ID: 3873 DOES THE PRENATAL PHENOTYPE OF CHARGE SYNDROME OVERLAP WITH THE POSTNATAL PHENOTYPE?

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CHARGE syndrome is a multiple congenital anomaly syndrome characterized by the variable combination of multiple anomalies, it is a rare disease with an incidence of 1 per 10,000 persons. In 97% of cases it is sporadic or shows an autosomal dominant pattern of inheritance. In most cases it is due to heterozygous mutations in CHD7 (8q12.2) encoding the chromodomain helicase DNA binding protein. Prenatal diagnosis involves ultrasound screening during the second and third trimester for polyhydramnios, CNS, cardiac, genitourinary malformations and ear anomalies.

Purpose

To assess whether the prenatal phenotype of CHARGE syndrome overlaps with the classic phenotype described for this syndrome that includes coloboma, cardiac defect, choanal atresia, growth and developmental delay, genital hypoplasia, and ear anomalies.

Materials and methods: Fetuses with a prenatal clinical exome sequencing performed after a normal QF-PCR and microarray result, during a 5-year period (June 2017 - January 2022) at our center were reviewed.

Results: Three cases of CHARGE syndrome were diagnosed by clinical exome sequencing revealing the same pathogenic variant c.5458C>T, p. Arg1820T in the CHD7 gene:

Case 1: 37-year-old pregnant woman. The anomaly scan at 21+5 weeks identified a moderate ventriculomegaly and a dysgenetic corpus callosum (no splenium identified) with a decreased length.

Case 2: 33-year-old pregnant woman. At a 17+3 weeks scan, a bilateral cleft lip and palate and a cono-truncal cardiac defect were detected. Post-mortem studies after termination of pregnancy identified a ventricular septal defect with aortic end-splitting and confirmed the bilateral cleft lip and palate.

Case 3: 36-year-old pregnant woman. Ultrasound at 32+1 weeks detected a mild bilateral ventriculomegaly of 11.5 mm. Magnetic resonance imaging reported the non-identification of the olfactory grooves. Post-mortem studies after termination found bilateral microtia, ponto-cerebellar hypoplasia and anomalous anterior medullary-pontine junction indentation.

FENOTIP:
- **C**oloboma →80-90%
- **H**eart defects → 75-85%
- **A**tresia choanae → 45-60%
- **R**etrardation of growth// development →~100%
- **G**enital / Urinary Abnormalities→ 50-60%
- **E**ar abnormalities →80-100%
-Cleft lip / cleft palate 25-50%
-Central nervous system malformation: VMG, corneal hypoplasia, Dandy Wlaker malformation → 50%
- Renal abnormalities → 30%

Biard JM, Payrat S, Clapuyt P, Barrea C, Benoit V, Baldin P, Bernard P, Van Grambezen B, Sznajer Y. Antenatal diagnosis of CHARGE syndrome: Prenatal ultrasound findings and crucial role of fetal dysmorphic signs. About a series of 10 cases and review of literature. Eur J Med Genet. 2021 Apr;64(4):104189. doi: 10.1016/j.ejmg.2021.104189. Epub 2021 Mar 2. PMID: 33662639.
Images: https://www.mun-h-center.se/en/research-and-facts/rare-diseases/charge-syndrome/

Conclusions: The fetal phenotype observed for CHARGE syndrome does not overlap with the classic description of CHARGE syndrome, since among the 6 signs classically defining CHARGE syndrome, only a cardiac defect was seen in one of the 3 cases. In the two other fetuses only complex central nervous system anomalies were prenatally observed.