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Prenatal Diagnosis of Okur-Chung Syndrome: Ultrasound Findings and Implications of CSNK2A1 and KCNQ5 Variants

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To editor:

Okur-Chung neurodevelopmental syndrome (OCNDS) is a rare autosomal dominant disorder caused by heterozygous mutations in the *CSNK2A1* gene. This multisystemic disease is primarily characterized by neurodevelopmental delay and facial dysmorphism. Brain magnetic resonance imaging (MRI) of affected patients typically reveals gyral simplification, cerebral atrophy, thinning of the corpus callosum, and cerebellar hypoplasia. To date, approximately 30 cases of OCNDS have been reported in the literature, all diagnosed postnatally. Recently, whole exome sequencing (WES) identified five pathogenic variants in the *KCNQ5* gene in patients with developmental and epileptic encephalopathy.[1] The *KCNQ5* gene, located on chromosome 6q13, regulates neuronal excitability and function by modulating synaptic inhibition.[2] Patient's consent to publish the clinical information in the article was obtained.

We report a 37-year-old multigravida South American woman with an uncomplicated personal and family history and a non-consanguineous partner. She regularly consumed tetrahydrocannabinol and tobacco throughout the pregnancy. Her obstetrical history includes voluntary pregnancy terminations and uncomplicated deliveries. Her first trimester was uneventful with negative serology screening for Cytomegalovirus (CMV), Rubella, or Toxoplasmosis. Combined screening showed low risk for trisomy 21-13-18 with normal nuchal translucency of 1.4 mm and crown-rump length of 58 mm at 12^{+2} weeks. At 21^{+3} weeks, an anatomy scan revealed cerebellar hypoplasia and posterior fossa cystic malformation. Fetal biometry indicated severe early-onset growth restriction, with all parameters and estimated fetal weight falling below the 5th centile on Intergrowth-21st charts. On the same day, amniocentesis was conducted. At 23^{+4} weeks, a detailed two-dimensional and three-dimensional transabdominal neurosonography revealed a cerebellar diameter below the 5th centile, asymmetry of the cerebellar hemispheres, and a significant volume loss in the left hemisphere (Fig. 1A).

Communication between the fourth ventricle and the cisterna magna was observed. Unilateral cerebellar hypoplasia and under-development of cerebellar foliation were noted (Fig. 1B). On the midsagittal posterior plane, Blake's pouch cyst and vermis rotation were identified, with normal torcular herophili positioning (Fig. 1C). Angles indicated brainstem-vermis (55.8°) and brainstem-tentorium (44.2°) hypoplasia, suggesting lower part of the vermis. The vermis' supero-inferior and anteroposterior diameters were below the 5th centile.[3] The anteroposterior diameter of the brainstem measured 8.8 mm (75th centile).[4] The ventricular system was symmetric with normal lateral ventricle dimensions. The corpus callosum was intact and proportioned normally. One of the calcarine fissures showed less development on the transcerebellar coronal plane. Extra-cerebral examination revealed facial dysmorphism, including retrognathism, a short nasal bone, and a protuberant philtrum (Supplementary Data, http://links.lww.com/MFM/A66).

Comparative genomic hybridization array (400 kb resolution) found no chromosomal or sub-chromosomal anomalies, but WES identified novel *de novo* variants in the *CSNK2A1* and *KCNQ5* genes, confirmed on Sanger sequencing. *KCNQ5* had a heterozygote nonsense mutation (p.Ser429Arg*fs**8) due to c.1287_1317delinsAGTAGGTGACAG deletion-insertion in exon 10, classified as pathogenic (class 5) according to ACMG classification criteria.[5] *CSNK2A1* had a probably pathogenic substitution c.118C>G (p.Gln40Glu), affecting a conserved ATP-binding loop, and not found in recent genetic databases (gnomAD, ClinVar, HGMD, and LOVD). A multidisciplinary team, including a pediatric neurologist, advised the

