Branchio-oto-renal Syndrome (Melnick-Fraser Syndrome)

See also: Second Arch Branchial Cleft Fistula Case Example

Branchio-oto-renal (BOR) syndrome, also known as Melnick-Fraser syndrome, is characterized by an association of: 1) brachial fistulae or cysts; 2) Ear malformations, which can include the inner, middle and outer ear; 3) Renal malformations, which can range in severity from renal hypoplasia to agenesis.

Inherited in an autosomal dominant fashion, each child of a parent with BOR syndrome has a 50% chance of presenting with the disease. It is thought that 90% of BOR syndrome cases are due to inheritance, while the remaining 10% of cases are due to acquired mutations. BOR displays variable expressivity, accounting for the differences in severity of symptoms among family members. Penetrance, however, is 100%. Anticipation (proclivity for successive generations to present with the disease at an earlier age) does not occur.

History

- In 1864 Heusinger was the first to recognize an association between branchial cleft fistulae, preauricular pits, and hearing impairment.
- In 1975, Melnick et al. and Fraser et al. described BOR syndrome as a specific entity with an autosomal dominant inheritance pattern.

Epidemiology

- BOR syndrome affects about 1 in 40,000 people.

Diagnosis

A family history positive for brachial, otologic, and renal malformations is suggestive of BOR syndrome.

If no family history of disease is known, clinical criteria can be utilized to make the diagnosis for patients with at least three major criteria. Alternatively, the diagnosis can be made for patients demonstrating two major criteria and two minor criteria.

Major Criteria

1. Pinnae malformation
2. Hearing loss
3. Preauricular pits
4. Renal anomalies
5. Second branchial arch anomalies
6. External auditory canal stenosis

Minor Criteria

1. Preauricular tags
2. Lacrimal duct aplasia
3. Middle ear anomalies
4. Inner ear anomalies
5. Palate malformations or facial asymmetry
6. Euthyroid goiter

Phenotypic Findings

Otologic

Otologic manifestations of BOR are the most common presenting symptoms, with over 90% of people experiencing at least one of the following:

1. Deafness may present as a conductive, sensorineural, or mixed classification. The magnitude of deafness is variable, ranging from mild hearing loss to profound. Furthermore, the magnitude of hearing loss can be stable or progressive. Hearing loss is well-established as the most common single trait among those with BOR syndrome, estimated to be 89% of individuals in a study by Fraser et al. Among those with hearing loss, 50% presented with mixed, 30% with conductive, and 20% with sensorineural presentations. It was also estimated that 2% of children with profound deafness have BOR.

2. Lop-ear deformity.
3. Preauricular pits.
4. Preauricular tags.
5. External auditory canal: stenosis
6. Middle ear: ossicular malformations, such as hypoplasia or displacement
7. Inner ear: hypoplastic cochlea, dysplastic lateral semicircular canals, enlargement of the vestibular or cochlear aqueducts.

Branchial Arch Anomalies

1. Branchial cleft cyst.
2. Branchial cleft sinus tract.

Renal malformations

1. A spectrum of renal malformations is possible, from hypoplasia to agenesis.
2. Calyceal cysts.
3. Uretero-pelvic junction obstruction.
4. Vesicoureteral reflux

Other associated findings

1. Mitral valve prolapse
2. Cleft palate
3. Lacrimal duct aplasia
4. Facial nerve paralysis
5. Retrognathia
Gene Studies

Currently, there are three known gene mutations which result in BOR syndrome. If a clinical diagnosis of BOR syndrome is made, confirmation should be attempted via sequence analysis for EYA1. If an EYA1 mutation is not found with sequence analysis, one should utilize duplication/deletion analysis for EYA1 and sequence analysis for SIX 1 and SIX 5.

EYA1 mutation

- About 40% of people with BOR syndrome will have an EYA1 mutation.
- EYA1 encodes for a transcription cofactor that is expressed in the metanephric mesenchyme during development of the kidneys.

SIX1 mutation

- The SIX1 mutation is estimated to be found in 2% of BOR syndrome cases.
- It encodes transcription factors that control expression of GDNF and PAX2.
- The majority of patients with this mutation do not demonstrate renal malformation.

SIX5 mutation

- The SIX5 mutation is present in about 2.5% of BOR syndrome cases.
- Hearing may be normal in these patients.

Management

Otologic Evaluation

- Testing should include ABR, pure tone audiometry, and emission testing.
- Imaging of the temporal bones with a CT scan is warranted.
- An annual auditory evaluation should be suggested.

Branchial Arch Evaluation

- Physical examination followed by computed tomography (CT), fistulogram, or magnetic resonance imaging (MRI) if masses are palpated or tracts are observed.

Renal Evaluation

- Renal ultrasound
- BUN and creatinine
- Patients should follow-up with nephrology and urology annually.

Genetic counseling

- It is important that patients affected with BOR realize that there is a 50% chance of transmission to each child due to autosomal dominant inheritance.
- Prenatal testing for BOR is available for those with a positive family history.

Treatment

Otologic anomalies

- Detect hearing impairment, use appropriate auditory treatment as indicated by severity of loss, such as hearing aid or cochlear implant.
- If the middle ear is intact with a stenotic external canal, consider a canaloplasty.
• Consider cosmetic procedures for pinna deformities.

Branchial anomalies

• Excision of cyst, fistula, or sinus, with full-length dissection of the tract and tonsillectomy.

Renal anomalies

• Treatment depends on the severity of renal complications, but both surgical and medical management should be utilized.
• Renal transplantation may be considered if end-stage renal disease develops.

References/Suggested Reading


