; SN, sensorineural hearing loss.*
Ear anomalies according to genetics

EAR ANOMALIES ACCORDING TO GENETICS

| EY1 | SX1 | SALL1 | 22q partial tetrasomy | No genetics |
|-----|-----|-------|------------------------|------------|
| 96  |     | 1     | 1                      | 2          |
|     |     |       | 70                     | 48         |
|     |     |       | 48                     | 87         |
|     |     |       | 100                    | 1          |
|     |     |       | 268                    | 96         |
|     |     |       | 97                     | 97         |
|     |     |       | 87                     | 61         |

FIGURE 2 Ear anomalies according to genetics

3.4 Management of hearing loss

A summary of the interventions and reported outcomes can be found in Table 3. In 22 studies, patients were managed with hearing aids, with variable success. In at least eight patients, hearing aids alone were successful when used in isolation. Surgical intervention was described in 28 studies, with details given for 58 operations. These included exploratory tympanotomies, myringotomies with grommet insertion, mastoidectomies, ossicular reconstruction, cholesteatoma removal, stapedectomy, tympanoplasty with external auditory canal (EAC) formation, myringoplasty, and bone-anchored hearing aid (BAHA) insertion. Of the 30 middle ear procedures reporting postoperative outcomes, benefit was noted in only 11 cases. Successful operations included a mastoidectomy with creation of neo-oval window resulting in significant hearing improvement at 2-year follow-up. An incus homograft prosthesis with improvement in air bone gap below 2000 Hz and one patient undergoing an unspecified middle ear procedure with only a small improvement in air conduction threshold. When used in conjunction with hearing aids, acceptable auditory function was reported in one patient undergoing grommet insertion with radical mastoidectomy, and another with myringotomy (with grommets), plus canalplasty and atticoectomy. Unsuccessful outcomes were described in a number of ossicular reconstructions and myringotomies with grommet insertion.

Cochlear implantation was reported in five studies, in at least six patients. Three studies were single case reports, and four authors described combined success in seven of 11 patients who underwent either CI, tympanoplasty, or grommet insertion. No further details regarding implantation were provided. The remaining four authors described a total of five cases who underwent CI, all of which had promising outcomes. Song et al. reported two adolescent patients with severe to profound mixed hearing loss who experienced significant improvements in hearing and language ability (no objective data) after unilateral implantation, one of which had failed to improve with ossiculoplasty. In both cases, computed tomography (CT) and magnetic resonance imaging (MRI) demonstrated bilateral dilated vestibule, enlarged vestibular aqueduct, ossicular anomalies, and bilaterally deviated facial nerves. A perilymphatic gusher was reported in one case; however, this was easily controlled by conventional methods. Ginat et al. also reported excellent subjective improvement in a 50-year-old gentleman who had a unilateral device implanted with a compressed array of electrodes, via round window approach. Initial postoperative sound detection thresholds were 40 dB or less for 250–2000 Hz and 50 dB or less for 4000–6000 Hz (no audiograms were recorded preoperatively). The patient was found to have extensive bilateral ossicular anomalies, malformed vestibules and semicircular canals, and bilateral cochlear hypoplasia with absent apical turns and J-shaped middle turn. The patient was also noted to have malformed facial nerve canals and a high-riding jugular bulb up to the round window on the contralateral side. No postoperative complications were reported.

Men et al. reported easy electrode implantation, with no complications in a patient with profound hearing loss, an enlarged vestibular

mastoid emissary vein, sclerotic mastoid, and absent or hypoplastic mastoid cells. External auditory canal anomalies and ankytosis were reported along with abnormal external ear appearances, including specific descriptions of cup-shaped pinnae, microtia, protuberant ears, and mastoid emissary vein.

Hearing loss was described in all 64 studies and were categorized into those with sensorineural, conductive, or mixed loss. 4,25,27,30,38,41,42,44,48,50,68

The reported degree, pattern, and onset were varied. The severity ranged from mild to profound, with 20 studies describing a progressive pattern, and 13 studies describing stable patterns of hearing loss. Where reported, the onset was predominantly from childhood; however, adult-onset cases were also described.

