Clinical challenges managing a non-immune hydrops with an underlying AARS2 gene mutation.

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OBJECTIVE: Case report on non-immune hydrops related to AARS2 gene mutation.

METHODS: Case Summary and Literature review

RESULTS: G2P1, previous vaginal delivery, BMI 27.4, normal NT, low PAPPA, on aspirin and GAP scans. Normal uterine artery Doppler with normal anatomy scan. First growth scan scheduled at 32 weeks as per current Saving Babies Lives Care Bundle. Blood group A Rhesus positive and no antibodies at booking or 28 weeks bloods.

Multiple episodes of absent fetal movements since 24 weeks. Delay in USS, carried out at 31weeks with extensive fetal hydrops, poor fetal movements, extensive polyhydramnios. Fetal medicine scan showed extensive hydrops, growth >99th centile, abnormal clubbing of both feet, bilateral pleural effusion, pronounced hydrothorax , raised PI in umbilical artery and ductus venosus showed reverse flow in A wave. Limited hand movements, hands showing flexed wrist in a fixed position, normal MCAD. Normal cardiac imaging. Potentially an underlying genetic condition and a poor prognosis was considered a most probably diagnosis and outcome. Invasive testing carried out in tertiary unit. Options of clause E interruption of pregnancy given to patient .Neonatology review and poor outcomes outlined. Options of both active management and comfort care given. Plan was finalized for comfort care if heart rate and breathing did not improve with chest drain and ventilation. ELSCS booked in referring unit.

Difficult delivery of baby during caesarean section due to extent of progressive hydrops at 31 +5 and 4L PPH. 2565 gm male, not responded to resuscitation.

Postmortem examination: bilateral pleural effusion and compression of lungs with a total lung volume of 8.6ml (mean expected at 31 weeks is around 40ml.), widespread hydrops, subcutaneous edema. The lung volume being extremely limited indicates pulmonary hyperplasia. No evidence of aneuploidy on QFPCR test. SNP array normal. Following genetics referral post -natally, pregnant again straightaway. Postnatal debrief extensive and combined with care for subsequent pregnancy.

Urgent trio whole genome sequencing a (WGS) R14 test sent. Came positive for AARS2 gene changes as cause of her last son hydrops, both parents found to be AARS2 carriers. The last child had c.1774C>T, p.Arg592Trp from mother and c.1380_1381 delp. (Val462Profs*23) from dad. This make up 1:4 chance of next baby getting affected. Opted for CVS. The current fetus unaffected with AARS2 related mitochondrial disorder.

CONCLUSION: The alanyl-tRNA synthetase 2 (AARS2) gene encodes the enzyme charging tRNA with alanine in the mitochondria is encoded in alanyl-tRNA synthetase 2 (AARS2) gene. The variants in AARS2 are divided in two separate phenotypes, an autosomal recessive infantile cardiomyopathy which is fatal[1] and a later-onset autosomal recessive leukodystrophy with premature ovarian insufficiency.[2]

A founder variant of European origin, c.1774C>T, p.Arg592Trp, has been reported in a number of patients who presented with lethal infantile cardiomyopathy.[3] Another case report discussed two siblings having the p.Arg592Trp variant, in trans with a frameshift variant, c.647dup, p.Cys218Leufs*6, who presented with lethal pulmonary hypoplasia in the absence of cardiomyopathy(similar to affected baby in case summary), extending the range of recessive AARS2 disorders.[4]

REFERENCES:

1. Taylor RW, Pyle A, Griffin H, Blakely EL, Duff J, He L, Smertenko T, Alston CL, Neeve VC, Best A, et al. 2014. Use of whole-exome sequencing to determine the genetic basis of multiple mitochondrial respiratory chain complex deficiencies. JAMA 312: 68–77. 10.1001/jama.2014.7184

2. Lynch DS, Rodrigues Brandão de Paiva A, Zhang WJ, Bugiardini E, Freua F, Tavares Lucato L, Macedo-Souza LI, Lakshmanan R, Kinsella JA, Merwick A, et al. 2017. Clinical and genetic characterization of leukoencephalopathies in adults. Brain 140: 1204–1211. 10.1093/brain/awx045

3. Euro L, Konovalova S, Asin-Cayuela J, Tulinius M, Griffin H, Horvath R, Taylor RW, Chinnery PF, Schara U, Thorburn DR, et al. 2015. Structural modeling of tissue-specific mitochondrial alanyl-tRNA synthetase (AARS2) defects predicts differential effects on aminoacylation. Front Genet 6: 21 10.3389/fgene.2015.00021

4. Kiraly-Borri C, Jevon G, Ji W, Jeffries L, Ricciardi JL, Konstantino M, Ackerman KG, Lakhani SA. Siblings with lethal primary pulmonary hypoplasia and compound heterozygous variants in the AARS2 gene: further delineation of the phenotypic spectrum. Cold Spring Harb Mol Case Stud. 2019 Jun 3;5(3):a003699. doi: 10.1101/mcs.a003699. PMID: 30819764; PMCID: PMC6549552.