Branchio-Oto-Renal Syndrome

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Abstract

Branchio-oto-renal syndrome is an autosomal-dominant disorder with branchial, otologic, and renal manifestations. The branchial manifestations are usually inconsequential; however, the hearing impairment and renal malformations can be significant. Appropriate evaluation of affected persons is necessary to minimize disease morbidity.

Key Words: Branchial, otologic, renal, BOR

Branchio-oto-renal (BOR) syndrome is an autosomal-dominant form of inherited hearing impairment characterized by: (1) a conductive sensorineural or mixed hearing loss; (2) preauricular pits; (3) auricular malformations of the outer ear and structural defects of the middle and inner ear; (4) branchial fistulae or cysts; and (5) renal anomalies, ranging from mild hypoplasia to a lethal condition of bilateral renal agenesis. Less common anomalies that occur include lacrimal duct stenosis, preauricular tags, facial nerve paralysis, palate defects, a narrow face with a high-arched palate, and a deep overbite. In spite of this broad constellation of findings, variable expressivity of the BOR gene can, at times, make the diagnosis very difficult. Gene penetrance is high, however, and most known carriers display some aspects of the disease phenotype if carefully examined (Fraser et al., 1978; Cremers and Fikkers-Van Noord, 1980).

Historical Perspective

Early reports of BOR syndrome can be traced to the nineteenth century. Aucherson (1832) was the first to recognize the familial occurrence of branchial anomalies. The combination of preauricular pits, branchial fistulae, and hearing impairment was reported by Heusinger in 1864 and by Paget in 1877 and 1878. Under the Nazi regime, the disease provoked a great deal of discussion by several German authors, notably Albrecht (1933), Schneider (1937), Loebell (1938), Steinberg (1938), and Langenbeck (1938), because of the eugenics problems it raised. BOR syndrome was referred to as Innenohrschwerhörigkeit, or "hereditary hardness of hearing" (Fourman and Fourman, 1955).

More frequent recognition of BOR syndrome followed the 1955 publication by Fourman and Fourman of a large family with preauricular pits, bilateral branchial fistulae, and progressive sensorineural hearing loss. Twenty years later, Melnick et al. (1975) recognized the possibility of associated renal anomalies and suggested the term branchio-oto-renal syndrome, underscoring the phenotypic anomalies of the branchial arches, otocysts, and renal primordia. The nomenclature for BOR syndrome, however, has varied. Terms applied to the disease reflect observation and author bias and include ear pits-deafness syndrome; preauricular pits, cervical fistulae, hearing loss syndrome; branchio-oto-dysplasia syndrome; branchio-oto-ureteral syndrome; branchio-oto-renal dysplasia; and Melnick-Fraser syndrome (Cremers and Fikkers-Van Noord, 1980; Fraser et al., 1983).

Prevalence

Congenital deafness affects 1 of every 1000 children, and an estimated 50 percent of these affected children have inherited hearing impairment (Fraser, 1976). The precise prevalence of BOR syndrome is unknown; however, two esti-
mates have been made by Fraser. In 1976, he surveyed 3460 children with profound hearing loss and found only 5 (0.15%) with a family history of branchial fistulae and preauricular pits (1:700,000) (Fraser, 1976; Fraser et al, 1978). Four years later, however, he presented evidence to suggest that the prevalence of BOR is much greater (Fraser et al, 1980). In a study of 421 white children in the Montreal schools for the deaf, he diagnosed BOR syndrome in 2 percent of the profoundly deaf students. Fraser, therefore, roughly estimated disease prevalence at 1:40,000. The true value is probably somewhere between these extremes.

Characteristic Findings

Hearing impairment is the most common feature of BOR syndrome and affects approximately 80 percent of carriers (Fraser et al, 1978; Creemers and Fikkers-Van Noord, 1980) (Table 1). The impairment may be congenital or late-in-onset and is either nonprogressive or progressive in nature. It is sensorineural (20%), conductive (30%), or mixed (50%) and ranges in severity from mild to profound (Fraser et al, 1980) (Fig. 1). Interestingly, all three types of hearing loss can be observed in individuals within the same pedigree, and the type of hearing loss may even differ in each ear within an individual. For example, carriers with a sensorineural loss in one ear and a conductive hearing loss in the other ear have been reported (Karmody, 1974).