In a patient with profound hearing loss, an enlarged vestibular

vestibule, enlarged vestibular aqueduct, ossicular anomalies, and bilaterally deviated facial nerves. A perilymphatic gusher was reported in one case; however, this was easily controlled by conventional methods. Ginat et al. also reported excellent subjective improvement in a 50-year-old gentleman who had a unilateral device implanted with a compressed array of electrodes, via round window approach. Initial postoperative sound detection thresholds were 40 dB or less for 250–2000 Hz and 50 dB or less for 4000–6000 Hz (no audiograms were recorded preoperatively). The patient was found to have extensive bilateral ossicular anomalies, malformed vestibules and semicircular canals, and bilateral cochlear hypoplasia with absent apical turns and J-shaped middle turn. The patient was also noted to have malformed facial nerve canals and a high-riding jugular bulb up to the round window on the contralateral side. No postoperative complications were reported.

Men et al. reported easy electrode implantation, with no complications in a patient with profound hearing loss, an enlarged vestibular
### TABLE 3  Summary of interventions and reported outcomes

|                  | Beneficial outcome | Nonbeneficial |
|------------------|--------------------|---------------|
| HA alone         | 8/13               | Fraser: HA with rehab unsuccessful (n = 1), Melnick: difficulty communicating (n = 1), Ginat: HA not sufficient (n = 1) |
| BAHA             | 2/2                |              |
| CI               | 5/5                | x            |
| Middle ear surgery 11/30 | Cremers: Mastoidectomy with creation of neo-oval window; significant hearing improvement at 2 years follow-up (from 55 to 15 dB PTA air bone gap closure) (n = 1), Gimsing: Incus homograft prosthesis; improvement in air bone gap below 2000 Hz (n = 1), nonspecified middle ear surgery; air conduction threshold improved only 20 dB (n = 1), Morisada: 64% (7/11) success with surgery including grommet insertion and tympanoplasty (n = unclear), Li: EAC formation, and tympanoplasty—significant improvement in hearing 1-year postoperative (preoperative hearing threshold: 56.25 (right) nd 62.5 dB (left) air conduction, postoperative: 52.5 (right) and 25 dB (left) (n = 1) |
| HA + surgery     | 2/6                | Fraser: unsuccessful stapedotomies (n = 4), Cremers: Teflon interposition unsuccessful (n = 3) not possible to attempt (n = 4), Graham: Poor postoperative healing after successful cholesteatoma removal (n = 1), Song: 3 ossiculoplasties, 2 stapedotomies, 1 cholesteatoma removal with incus interposition—all unsuccessful (n = 6), Slack: stapes reconstruction with interposed homograft incus between malleus handle and oval window, no improvement in hearing on PTA (figures not provided, n = 2) |

