Pre And Post Natal Findings Of A Portuguese Case Of Neu-Laxova

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INTRODUCTION:
Neu-Laxova Syndrome was first described and characterized by Neu in 1971 (4) and later by Laxova (5). Thought to be autosomic recessive (6), multisystemic, the syndrome is characterized by lethal microcephaly and multiple congenital anomalies including central nervous system defects (lissencephaly, cerebellar hypoplasia and hypoplasia of the corticomedullary tracts), facial dimorphism (ocular proptosis, hypertelorism, micrognathia) (1), bone anomalies, joint contractures, ichthyosis, generalized edema and intrauterine growth restriction (IUGR) (1,2,6,7,8,9,10,11). For most affected individual’s, death occurs in the perinatal period or correspond to stillborn and a single case of longer survival has been reported (2). Thus, it is clear that NLS exhibits a spectrum of disease, with varying degrees of phenotypic expression (2). Biallelic pathogenic variants in one of the PHGDH or PSAT1 genes have been identified and associated with NLS (1). NLS caused by either PHGDH or PSAT1 variants is clinically indistinguishable (7).

CASE REPORT:
A non-consanguineous couple was referred to the high-risk obstetric consultation after performing first trimester ultrasound, at 13 weeks of gestation. The fetus presented a crown rump length (CRL) of 68 mm, NT of 2.31 mm, reverse flow in DV, pronounced retrognathism (image 1 + image 2) and hand in claw. Informed consent was obtained for publication of the case.

Clinical Case:
A fetal chromosomal study was proposed and requested a cariotype and an array, through amniocentesis, at 16 weeks and 3 days of gestation. The results obtained were a normal male cariotype, 46, XY and a genomic profile corresponding to a normal male pattern, arr(1-22)x2,(X,Y)x1. Fetal echocardiography was performed at 23 weeks of gestation with a result within the limits of normality (Image 3 + Image 4).

On morphological ultrasonography, performed late at 25 weeks of gestation, due to the couple’s lack of compliance, multiple malformations were visualized and found, including retrognathia (Image 5), claw hands (Image 6 + Image 7), face edema (Image 8), microcephaly (Image 9), cerebellar hypoplasia (Image 10) and IUGR less than 1st percentile (BPD 47 mm, HC 172 mm, AC 161 mm , FL 32 mm, EFW 388g) (Image 11 + Image 12 + Image 13) with normal Doppler study of the umbilical artery (Image 14), middle cerebral artery (Image 15) and right uterine artery (Image 16).
Given the severity of the sonographic findings, the possibility of medical interruption of pregnancy was addressed, which the couple rejected. The need to continue the etiological investigation was discussed in a multidisciplinary meeting with obstetricians and geneticists, and it was decided to perform a Whole Exome Sequencing (WES) through cell culture. The probably pathogenic variant c.1468G>A p.(Val490Met) and the variant of unknown clinical significance c.487C>T p.(Arg163Trprp), both in heterozygous, in the PHGDH gene (chr.1) were found. Pathogenic variants in this gene cause, among other pathologies, Neu-Laxova syndrome type 1 (MIM 256520) of autosomic recessive transmission. The result could indicate a genetic etiology for the clinical picture presented by this fetus, and for this reason a study of the parents was proposed. The study of the family variant in the mother, in peripheral blood, revealed the family variant c.1468G>A p.(Val490Met) in heterozygous in the PHGDH gene, while the other family variant under study in the same gene was
not found. The study of the family variant in the father, in peripheral blood, revealed the family variant c.487C>T p.(Arg163Trp), in heterozygous, in the PHGDH gene. No other family variant under study in the same gene was found.

After the probable diagnosis of NLS, the couple was informed about the fetal prognosis and the possibility of medical interruption of pregnancy was again discussed. The couple chose to continue their pregnancy. Serial ultrasounds were performed to follow up IUGR, maintaining biometrics compatible with growth percentile less than 1th.

At 41 weeks of gestation, the pregnant woman accessed the emergency department of the HDNM to induce labor by late gestational age. Labor proceeded linearly respecting Friedman’s curves with single eutocic live birth. Birth weight was 1585g and Apgar Index (AI) was 3/1/0 at 1st, 5th and 10th minute of life. The neonate presented microcephaly, facial dysmorphia with flattened forehead (Image 17 and 18), prominent nasal bridge (Image 19), hypertelorism (Image 19), micrognathia (Image 18), short neck (Image 18), contracture of the extremities (Image 20), edema and ichthyosis (Image 17). Death was reported fifteen minutes after birth.

DISCUSSION:

Prenatal ultrasound diagnosis of NLS is difficult and requires a high level of suspicion (11), but remains the only modality to identify the condition (2). Although none of the echographic findings are pathognomonic of NLS, the combination of microcephaly, retrognathia, claw hands, general edema, and intrauterine growth restriction should lead to suspicion of these disease. In addition to the prenatal findings, the postnatal macroscopy reported here are consistent with the few reported in literature (12). Results of karyotyping have generally been normal (3). The whole fetal exome sequencing (WES) is essential in the investigation of fetal malformations associated with IUGR when the diagnostic tests of aneuploidy are negative (3). Prenatal diagnosis is key in counseling these couples, both in present pregnancy and in terms of prenatal genetic diagnosis in future pregnancies, as well as a possible explanation for miscarriages (previous and futures).

References

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