The otologic aspects of the external ear are often the most striking feature of BOR syndrome. Most commonly, the antihelix of the pinna is malformed, and the result is a lop-ear deformity (Fig. 2). This type of abnormality is reported in about 40 percent of affected individuals (Fraser et al, 1978; Creemers and Fikkers-Van Noord, 1980), although in our experience this number is underestimated. Severe microtia also occurs.

Anterior to the pinna, preauricular cartilaginous appendages may be found. A more subtle finding is the presence of preauricular pits.
This hallmark feature is typically noted as a shallow, pinhead-sized depression near the superior attachment of the helix. Approximately 1 percent of the general population of newborns has preauricular pits (Fraser et al, 1980; Melnick, 1980), and it is estimated that 1 child in 500 with pits has BOR syndrome (Fraser et al, 1980).

There may be substantial malformations of the middle ear (Fitch and Srolovitz, 1976). Abnormalities have been observed by computerized tomography and surgical exploration. The ossicles can be malformed, displaced, fixed, fused, enlarged, hypoplastic, or even absent (Ostri et al, 1991). Specific findings include interruption of the ossicular chain, footplate fixation, shortening of the lenticular process of the incus, and aberrant fixation of the incus and stapes. These types of ossicular abnormalities result in a conductive hearing loss.

Inner ear abnormalities also occur. The horizontal semicircular canals can be asymmetrical, dysplastic, or absent. The cochlea can be hypoplastic or dysplastic, and the internal auditory canal can be widened (Fig. 3). These abnormalities may result in vestibular hypoactivity and a sensorineural hearing loss (Fraser et al, 1978; Gimsing and Dyrmose, 1986).

A branchial fistula or cyst occurs in approximately 63 percent of carriers (Fig. 4). This hallmark feature may be either unilateral or bilat-
Figure 4  Branchial fistula in a neck skin crease. These small openings lie anterior to the sternocleidomastoid muscle and may track internally to open in the tonsillar fossa.

Fistulae are located in the mid-to-lower third of the neck as small openings anterior to the sternocleidomastoid muscle. The openings may be inconspicuous or may ooze fluid and become infected. Cysts are usually palpable deep to the sternocleidomastoid muscle and may present with a cutaneous opening. In the absence of a cutaneous opening, diagnosing a branchial fistula as an isolated finding and do not have BOR syndrome (Smith et al, 1984).

The spectrum of renal malformations in BOR syndrome ranges from mild to severe. The majority of renal anomalies are minor and often remain asymptomatic. In fact, many renal anomalies are subtle and can be missed on routine intravenous pyelography (IVP) (Fraser et al, 1978). With close scrutiny, however, IVP demonstrates some structural anomaly of the renal system in two-thirds of persons with BOR syndrome (Cremers and Fikkers-Van Noord, 1980). Ten percent of affected persons have clinically significant renal involvement. Severe renal anomalies include bilateral renal agenesis, polycystic kidneys, and enlarged, blunted kidneys. Other anomalies of the renal system include unilateral renal agenesis, vesiculoureteral reflux, crossed renal ectopia, bilateral bifid renal pelvis, ureteropelvic junction obstruction, duplication of the ureter and collecting system, extrarenal pelvis, fetal lobulation, abnormal rotation of the kidney, calyceal diverticuli or distorted calyceal system, abnormal renal parenchymal thickness, and tapered superior pole of the kidney (Fig. 5). Renal function studies have shown normal urinary sediment in all patients (Wildervanck, 1962). A small number of patients have a disturbed concentration capac-
Anomalies of the fourth and sixth branchial arch vessels have been noted, including a right aortic arch with an anomalous left subclavian artery (Legius et al, 1990), an aberrant right subclavian artery (Melnick et al, 1978), and preductal coarctation of the aorta (Chitayat et al, 1992).

**Differential Diagnosis**

In general, the diagnosis of BOR syndrome is straightforward. Individuals exhibit the characteristic disease phenotype, and an autosomal-dominant line of transmission is evident. Family histories, however, can be obscure, new mutations do occur, and phenotypic expression varies, making it helpful to have some knowledge of other syndromes considered in the differential diagnosis.