**Abbreviations:** BAHA, bone-anchored hearing aid; CI, cochlear implantation; HA, Hearing aid.
| Study                        | 1   | 2   | 3   | 4   | 5   | 6   | 7   | 8   | 9   | 10  | 11  | 12  | 13  | 14  | 15  | 16  | 17  | 18  |
|------------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Melnick et al 1976           | Yes | No  | No  | No  | Yes | No  | NA  | NA  | No  | Undear | Undear | Yes | No  | No  | Undear | No  | Yes | NA  | Yes |
| Fraser et al 1978            | Yes | No  | No  | Yes | No  | NA  | Yes | Undear | Undear | Yes | No  | No  | Undear | Yes | No  | No  | Yes | NA  | Yes |
| Cremers et al 1980           | Yes | No  | No  | Yes | No  | NA  | Yes | Undear | Undear | Yes | No  | No  | Undear | Yes | No  | No  | Yes | NA  | Yes |
| Smith et al 1984             | No  | No  | No  | No  | NA  | Yes | Undear | Undear | Yes | No  | No  | Undear | Yes | No  | No  | Yes | NA  | Yes |
| Slack et al 1985             | Yes | No  | No  | Yes | No  | NA  | Yes | Yes | Yes | Yes | Yes | No  | Undear | No  | Yes | NA  | Yes |
| Gimsing et al 1986           | Yes | No  | No  | Yes | No  | NA  | No  | Yes | Yes | Yes | Yes | No  | Yes | No  | Yes | No  | Yes | NA  |
| Lipkin et al 1986            | No  | No  | Yes | No  | Yes | NA  | Yes | Undear | Undear | Yes | No  | No  | No  | Yes | No  | Yes | NA  | Yes |
| Martin et al 1987            | No  | No  | Undear | No  | NA  | Yes | Undear | Undear | No  | No  | No  | NA  | No  | Yes | NA  | Yes | NA  | Yes |
| Ostri et al 1991             | Yes | No  | No  | Yes | No  | NA  | No  | NA  | NA  | No  | Yes | No  | No  | Yes | No  | Yes | NA  | Yes |
| Doggias et al 1992           | No  | No  | NA  | NA  | NA  | NA  | NA  | No  | Undear | Undear | Yes | No  | No  | No  | Yes | No  | Yes | NA  |
| Cremers et al 1993           | No  | No  | Undear | No  | NA  | Yes | Yes | Yes | Yes | Yes | Yes | No  | Yes | No  | Yes | No  | Yes | NA  |
| König et al 1994             | No  | No  | Yes | Yes | No  | NA  | NA  | NA  | NA  | NA  | No  | NA  | No  | Yes | No  | Yes | NA  | Yes |
| Chen et al 1995              | Yes | Unclear | No  | Yes | No  | NA  | NA  | NA  | NA  | No  | NA  | NA  | Yes | No  | Yes | NA  | Yes | NA  |
| Millman et al 1995           | No  | No  | NA  | NA  | NA  | NA  | NA  | No  | No  | Yes | No | Yes | Yes | No  | Yes | NA  | Yes | NA  |
| Misra et al 1998             | No  | No  | NA  | NA  | NA  | NA  | NA  | No  | No  | Yes | Undear | Undear | Yes | No  | No  | Yes | No  | Yes |
| Graham et al 1999            | No  | No  | No  | Yes | No  | NA  | Yes | Undear | Undear | Yes | No  | No  | No  | Yes | No  | Yes | NA  | Yes |
| Weber et al 1999             | No  | No  | No  | Yes | No  | NA  | NA  | NA  | NA  | NA  | No  | NA  | No  | Yes | No  | Yes | NA  | Yes |
| Worley et al 1999            | No  | No  | NA  | NA  | NA  | NA  | NA  | No  | Yes | Yes | Yes | Yes | Yes | Yes | No  | Yes | NA  | Yes |
| Prabhu et al 1999            | No  | No  | NA  | NA  | NA  | NA  | NA  | No  | No  | Yes | No  | Yes | No  | Yes | No  | Yes | NA  | Yes |
| Usami et al 1999             | No  | No  | No  | No  | No  | NA  | NA  | NA  | NA  | No  | Yes | Yes | Yes | Yes | Yes | No  | Yes | NA  |
| Bamiou et al 2000            | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Kemperman et al 2001         | No  | No  | No  | Yes | No  | NA  | Yes | Undear | Undear | Yes | No  | No  | No  | Yes | No  | Yes | NA  | Yes |
| Bellini et al 2001           | Yes | Yes | Unclear | Yes | No  | NA  | NA  | NA  | NA  | NA  | No  | NA  | No  | Yes | No  | Yes | NA  | Yes |
| Stincakens et al 2001        | Yes | No  | No  | Yes | No  | NA  | NA  | NA  | NA  | NA  | No  | NA  | No  | Yes | No  | Yes | NA  | Yes |
| Klingebiel et al 2001        | Yes | Yes | Unclear | Yes | No  | NA  | NA  | NA  | NA  | NA  | No  | NA  | No  | Yes | No  | Yes | NA  | Yes |
| Fukuda et al 2001            | No  | No  | No  | Yes | No  | NA  | Yes | Undear | Undear | No  | No  | No  | No  | Yes | No  | Yes | NA  | Yes |
| Kemperman et al 2002         | Yes | Yes | No  | Yes | No  | NA  | Yes | Undear | Undear | Yes | No  | No  | No  | Yes | No  | Yes | NA  | Yes |
| Pierides et al 2002          | Yes | No  | Yes | Yes | No  | NA  | NA  | NA  | NA  | NA  | No  | NA  | No  | Yes | No  | Yes | NA  | Yes |
| Ceruti et al 2002            | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Yamshita et al 2003          | No  | No  | No  | Yes | No  | NA  | NA  | NA  | NA  | NA  | No  | NA  | No  | Yes | No  | Yes | NA  | Yes |
| Kemperman et al 2004         | Yes | Yes | No  | Yes | No  | NA  | NA  | NA  | NA  | NA  | No  | NA  | Yes | Yes | Yes | Yes | Yes | Yes |
| Propst et al 2005            | Yes | Yes | Unclear | Yes | No  | NA  | NA  | NA  | NA  | NA  | No  | NA  | No  | Yes | NA  | Yes | No  | Yes |
| Rana et al 2005              | No  | No  | NA  | NA  | NA  | NA  | NA  | No  | No  | Yes | No  | Yes | No  | Yes | NA  | Yes | NA  | Yes |
| Kim et al 2005               | No  | No  | NA  | NA  | NA  | NA  | NA  | No  | No  | Yes | No  | Yes | No  | Yes | NA  | Yes | NA  | Yes |
| Ito et al 2006               | No  | No  | NA  | NA  | NA  | NA  | NA  | No  | No  | Yes | No  | Yes | No  | Yes | NA  | Yes | NA  | Yes |
| Kameswaran et al 2007        | No  | No  | NA  | NA  | NA  | NA  | NA  | No  | Yes | Undear | Undear | Yes | No  | No  | No  | Yes | NA  | Yes |
| Dogru et al 2007             | No  | No  | NA  | NA  | NA  | NA  | NA  | No  | No  | Yes | No  | Yes | No  | Yes | NA  | Yes | NA  | Yes |
| Matsunaga et al 2007         | No  | No  | Yes | Yes | No  | NA  | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |

