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Prenatal diagnosis and follow-up of a case of branchio-oto-renal syndrome displays renal growth impairment after the second trimester

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Abstract

Branchio-oto-renal syndrome combines branchial arch defects, hearing impairment and renal malformations or hypoplasia. Due to the high phenotypic variability, prenatal diagnosis has a limited prognostic value in mutation-positive cases. We report the first branchio-oto-renal syndrome molecular prenatal diagnosis and ultrasonographic follow-up, showing a normal renal growth until the 24th week of pregnancy, a growth deceleration during the third trimester and a renal volume recovery during the first months of life.

Key words: branchio-oto-renal syndrome, genetic test, prenatal diagnosis.

Introduction

Branchio-oto-renal (BOR1; MIM #113650) syndrome is a rare autosomal dominant condition with an incidence of approximately 1 out of 40 000, which is characterized by a triad of signs featuring branchial arch anomalies (branchial clefts, fistulae, cysts), hearing impairment (conductive, sensorineural or mixed) and renal malformations (hypoplasia or agenesis, dysplasia, renal cysts and urinary tree malformations).[1] The high inter- and intrafamilial phenotypic variability of BOR syndrome occurs with a correspondingly high genetic heterogeneity, with 40% of patients having mutations on the *EYA1* gene, encoding a transcriptional co-factor and about 10% with mutations in the *SIX1* and *SIX5* genes, whose products interact with EYA1 protein to form transcription factor complexes.[1] About 50% of patients with BOR syndrome do not show mutations in the currently known genes.

In families in which the disease-causing mutation has been identified, prenatal testing can be offered, but fetal prognostic counseling in cases with a positive test result is complicated by the wide range of possible impairments of both the hearing and renal functions. In the present report, we characterize the prenatal and postnatal features of a case of familial BOR, in which the prenatal follow-up of the kidneys and urinary tract showed a normal renal growth until the 24th week of pregnancy, a deceleration during the third trimester and an apparent renal volume recovery during the first months of life.

Case Report

A 32-year-old primigravida with congenital profound deafness due to the *GJB2* 35delG homozygous mutation was referred for prenatal counseling after the diagnosis in her husband of BOR syndrome, which was confirmed by genetic testing. More specifically, a deletion of the whole *EYA1* gene was shown by Multiplex Ligation-dependent Probe Amplification (MLPA) analysis (SALSA MLPA KIT P153 EYA1, MRC Holland) after the direct sequencing of the *EYA1* and *SIX1* genes had

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resulted negative and the preconceptional screening for *GJB2* mutations had excluded a carrier status. The man, 35 years old at the time of diagnosis, presented profound sensorineural hearing loss, preauricular pits, bilateral branchial blind fistula, chronic renal impairment with a reduced bipolar diameter of both kidneys (8.2 cm in the right and 8.5 cm in the left, both under the 5th centile for renal length in adults[2]), sclerosing glomerular lesions and a moderate reduction of the renal cortex. The renal function was monitored on a yearly basis and showed a moderate increase in the serum creatinine levels, which were treated with renin inhibitors, vitamin D2 analogues and uric acid synthesis inhibitors.

Due to the autosomic dominant pattern of inheritance of the BOR syndrome, a genetic risk of the disease was attributed for 50% of the children of both sexes and chorionic villus sampling was carried out at the 11th gestational week. The *EYA1* analysis by MLPA demonstrated the presence of the familial whole gene deletion, resulting in the diagnosis of BOR syndrome for the fetus and prompting a close follow-up of the renal volume and echo-pattern. An informed consent was given for the genetic tests and for the publication of the instrumental and photographic data.