**Oculo-Auriculo-Vertebral (OAV) Dysplasia (Hemi facial Microsomia, Goldenhar Syndrome)**

The OAV dysplasia spectrum is a disease phenotype in which the predominant malformations reflect abnormalities in morphogenesis of the first and second branchial arches, vertebrae, and eyes. OAV dysplasia usually occurs sporadically and, in general, only about 2 percent of first-degree relatives of carriers are affected by major or minor phenotypic features of the disease (Cohen et al, 1989).

Included in the OAV spectrum are malformations of the auricle, preauricular tags anywhere along an imaginary line from the tragus to the oral commissure, preauricular pits, and, in over 50 percent of carriers, varying degrees of hearing impairment. Renal anomalies are also reported and include absent kidneys, double ureters, crossed renal ectopia, hydronephrosis, hydrourereter, and an anomalous blood supply to the kidneys (Cohen et al, 1989).

The feature distinguishing BOR syndrome from the OAV spectrum is the facial abnormalities. The OAV spectrum is characterized by hypoplasia of the malar, maxillary, and mandibular regions, especially the ramus and condyle, and ocular findings such as narrowed palpebral fissures on the affected side, epibulbar dermoids, colobomas, lipodermoids, notched upper lids, strabismus and, rarely, microphthalmia or anophthalmia. Often, there is an obvious facial asymmetry in OAV dysplasia, with one side being more severely affected than the other. In contrast, in BOR syndrome, the facial skeleton is normal.

**Treascher Collins Syndrome (Mandibulofacial Dysostosis)**

Like OAV and BOR syndromes, Treascher Collins syndrome also results from abnormal development of the first and second branchial arches. The characteristic phenotype includes antimongoloid slanting palpebral fissures, malar bone hypoplasia, mandibular hypoplasia, and lower lid coloboma. Auricular malformations, including microtia, hypoplasia, cupping, preauricular tags and pits, and external auditory canal defects occur in 77 percent of patients. The middle ear ossicles also are often malformed, and 40 percent of patients have a conductive hearing loss. Inheritance is autosomal dominant, and, like BOR syndrome, expression is highly variable. Affected individuals may exhibit only a few characteristics of the disease spectrum (Smith, 1986). See Jahrsdoerfer and Jacobson (1995) in this volume for a detailed account of Treascher Collins syndrome.

**Otomandibular Dysostosis**

This syndrome, questionably distinct from Treascher Collins syndrome, includes prominent lop ears, long thin nares, micrognathia, and bilateral fixation of the stapes foot plate. Only one family has been reported; inheritance is autosomal dominant (Konigsmark and Gorlin, 1976).

**Towns-Brockes Syndrome**

This syndrome consists of lop ears, ear tags, sensorineural deafness, renal anomalies, thumb malformations, imperforate anus, and skeletal anomalies. Inheritance is autosomal dominant (Walpole and Hockey, 1982).

**Branchio-oculo-facial (BOF) Syndrome**

BOF syndrome consists of bilateral branchial cleft sinuses, congenital strabismus, obstructed nasolacrimal ducts, a broad nasal bridge, a protruding upper lip, a pseudocleft of the upper lip, hemangiomatous branchial clefts, malformed ears, and linear skin lesions behind the ears. Other associated anomalies include colobomas, microphthalmia, auricular pits, lip pits, high-arched palate, dental anomalies, subcutaneous cysts of the scalp, premature graying, and poor growth. Legius et al (1990) described a father and son with overlapping features of both BOR and BOF syndromes. Inheritance is autosomal dominant (Legius et al, 1990).
Branchial Arch Syndrome (X-Linked)

There is one report of this syndrome, which consists of microcephaly, downslanting palpebral fissures, high-arched palate, low-set protruding ears, bilateral sensorineural hearing loss, slightly webbed neck, short stature, and learning disability. It may occur with cryptorchidism, subvalvular pulmonic stenosis, and body asymmetry (Toriello et al, 1985).

Other Syndromes

Other syndromes in the differential diagnosis include Wildervanck's syndrome, frontal nasal dysplasia sequence, Bixler's syndrome, VACTERL association, CHARGE association (see Toriello [1995] in this volume), MURCS association, otofaciocervical syndrome, deafness-craniofacial syndrome, Ladd's syndrome, otocephaly anomaly, Mengel's syndrome, congenital conductive or mixed deafness-preauricular sinus-external ear anomaly and commissural lip pit syndrome, PHEP syndrome, and Nager syndrome.