(Continues)
| Study                  | Year | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 |
|-----------------------|------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|
| Sanggaard et al 2007  | Yes  | No | Yes | No | Yes | No | NA | NA | NA | NA | No | NA | No | Yes | Yes | NA | Yes | NA | Yes | NA |
| Garg et al 2008       | No   | No | NA  | NA | No  | NA | Yes | Yes | Yes | Yes | No  | No  | Yes | No  | Yes | NA | NA  | Yes | No  | Yes | NA |
| Senel et al 2009      | No   | No | NA  | NA | No  | Yes | NA | NA | NA | NA | No  | NA | Yes | No  | Yes | NA | Yes | No  | Yes | NA |
| Ayçiçek et al 2010    | No   | No | Yes | Yes | No  | NA | Yes | Yes | Yes | Yes | No  | No  | Yes | No  | Yes | NA | Yes | No  | Yes | NA |
| Johnston et al 2011   | No   | No | NA  | NA | No  | Yes | Yes | Yes | Yes | Yes | No  | No  | Yes | No  | Yes | NA | Yes | No  | Yes | NA |
| Bisanna et al 2011    | No   | No | NA  | NA | Yes | Yes | Yes | Yes | Yes | Yes | No  | No  | Yes | No  | Yes | NA | Yes | No  | Yes | NA |
| Noguchi et al 2011    | No   | No | NA  | NA | No  | Yes | Yes | Yes | Yes | Yes | No  | No  | Yes | No  | Yes | NA | Yes | No  | Yes | NA |
| Song et al 2013       | Yes  | Yes | No  | Yes | No  | NA | Yes | Unde | Uncl | Yes | No  | No  | Yes | No  | Yes | NA | Yes | No  | Yes | NA |
| Jankauskiè et al 2013 | No   | No | NA  | NA | No  | NA | NA | NA | NA | NA | No  | NA | No  | Yes | NA | No  | Yes | NA | No  |
| Lapeña et al 2013     | No   | No | NA  | NA | No  | NA | NA | NA | NA | NA | No  | NA | Yes | No  | Yes | NA | Yes | No  | Yes | NA |
| Castiglione et al 2014| Yes  | Yes | No  | Yes | No  | NA | NA | NA | NA | NA | No  | NA | No  | Yes | NA | No  | Yes | NA | No  |
| Jalil et al 2014      | No   | No | NA  | NA | No  | Yes | Yes | Yes | Yes | Yes | No  | No  | Yes | No  | Yes | NA | Yes | No  | Yes | NA |
| Morisada et al 2014   | Yes  | Yes | Yes | Yes | No  | NA | No  | Unde | Uncl | Yes | No  | No  | Yes | No  | Yes | NA | Yes | No  | Yes | NA |
| Schmidt et al 2014    | No   | No | NA  | NA | No  | NA | NA | NA | NA | NA | No  | NA | Yes | No  | Yes | NA | Yes | No  | Yes | NA |
| Ječmenica et al 2015  | No   | No | NA  | NA | No  | Yes | Unde | Yes | Yes | No  | No  | Yes | No  | Yes | NA | No  | Yes | NA | No  |
| Ginat et al 2016      | No   | No | NA  | NA | No  | Yes | Yes | Yes | Yes | Yes | No  | No  | Yes | No  | Yes | NA | Yes | No  | Yes | NA |
| Unzaki et al 2018     | Yes  | Yes | Uncl | Yes | No  | NA | NA | NA | NA | NA | No  | NA | No  | Yes | NA | No  | Yes | NA | No  |
| Nasir et al 2018      | No   | No | NA  | NA | No  | Yes | NA | NA | No  | No  | No  | No  | No  | No  | Yes | NA | No  | Yes | NA | No  |
| Hsu et al 2018        | Yes  | Yes | Uncl | Yes | No  | NA | NA | NA | NA | Yes | NA | No  | Yes | NA | Yes | NA | Yes | No  | Yes | NA |
| Parkes et al 2018     | Yes  | Yes | Uncl | Yes | No  | NA | NA | NA | Yes | No  | NA | No  | Yes | NA | Yes | NA | Yes | No  | Yes | NA |
| Wang et al 2018       | No   | Yes | No  | Yes | No  | NA | NA | NA | NA | No  | NA | No  | Yes | NA | No  | Yes | NA | No  | Yes | NA |
| Chen et al 2019       | No   | No | Uncl | Yes | No  | NA | NA | NA | NA | No  | NA | No  | Yes | NA | No  | Yes | NA | No  | Yes | NA |
| Mironovich et al 2019| No   | No | No  | No  | No  | NA | Yes | Yes | Yes | Yes | No  | No  | Yes | No  | Yes | NA | No  | Yes | NA | No  |
| Men et al 2020        | No   | No | Yes | Yes | No  | NA | Yes | Yes | Yes | Yes | No  | No  | Yes | No  | Yes | NA | Yes | No  | Yes | NA |
| Li et al 2020         | No   | No | NA  | NA | No  | Yes | Unde | Yes | Yes | Yes | No  | No  | Yes | No  | Yes | NA | Yes | No  | Yes | NA |
| Xing et al 2020       | No   | No | No  | Yes | No  | NA | Yes | Unde | Uncl | Yes | No  | No  | Yes | No  | Yes | NA | Yes | No  | Yes | NA |