At the 11th week, the ultrasonographic examination showed a crown–rump length on the 50th centile (45 mm) and a nuchal translucency in the normal range (1 mm). At the 18th gestational week, the fetal biometry was on the 30th centile and the anomaly scan showed a bilateral pyelectasis (anteroposterior diameter: 5 mm) and a diffuse hyperechoic pattern of both kidneys without a clear separation between the cortex and the medulla. The ultrasonographic scan of all the other organs, including the neck for fistulae and the preauricular zone for skin tags, was normal, as well as the filling of the bladder and the amount of amniotic fluid; both renal arteries were visualized by pulsed wave Doppler sonography. At the 32nd week, all the fetal biometric parameters were on the 50th centile; a renal pyelectasis (anteroposterior diameter: 6 mm) and a parenchymal structure characterized by a hyperechoic cortex and hypoechoic medullary pyramid were bilaterally visualized together with a normal filling of the bladder and a normal amniotic fluid volume. The values and centiles of the renal longitudinal length at the 18th, 24th and 32nd week of gestation are reported in Figure 1.

The baby boy was born by vaginal delivery at the 40th gestational week and presented normal adaptation to life (Apgar scores were 9 and 10 at the 1st and 5th min of life) with the following parameters: weight 2670 g (2nd centile), length 49 cm (10th centile), and head

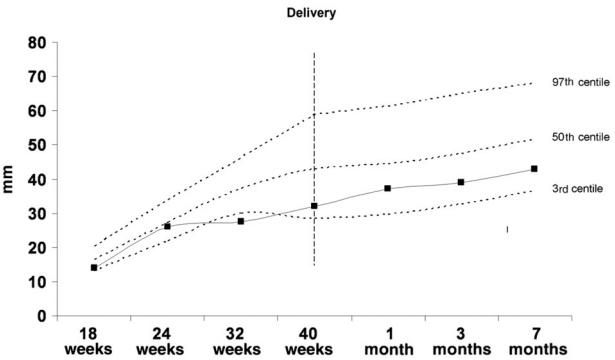

Figure 1 Graph of the left kidney describing the prenatal and postnatal renal longitudinal growth recorded during the ultrasonographic follow-up (for brevity only one of the two kidneys is reported). The dotted lines refer to the 3rd, 50th and 97th centiles of the growth curves (according to[3]), and the black line to the patient.

circumference 32 cm (1st centile). He showed bilateral preauricular pits, deep notches between the antitragus and the ear lobe and a right facial nerve peripheral palsy resulting in the defect of the right orbicularis oris, right palsy of facial muscles of expression and incomplete closure of the right palpebral fissure, especially evident during crying (Fig. 2). The child failed the neonatal otoacoustic emission-screening test and underwent an auditory brainstem response test, which revealed a threshold of 90 dB above the normal hearing level (nHL) for the left ear and 50 dB nHL for the right. Cerebral computed tomography and magnetic resonance imaging showed, for the ossicular chain, a bilateral fusion of the stirrup and anvil and fixity of the hammer, whereas, for the inner ear, cochlear hypoplasia, absent modiolus, dilated vestibule and a cystic appearance of the lateral semicircular canal bilaterally. Both of the 7th cranial nerves were hypoplastic, whereas the vestibulocochlear nerves were normal. The renal function at birth was within the normal range (creatinine, 0.57 mg/dL; glomerular filtration rate, 39 mL/min). The renal bipolar diameter at birth was 3.2 cm bilaterally (5th centile of the postnatal growth curve for children[4]), with a progressive increase during the follow-up until the 7th month control when the diameter was 4.5 cm for the right and 4.3 cm for the left kidney (between the 5th and the 50th centile for both). The parenchymal width was normal (4.5 mm), but the echo-pattern could not well differentiate the cortex from the medulla. The renal pelvis was less than 1 cm bilaterally. The renal function was normal throughout the follow-up period: at 3 and 7 months the serum creatinine levels were 0.43 and 0.45 mg/dL with a glomerular filtration rate of 65 and 62 mL/min, respectively.

