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Postnatal diagnosis of Congenital Cutis Laxa syndrome in a fetus with increased nuchal translucency and ductus venosus agenesis with normal prenatal microarray and Trio-CES

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Objective

Congenital cutis laxa syndrome is an extremely rare and heterogeneous group of inherited connective tissue disorders (estimated incidence of 1 in 1,000,000 births) and it is characterized by redundant and inelastic skin, with premature aging appearance and variable systemic involvement. Both X-linked and autosomal forms of cutis laxa have been reported. We report a case of postnatal diagnosis of cutis laxa syndrome in a fetus with first trimester nuchal translucency above the 99th centile.

Methods

We reviewed a case of postnatal diagnosis of X-linked monogenic form of congenital cutis laxa syndrome by Clinical Exome Sequencing (CES) in a fetus with increased nuchal translucency (>99th centile) and ductus venosus agenesis with normal CGH-microarray and trio-CES without relevant findings in the prenatal assessment.

Results

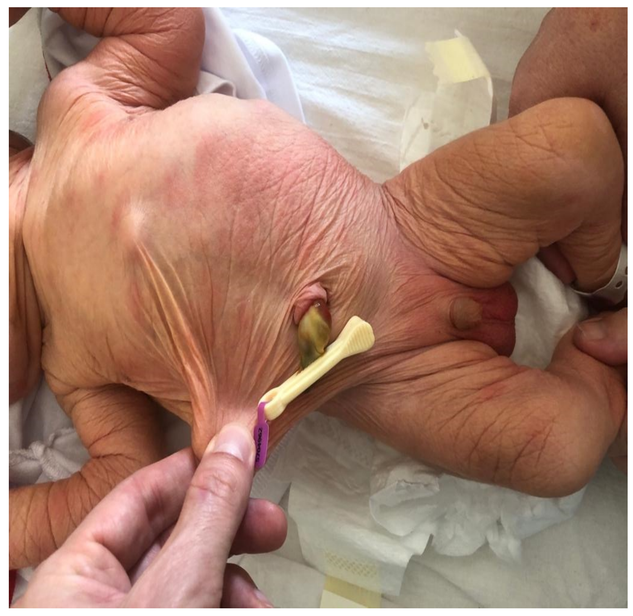
A 42-years-old woman (Gravida 4, Parity 1) attended our department for her routine first trimester ultrasound screening at 12^{+6} weeks of gestation. The scan showed a nuchal translucency of 4.5 mm (above the 99th centile) and a ductus venosus agenesis. The combined aneuploidy screening yielded a 1/3 risk of trisomy 21 and 1/8 for trisomies 18 and 13. A chorionic villous sampling was performed with normal QF-PCR and CGH-array results were documented. A trio-CES was performed without pathological variants related to phenotype were identified.

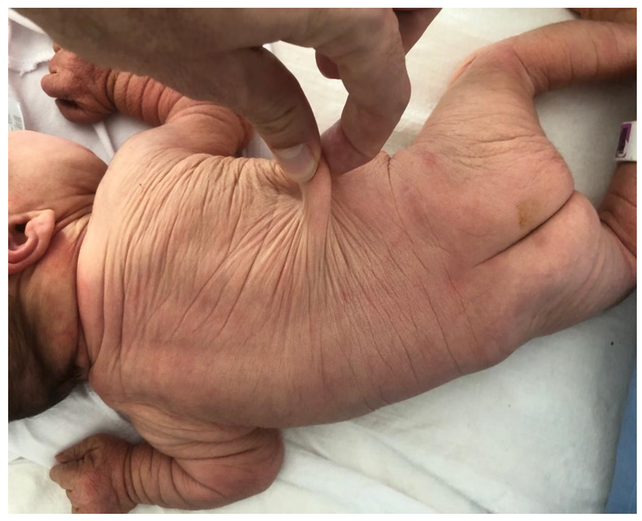
A fetal ecocardiography was performed at 15^{+3} weeks of gestation confirming the ductus venosus agenesis with no other cardiac malformations. At 20^{+6} weeks of gestation the increased nuchal fold persisted (7.2mm) and low suspicion of hypospadias, that was not confirmed. Follow-up scans did not detect any other abnormalities or impaired fetal growth.

At 40^{+1} weeks of gestation the patient woman was admitted for labour induction and delivered by forceps due to a non-reassuring fetal heart rate trace obtaining a male newborn of 3230 g with Apgar score 9-10-10 and normal arterial and venous cord pH (7.18/ 7.26).

The newborn's phenotype was abnormal, with loose, creased and non-elastic skin associated to prominent skin folds areas in the limbs, and the torso. The facial region remained unaffected. A review of the trio-CES considering the postnatal findings, it was identified one variant of unknown significance (VOUS) on gene ATP6AP1 X:153660778 NM_001183.6 cDNA c.530T>C, found in hemizygosity in the newborn, and in heterozygosity in the mother. The candidate variant was reclassified as likely pathogenic mutation and the infant was diagnosed with an X-linked monogenic metabolic disease caused by a mutation in ATP6AP1 gene, which defective proteins and lipid glycosylation processes affect multiple tissues and organs with cutis laxa as one of its manifestations.

Currently, he is 5 months old, the infant is under close multidisciplinary surveillance (geneticists, dermatologists, paediatricians, immunologists and hepatologists) and a month ago he underwent a liver transplant due to severe liver disease.





Conclusion

This case report emphasizes the major limitations associated with CES data interpretation. In our case, the X-linked monogenic metabolic disease was diagnosed postnatally by correlation of the VOUS with the neonatal phenotype. Given that CES is starting to be used prenatally in selected cases, it is essential to establish a shared prenatal database to further understand prenatal phenotypes and genetic variants.