Note: 1. Were participants a representative sample selected from a relevant patient population (e.g., randomly selected from those seeking treatment despite age, duration of disease, primary or secondary disease, and severity of disease)? 2. Were the inclusion/exclusion criteria of participants clearly described? 3. Were participants entering the study at a similar point in their disease progression (i.e., severity of disease)? 4. Was selection of patients consecutive? 5. Was data collection undertaken prospectively? 6. Were the groups comparable on demographic characteristics and clinical features? 7. Was the intervention (and comparison) clearly defined? 8. Was the intervention undertaken by someone experienced at performing the procedure ("Yes" if the practitioner received training on conducting the procedure before or conducted same kind of procedure before [i.e., no learning curve]). 9. Were the staff, place, and facilities where the patients were treated appropriate for performing the procedure (e.g., access to back-up facilities in hospital or special clinic)? 10. Were any of the important outcomes considered (i.e., on clinical effectiveness, cost-effectiveness, or learning curves)? 11. Were objective (valid and reliable) outcome measures used, including satisfaction scale? 12. Was the assessment of main outcomes blind? 13. Was follow-up long enough (≥1 year) to detect important effects on outcomes of interest? 14. Was information provided on nonrespondents, dropouts? ("No" if participants were those whose follow-up records were available [retrospective].) 15. Were the characteristics of withdrawals/dropouts similar to those that completed the study and therefore unlikely to cause bias? ("Yes" if no withdrawal/dropout; "No" if dropout rate ≥30% or differential dropout). 16. Was length of follow-up similar between comparison groups? 17. Were the important prognostic factors identified (e.g., age, duration of disease, and disease severity)? ("Yes" if two or more than two factors were identified). 18. Were the analyses adjusted for confounding factors?
aqueduct with enlarged endolymphatic sacs. Incomplete partition type II/Mondini cochlear and middle ear anomalies. Preoperatively, auditory brainstem response demonstrated bilateral profound hearing loss. At 4 months postimplantation, the patient had pure-tone average of 55–70 dB and thresholds for Ling sounds of 55–70 dB at 6 months. The authors described good progression in listening comprehension and no aversion to loud sounds.

