Clinical and genetic characterization of a cohort of Brazilian patients with congenital ataxias

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Congenital ataxia is a heterogeneous group of disorders characterized by hypotonia and developmental motor delay, followed by cerebellar ataxia in early childhood. The course of the disease is mainly non-progressive, and a lot of patients have been mistakenly diagnosed with ataxia cerebral palsy.
Despite the wide development of next generation sequence, a lot of patients with congenital ataxia remains without a genetic diagnosis.
OBJECTIVES: To analyze patients with congenital ataxia and characterize the clinical, neuroimaging, and genetics features involved.
METHODS: We recruited 29 patients with congenital cerebellar ataxia from the Ataxia Unit, in Federal University of São Paulo (UNIFESP). Neurological evaluation, brain magnetic resonance imaging (MRI), and Whole-exome sequencing (WES) analysis were done in all patients. We excluded patients whose ataxia was associated with secondary cerebellar ataxia.
RESULTS: Apparent intellectual impairment was identified in all patients. Abnormal ocular external ocular movements (14/29) and epilepsy (7/29) were common factors associated with cerebellar dysfunction. Global cerebellar hypoplasia was the most frequent neuroimaging pattern (58.62%). It was identified pathogenic variants in 48,27% of patients, involving twelve genes (*ALDH5A1*, *CACNA1A*, *EXOSC3*, *MME*, *ITPR1*, *KIF1A*, *STXBP1*, *SNX14*, *SPTBN2*, *TMEM240*, *TUBB4A*, *THG1L*), with an additional 31,03% with variants of uncertain significance involving nine genes (*BRF1*, *CACNA1G*, *CCD2DA*, *CWF19L1*, *ITPR1*, *PEX10*, *SCN2A1*, *STXBP1*, *TMEM240*).
Conclusions: Our study reinforces the genetic heterogeneity of congenitais ataxias and contributes to its genetic unraveling. WES was pointed as an effective diagnostic tool, and highlighted heterozygous inheritance (*de novo* mutations) were as an important genetic pattern in congenital ataxia.