Management

The medical management of BOR syndrome requires special emphasis on hearing impairment, renal abnormalities, perinatal complications, and genetic counseling. The prompt recognition of hearing impairment is important, and children with the phenotypic characteristics of BOR syndrome should undergo thorough audiologic testing as early as possible. We would also recommend auditory screening for children with only preauricular pits or tags. If hearing loss is documented, appropriate aural habilitation should be initiated. Infants who experience otitis media should be maintained on chemoprophylactic antibiotics to prevent fluctuations in hearing, and if a middle ear effusion is present for longer than 3 months, pressure-equalizing tubes are indicated. An annual audiologic evaluation is essential, as hearing loss can be progressive.

The role of surgery in correcting fixed losses has not been established. Cremers et al (1981) have noted that stapedectomy in carriers with a mixed loss is generally followed by a poor outcome. If stapedectomy is to be considered, computerized tomography is essential to delineate malformations of the inner ear that may predispose to a stapedial gusher (Gimsing and Dyrmos, 1986; Ng et al, 1989) (Fig. 3). In general, surgical intervention should be recommended only when the hearing loss is confined to the lateral ossicular chain.

Renal anomalies can be severe and even incompatible with life. Fatal malformations are not typically diagnosed in utero, and the perinatal care of newborns with BOR syndrome has received only minimal attention. There are at least nine documented deaths in neonates with confirmed BOR syndrome (Fitch and Srolovitz, 1976; Melnick et al, 1978; Carmi et al, 1983; Greenberg et al, 1988; Chitayat et al, 1992). In each instance, the neonate was born with renal agenesis or dysplasia. Death occurred within hours of delivery from respiratory distress secondary to pulmonary hypoplasia. It was not possible to predict, based on the phenotype of the affected parent, whether the neonate would exhibit a severe form of BOR syndrome. Even parents with asymptomatic or radiologically undetectable renal anomalies were at risk for progeny with renal agenesis. If one child had severe renal malformation, couples were at increased risk for having other similarly affected children.

Based on these reports, we recommend careful monitoring of any pregnancy in which either parent has BOR syndrome. Special attention should be given to fundal height, and serial ultrasounds should be done to detect the presence of oligohydramnios (Carmi et al, 1983). The presence of renal tissue and an estimate of lung volume should be established. If severe abnormalities are present, the child should be delivered in a hospital with a level III neonatal intensive care nursery, so that neonatologists skilled in the management of respiratory distress can provide optimal care.

We also would recommend an IVP to evaluate renal structure and function in affected individuals. This procedure is superior to a renal ultrasound or abdominal X-ray in delineating structural abnormalities and variations found in BOR syndrome. The potential complications from reflux, impaired renal function, and a predisposition for urinary tract infections cannot be dismissed. Furthermore, prior knowledge of an affected individual's renal anatomy and function are invaluable in an emergency situation involving an accident or trauma to the kidneys. If a renal abnormality is detected on IVP, referral to a nephrologist is in order.

Genetic counseling is invaluable for persons with BOR syndrome. Counseling assures that the pattern of disease inheritance is understood by affected persons. Phenotypic variabil-
ity also can be explained, stressing the need for appropriate medical and audiologic evaluation and care. Counseling is especially important in instances where BOR syndrome has been associated with severe renal anomalies.

**Pathogenesis**

The pathogenesis of BOR syndrome is not known. Malformations in BOR syndrome are the result of the simultaneous occurrence of aberrant differentiation of three separate embryologic formations: the branchial apparatus, the otocyst, and the renal primordia. Genetic studies (Haan et al., 1989; Kumar et al., 1992; Smith et al., 1992) suggest that a single gene defect results in the BOR phenotype. The gene defect may result in alterations in cell-to-cell recognition surface proteins or enzyme receptors, alterations in directed cell movement, alterations in cellular division, or a deficiency of mesodermal cellular components in the branchial arch and metanephros. To answer these questions and increase our understanding of auditory and renal development, research efforts are underway to clone the BOR gene.

**Conclusion**

Most individuals with BOR syndrome do not have a life-threatening condition, and, in many families, it is not uncommon for the disease to go undiagnosed until the birth of a child with severe manifestations of the BOR phenotype. This is unfortunate, as recognition of the hallmark features of BOR syndrome could ensure that affected persons receive appropriate medical information and care. Integral elements of medical care include audiologic, otologic, head and neck, urologic, and genetic evaluation.

**REFERENCES**


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