Kameswaran et al. reported implantation with a Nucleus 24 channel straight array, with and 19 electrodes successfully inserted in a 3-year-old with profound sensorineural hearing loss. Severe vestibular dysplasia, dilated semicircular canals, ossicular malformations and a contracted mastoid antrum were demonstrated on high-resolution CT and MRI studies. There were no intraoperative complications; however, as the cochlea was rotated, the cochleostomy was sited more anterosuperior to the round window niche than usual. The device was switched on at 3 weeks postoperatively with good initial mapping responses. The authors reported that the child was showing good improvement in closed-set speech recognition while undergoing intensive auditory verbal rehabilitation.

3.5 | Quality of studies

The methodological quality of included studies was modest, predominantly consisting of case reports and noncontrolled case series with a small number of patients. All studies were OCEBM grade IV and were conducted retrospectively. Heterogeneity of audiological outcomes precluded a meta-analysis. There were also limitations in reporting of hearing loss type, onset, severity, and the interventions performed. The Risk of Bias table can be found in Table 4. Only nine studies reported objective outcomes for the interventions described. Pre and post PTA were used to assess audiological interventions in five studies. Smith et al. used speech reception thresholds and PTA to assess two patients with grommets and/or ossicular prosthesis and reconstruction. In one study (Ginat et al.) just post-intervention PTA was recorded. Men et al. reported preimplantation auditory brainstem response and postoperative PTA (Ling sounds). Kemperman et al. reported longitudinal changes (no direct preintervention and postintervention comparison).

Cremers co-authored seven studies, including five from The Netherlands and two from Belgium. A crossover of authorship was also seen in six Japanese studies, and a further two studies from Japan. It is therefore possible that there may be some duplication of included patients. Sanggaard et al. reported on six Danish families, four of which had already been reported by Gimsing et al. and Ostri et al. Similarly, Kemperman et al. reported on six families over three studies. In these instances, patient numbers have only been included once in the final totals and for calculating percentage data.

4 | DISCUSSION

The aim of this systematic review and narrative synthesis was to report audiometric outcomes in patients with BO/BOR undergoing ear surgery, or other forms of hearing rehabilitation. We successfully identified all the relevant literature, however the conclusions drawn from the literature are limited by the quality of evidence available.

This review reports on the outcomes of anatomical and audiological profiles of patients with BOR/BO syndrome, reporting on an additional 30 studies to the previously published review by Lindau et al. Casazza and Meier’s review of syndromic hearing loss demonstrated mild-to-profound hearing loss to occur in 70%–93% of reported BOR cases. In accordance with Lindau et al.’s findings, we found mixed hearing loss to be the most common type reported, with wide variability in pattern and severity. Huang et al. reported the loss of hearing from childhood to early adulthood. In our review, onset ranged from birth to middle age, demonstrating further variability.

It is well documented in the literature that a wide variety of inner, middle, and external ear anomalies may present in BOR syndrome. Many of the anatomical variations identified in our review are also features of other causes of syndromic hearing loss including oculoauriculo-vertebral dysplasia spectrum, Klippel Feil syndrome, Pierre Robin sequence, and CHARGE syndrome. In particular, Pendred syndrome shares many anatomical features; commonly presenting with progressive, fluctuant hearing loss, an enlarged vestibular aqueduct, cochlear hypoplasia, and enlarged endolymphatic ducts.