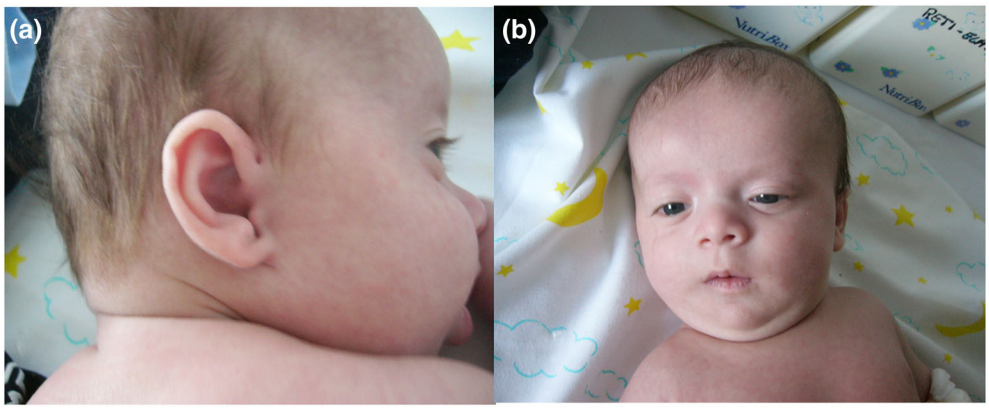

Figure 2 (a) Picture of the baby at birth documenting the ear anomaly. (b) The baby at 3 months of age: the presence of a right facial nerve peripheral palsy is displayed by the wider opening of the right palpebral fissure, the flattening of the right nasolabial fold and the inability to lift the right side of the mouth.

At 7 months, the visual response audiometry displayed bilateral severe/profound neurosensorial deafness.

Discussion

The only previous report of prenatal diagnosis of BOR syndrome dates back to 1988,[5] when the diagnosis was based on the unilateral renal agenesis in a fetus with an affected father. In the present case, a positive genetic test at the 12th week of pregnancy allowed a close follow-up of the pregnancy, with the purpose of gaining prognostic data essentially about the renal function (about the degree of hearing loss, which is highly variable in BOR syndrome patients, no prenatal information could be given).[6] During the follow-up, we assessed a normal fetal renal development until the 24th week, with a sudden arrest thereafter (in humans the development of the nephronic units and of the ureteric bud normally continues until the 32nd to the 36th week of gestation) and an apparent growth recovery in the first months after birth (Fig. 1), paralleling the interruption of the renal development caused by prematurity,[7] in which also a volume recovery after birth is reported. From the molecular point of view, the arrested development of the fetal nephronic units in BOR syndrome is the result of the haploinsufficiency of the EYA1/SIX1 pathway, although the observed timing is in contrast with the findings in mice, in which the Eya1 knock-out is featured by a complete renal agenesis,[8] suggesting a higher complexity of the human renal development regulations. This is also evident from the wide spectrum of kidney abnormalities in BOR syndrome: a report of 21 patients showed unilateral renal agenesis in 29%, hypoplasia in 19%, dysplasia in 14%, ureteropelvic junction obstruction in 10%, calyceal cyst or diverticulum in 10% and caliectasis, pelviectasis, hydronephrosis and vesicoureteral reflux at 5% each.[9] Bilateral renal agenesis has also been documented in several instances. Therefore, in contrast with other disorders in which a specific nomogram of the prenatal growth has been proposed (i.e. in familial Beckwith–Wiedemann syndrome[10]), the variable renal involvement in BOR syndrome prevents us from generalizing our experience, limiting the observation of the renal growth pattern to the BOR syndrome cases with renal hypoplasia (one fifth of all the BOR cases[9]), which we found associated with a normal renal function throughout the postnatal 7-month follow-up period.

In conclusion, a close ultrasonographic prenatal follow-up of the kidneys in a fetus after a positive BOR syndrome genetic test revealed a specific growth pattern due to the disease and offered some reassurance to the parents regarding the child's renal function at birth.

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Disclosures

None declared.

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