TÍTULO: PRENATAL DIAGNOSIS IN THE ERA OF NEXT GENERATION SEQUENCING: CILIOPATHIES

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Resumo:
Introdução
Primary cilia are immotile microtubule-based structures present on the surface of most cells in vertebrates, act as sensors of extracellular signals and play an important role during tissue development. Therefore, defects in cilia function cause multisystem pathology with a broad spectrum of clinically and genetically overlapping phenotypes. Most syndromic forms of ciliopathies are genetically heterogeneous and for, Bardet-Biedl Syndrome (BBS) and Meckel-Gruber Syndrome (MKS) at least 19 and 11 genes have been identified to date, respectively.

Caso Clínico
We report 3 cases of prenatal clinical presentation of Ciliopathies. Case 1: 37yo female patient, with 12w4d gestational age, non consanguineous couple; 1\textsuperscript{st} trimester ultrasound revealed posterior encephalocele and bilateral multicystic renal dysplasia. Case 2: 36yo female patient, 5\textsuperscript{th} pregnancy of a healthy non consanguineous couple that at 12w3d of gestation the fetus presented with occipital encephalocele, bilateral renal dysplasia and absent urinary bladder. Previous pregnancy was terminated due to fetal ultrasound anomalies. Case 3: 29yo female patient, healthy non consanguineous couple, previous pregnancy terminated due to fetal malformations (micrognathia, polydactyly, renal dysplasia and cardiac defect) with normal microarray. Current pregnancy with normal 1\textsuperscript{st} trimester ultrasound and screening and at 18w2d of gestation the kidneys showed poor corticomedullary differentiation and polydactyly. Invasive prenatal testing was performed in the 3 cases. The molecular diagnosis was established by multigene NGS panel.
The MKS gene panel performed in both case 1 and case 2 revealed the presence of a compound heterozygote and homozygote for TMEM67 pathogenic variants, respectively. In case 3 a Ciliopathy gene panel analysis revealed the presence of two heterozygous pathogenic variants in the BBS12 gene. In all cases termination of pregnancy was requested. Fetal anatomopathological examination confirmed the prenatal findings in the 3 clinical cases.

Conclusões
Ciliopathies are rarely recognised in the fetus but can be appreciated by observing subtle imaging findings in kidneys, brain and extremities. Recognition of one characteristic finding should prompt search for corroborative abnormalities. Since ciliopathies are predominantly autosomal recessive with a recurrence risk of 25%, it is important to recognise antenatal findings in order to establish molecular diagnosis allowing proper genetic counseling to the parents.

Palavras Chave: Ciliopathies; Bardet-Biedl; Prenatal diagnosis