Cochlear abnormalities were among the most commonly reported anatomical changes, with hypoplasia of the apical turn described in 100% of patients with BOR syndrome in two studies. Hsu and colleagues identified the presence of an “unwound cochlea” as diagnostic marker for BOR, with 89% sensitivity and 100% specificity. On CT images, the authors describe the dysmorphology as an anteromedial rotation and displacement of the middle and apical turns of the cochlea away from the basal turn. This cochlear abnormality was previously described in patients with BOR syndrome by Robson. Furthermore, the medialization of the facial nerve to the cochlea was described in 78%–100% of BOR syndrome patients but 0% of those with other causes of hearing loss. Given the varied phenotype and genotype, the identification of these features may provide a useful tool in the diagnosis of BOR syndrome.

CT scanning is a routine investigation at many hearing loss centers; however, with concerns regarding radiation exposure for young children, some otology departments are moving toward MR imaging. Several studies have researched trends in phenotypic presentation of BOR syndrome. Sanggaard et al. reported Danish families with SIX1 mutations were observed to have fewer temporal bone malformations compared to those families with EYA1 mutations. Furthermore, two Japanese studies reported isolated unilateral EVA in two unrelated patients with SIX1 mutation. Both patients presented...
with nonprogressive mixed hearing loss with no renal anomalies.\textsuperscript{25,26} Conversely, Kemperman et al. found an association between EVA and progressive, fluctuant sensorineural type of hearing loss.\textsuperscript{76}

Molecular genetic testing can confirm the diagnosis, allow accurate genetic counseling and provide families with information on recurrence risks. However, due to the variable expressivity, severity of the phenotypic presentation is not possible, even when the mutation is identified.\textsuperscript{85} Given the lack of association between phenotype and genotype, several authors have suggested clinical\textsuperscript{2} or radiological\textsuperscript{9} criteria to stratify patients for genetic testing. Similarly Sanggaard et al. recommended genetic testing in clinically suspicious cases.\textsuperscript{24} It is also relevant to note, Chang et al. estimated that single-stranded conformation polymorphism (SSCP)-based genetic screening can identify \textit{EYA1} mutations in approximately 30% of those fulfilling their clinical criteria (Table 1); however, up to one-fifth of \textit{EYA1} mutations represent complex genomic rearrangements and would not be detected by this method.\textsuperscript{3} More recently, Unzaki et al. used direct sequencing, multiplex ligation-dependent probe amplification (MLPA), array-based comparative genomic hybridization (aCGH), and next-generation sequencing (NGS) to identify causative genes in 38 of 51 patients.\textsuperscript{33} As more effective sequencing methods become available with technological advancements, the link between genotype and phenotype may become more apparent. To further our scientific understanding, the prospective accumulation of genetic data is advised to refine the underlying pathophysiology, disease variability, and prognosis.

The effectiveness of hearing aids reported in the included studies was varied. Morisada et al. conducted a national surveillance survey of patients with BOR in Japan with 80.1% of subjects reporting successful treatment with hearing aids.\textsuperscript{16} Subjective success with hearing aids alone was also described in two studies,\textsuperscript{45,55} and postoperatively in a further two studies.\textsuperscript{31,50} In addition, Xing et al. reported good responses in two patients with inner and middle ear anomalies who underwent BAHA surgery.\textsuperscript{68} Studies of adult hearing-aid users found better speech intelligibility to be associated with younger age, increased working memory capacity and milder hearing loss.\textsuperscript{86,87} In our review, unsuccessful use was described in seven studies with severity ranging from mild to profound in both adults and children.\textsuperscript{1,30,32,39,54,60,78} Many patients had substantial hearing loss, which was outside of the decibel range where one can expect satisfactory results with conventional hearing aids.

A range of surgical interventions were described in our review. Despite being commonly reported, external ear malformations were managed surgically in only three studies.\textsuperscript{1,28,71} Six studies reported unsuccessful middle ear operations\textsuperscript{30–32,39,40,69}; however, significant audiological improvement was seen with ossicular reconstruction,\textsuperscript{42} and with the creation of a neo-oval window during mastoidectomy.\textsuperscript{71} This technique has previously been described with success by Plester.\textsuperscript{88} Improvements were also reported one-year postoperatively in a child undergoing EAC reconstruction and tympanoplasty.\textsuperscript{63}

In a total of 64 studies, CI was only clearly described in five patients. Beneficial responses were reported in all five patients; however, the studies lacked formal audiological assessment and postoperative follow-up.\textsuperscript{32,35,54,78} Subjective improvement was reported by Song et al.,\textsuperscript{32} Kameswaran et al.,\textsuperscript{54} and Ginat et al.\textsuperscript{78} Men et al.\textsuperscript{35} reported a pure-tone average of 55 to 70 dB under field conditions at 4 months (compared to profound hearing loss on auditory brainstem response preoperatively), and Ginat et al. reported initial postimplantation thresholds at 40 dB (250–2000 Hz) and 50 dB (4000–6000) but provided no preoperative comparison.

