CLINICAL QUIZ (p246) ANSWER

What is the diagnosis?

The clinical features of this child (bilateral profound hearing loss, bilateral preauricular pits, neck sinus with discharge and facial asymmetry) were compatible with Branchio-otorenal Spectrum Disorder (BORSD). Under this umbrella entity, it contains two phenotypes: Branchiootorenal (BOR) syndrome and Branchiootic syndrome (BOS). In view of absence of renal involvement, our patient is likely suffering from BOS. She attended the genetic clinic at 15 months of age, we performed hearing impairment panel on her. Genetic analysis confirmed she had heterozygous missense variants NM_005982.3(SIX1)c. 517A>C p.(Lys173Gln). Parental testing showed the variant was de novo. This variant is not present in normal population genomic database (ExAC and gnomAD). A different amino acid change (Lys173Asp) in the same codon has been reported in literature with Branchiootic syndrome phenotype. In-silico computation program predicted this variant to be deleterious. Together with denovo change, this variant is classified as likely pathogenic according to ACMG guideline.[1] *SIX1* gene [OMIM*601205] is associated with Branchiootic syndrome 3 [OMIM #608389] which is inherited in autosomal dominant manner.

Branchio-otorenal spectrum disorder (BORSD) is characterised by malformations of the outer, middle, and inner ear together with conductive, sensorineural, or mixed hearing impairment, branchial fistulae and cysts, and renal malformations ranging from mild renal hypoplasia to renal agenesis. Prevalence of BORSD is not known. Previous studies predicted the prevalence may range from 1 in 40,000 to 1 in 70,000 but may be subjected to ethnic group difference.[2,3] The clinical presentation is heterogeneous. Extreme variability can be observed in the presence, severity, and type of branchial arch, otologic, audiologic, and renal abnormality from right side to left side in an affected individual and among other affected family members.[4]

How is the clinical diagnosis established in BORSD?

The diagnosis of BORSD relies on clinical suspicion and pattern recognition. Major and minor diagnostic criteria for Branchiootorenal Spectrum Disorder were shown below Table:[5]

Major Criteria	Minor Criteria
Second branchial arch anomalies	External auditory canal anomalies
Deafness	Middle ear anomalies
Preauricular pits	Inner ear anomalies
Renal anomalies	Preauricular tags
	Other: facial asymmetry, palatal abnormalities

Second branchial arch anomalies include branchial cleft sinus tract which may appear as a pinpoint opening anterior to sternocleidomastoid muscle (usually in lower third of the neck) and branchial cleft cyst. Middle ear anomalies include malformation, malposition, dislocation or fixation of the ossicles or malformation of the middle ear space. Inner ear abnormalities, e.g. cochlear hypoplasia, enlargement of cochlear and vestibular aqueducts or structural hypoplasia of lateral semicircular canal which are detected by MRI temporal bone.[6] Renal anomalies include renal agenesis, hypoplasia or dysplasia, uretero-pelvic junction obstruction, calyceal cyst / diverticulum, hydronephrosis, vesicoureteral reflux...etc.[4]

In the absence of a family history, three or more major criteria OR two major and two minor criteria must be present to make the clinical diagnosis of BORSD. With one first degree relative meeting the above criteria, one major criteria is sufficient to establish the clinical diagnosis.

Molecular diagnosis of BORSD and Genetic counseling

The diagnosis of Branchiootorenal spectrum disorder is established in a proband fulfilled the diagnostic criteria and/or by identification of a heterozygous pathogenic variant in one of the following genes *EYA1* (OMIM* 601653)*, SIX1 (*OMIM*601205*) and SIX5* (OMIM*600963). Around 40% of BORSD genetically confirmed patients had *EYA1* pathogenic variants and among them, 80% is related to sequence error while 20% is related to deletion of *EYA1*.[7] *SIX1* and *SIX5* sequence error attributed to 2% and 2.5% to the genetically confirmed BORSD patients respectively.[4,7] Thus over 50% BORSD patients cannot identify a heterozygous pathogenic variant in those related genes despite extensive genetic workup. Based on current evidence, no genotype-phenotype correlation has been drawn for BORSD.

BORSD is inherited in an autosomal dominant manner. The offspring of an affected individual is at a 50% risk of inheriting the pathogenic variant. Once the pathogenic variant has been identified in an affected member, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis are possible. Branchiootorenal spectrum disorder would have 100% penetrance, although expressivity is highly variable and intrafamilial variation exists.

What are the management issues for BORSD?

Management of BORSD adopts a multi-disciplinary approach. ENT doctors, audiologists, surgeons, pediatricians, urologists, clinical geneticists and speech therapists…etc. inputs are important. Surgical treatment e.g. excision of branchial cleft cysts / fistula depends on clinical presentation. Medical and surgical treatment for vesicoureteral reflux may help to prevent the development to renal failure. Semi-annual examination for hearing impairment and annual audiometry were indicated to monitor the progression of hearing loss. Regular monitoring of renal function was needed for those with underlying renal impairment or structural abnormalities. At-risk relatives should be screened for hearing loss and renal involvement to allow for early diagnosis and treatment. Affected individuals should avoid nephrotoxic drug.

Acknowledgement

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