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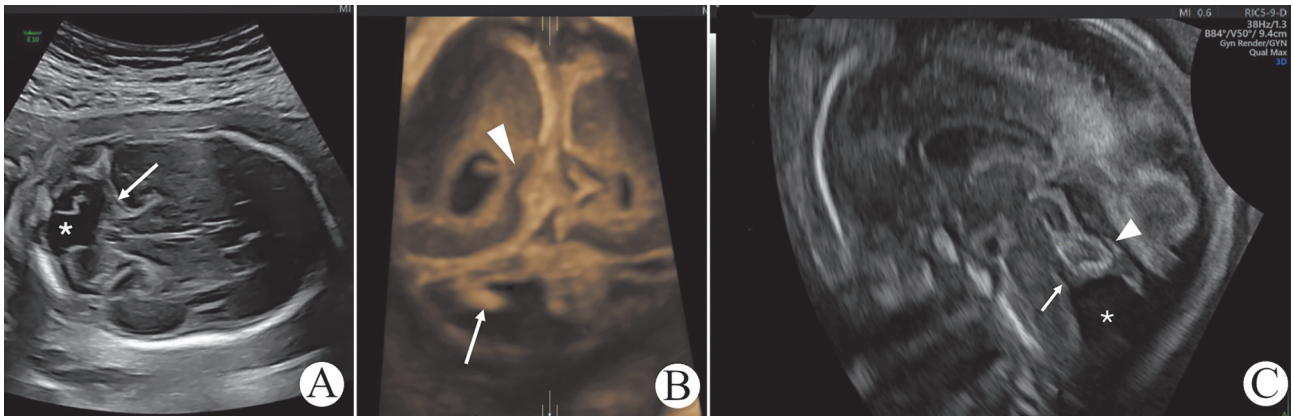

Figure 1. Imaging features of Blake's pouch cyst and associated cerebellar abnormalities. A A two-dimensional ultrasound image of the posterior fossa on the axial plane revealing a communication between the fourth ventricle and the cisterna magna, attributed to a Blake's pouch cyst (indicated by *), accompanied by unilateral cerebellar hypoplasia (highlighted by the arrow). B On the three-dimensional coronal plane, an underdevelopment of the left calcarine sulcus (marked by the arrowhead) and unilateral cerebellar hypoplasia (indicated by the arrow). C A three-dimensional ultrasound image on the midsagittal plane demonstrates partial vermis agenesis and a Blake's pouch cyst (indicated by *), causing upward rotation of the vermis. The fastigium (highlighted by the arrow) and the primary fissure (marked by the arrowhead) are absent.

patient of high neurodevelopmental delay risk and poor prognosis due to cerebral and extra-cerebral abnormalities and genetic findings. The couple chose termination of pregnancy at 26 weeks and 3 days, delivering a 770g fetus without autopsy consent.

As Sanger sequencing of parents' DNA did not detect these variants, the mutations were considered to be *de novo*. The risk of recurrence is low for a future pregnancy, but it is not zero in relation to the possibility of germinal mosaicism.

Recent advance in the accessibility of WES have facilitated the identification of causative genetic variants in the context of fetal malformations. In this case report, WES identified dual novel molecular variants in the *KCNQ5* and *CSNK2A1* genes in a fetus at 23 weeks' gestation, presenting severe growth restriction, posterior fossa malformation, occipital cortical underdevelopment and facial dysmorphism. Mutations in the *CSNK2A1* gene are known to cause OCNDS,[2] while mutations in *KCNQ5* have been associated with various types of epilepsy, sometimes acompanied by intellectual disability, cerebral vasospasm and ischemic stroke.[6,7] The main characteristics of the 30 postnatal cases of OCNDS reported so far include various degrees of developmental delay, epilepsy and facial dysmorphism and nonspecific brain abnormalities on MRI.[2] The main posterior fossa anomaly in our case was unilateral cerebellar hypoplasia (UCH) with partial vermis agenesis. The largest prenatal series of UCH, published in 2014, identified common etiologies: such as genetic disorders, ischemic/hemorrhagic insults, congenital CMV infection, and prenatal drug exposure.[8]

Regarding prenatal counselling, the postnatal prognosis for UCH ranges from asymptomatic to severe, depending on factors such as vermis involvement, the extent of surface loss in the affected hemisphere, associated findings, and the underlying etiology. In our case, the combination of UCH, abnormal cerebellar foliation, partial cerebellar vermis agenesis, Blake's pouch cyst, underdevelopment of the left calcarine sulcus, facial dysmorphism, early growth restriction, and a pathogenic variant in the *CSNK2A1* gene suggested a poor postnatal prognosis. It is plausible that the polymalformative fetal phenotype observed is due to the mutation in *CSNK2A1*, and that the mutation in *KCNQ5* poses a significant risk of inducing an additional neurodevelopmental disorder. Given that *KCNQ5* regulates microvascular tone, it is conceivable that pathogenic variants could reduce cerebellar blood supply, potentially contributing to UCH. However, further observations are needed to confirm or refute this hypothesis.

Funding

None.

Conflicts of Interest

None.

Data Availability

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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