In terms of surgery, Parkes et al. reported extensive bony dysplasia in BOR mastoids, which given their importance as landmarks, may pose as an obstacle for CI.\textsuperscript{11} Kameswaran et al. reported a challenging operation with cochleostomy sited more anterosuperior to the round window in patient with a contracted mastoid antrum.\textsuperscript{54} No other mastoid anomalies were reported in the implanted patients; however, extensive cochlear, vestibular, and ossicular malformations were observed alongside deviation of the facial nerve. In a case series conducted by Palomeque Vera et al.,\textsuperscript{45} all five patients with inner ear malformations (including cochlear hypoplasia), benefitted from CI; however, those with major malformations had worse audiological outcomes.\textsuperscript{89} Successful implantation has also been reported in patients with EVA, a feature noted in three patients receiving implants.\textsuperscript{90} Intraoperatively, one perilymphatic gush was described in a patient with EVA, a malformation associated with the release of cerebrospinal fluid upon cochleostomy.\textsuperscript{91} No other intraoperative events were described in the remaining studies, with easy insertion described by Men et al. and Ginat et al.\textsuperscript{35,78} Given the potential intraoperative disorientation, CT in the preoperative period is recommended and can be used to estimate the potential depth if electrode insertion in the presence of cochlear hypoplasia.\textsuperscript{11,78}

Decision-making surrounding hearing rehabilitation in patients with BOR is extremely complex, given the variation in phenotypes, and should be considered on a case-by-case basis. As with most hearing rehabilitation, management should be considered as a stepwise approach with more conservative measures, such as HAs, used initially if indicated. Surgery does have a role; however, surgical planning (including temporal bone imaging) is key and the consent process should reflect this complexity, including the potential for suboptimal or adverse outcomes. Preoperative counseling and involvement of the multidisciplinary team (including audiologists and pediatrics) are vital.

The main limitation of this review regards the quality of the individual studies, with the majority being case series or single-case reports with a lack of objective outcomes. Due to the heterogeneity in reporting, there were missing data values across the articles, including a lack of genetic information. It was not possible to conduct a meta-analysis. Many studies also failed to report the audiological outcomes of hearing loss management, which would have been useful in assessing the appropriateness of different surgical or rehabilitation approaches. Without objective data, it remains difficult to provide reliable recommendations.

\textbf{5 | CONCLUSIONS}

The range of audiological and anatomical variations in BO/BOR patients with hearing loss is extensive. Hearing loss is most commonly
of a mixed type; however, considerable cases reported conductive or sensorineural loss. Impairment can be mild to profound, stable, or progressive and may present from birth up to adulthood. Considerable malformations were reported in the inner, middle, and outer ears, particularly the cochlear, ossicles, and auricles. Our review focused on hearing outcomes and ear anatomy; however, it is of note than a wide range of additional features were reported. Given the variable phenotypic presentation, it is possible that many BO/BOR patients are underdiagnosed. Patients presenting to otolaryngology departments for audiological work-up should be examined other syndromic features, including preauricular or branchial sinuses, prompting renal investigations.

The use of hearing aids was of uncertain benefit, with surgical intervention required in a significant number of cases. Limited success was reported with middle ear operations however all five patients receiving cochlear implants subjectively reported some benefit. In view of the anatomical landmarks, prior radiological investigation is imperative in surgical planning.

5.1 | Summary of impact

This review provides an up-to-date, comprehensive review of BO/BOR syndrome to summarize the reported audiological and anatomical presentations. Surgical intervention has been poorly reported, with varying success. Given the wide variety in phenotypic features, we highlight the importance of careful clinical and radiological assessment when prior to surgery.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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