P-069 - NEURONAL CEROID-LIPOFUSCINOSES IN CHILDREN: IMPACT OF A NEXT-GENERATION SEQUENCING PANEL FOR DIAGNOSING

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INTRODUCTION: The neuronal ceroid lipofuscinoses (NCL) are a group of neurodegenerative disorders characterized by epilepsy, visual loss, myoclonus, and progressive mental and motor deterioration. In recent years, molecular genetics has emerged as a useful tool for enhancing NCL subtype classification (CLN1 to CLN14), recognizing more than 430 mutations in 13 genes.

OBJECTIVE: Molecular characterization of children with a presumptive diagnosis of NCL at an Argentinean public hospital. PATIENTS AND METHODS: 4 late-infantile NCL (INCL) and 2 juvenile NCL (JNCL) pediatric patients were selected. Clinical data and complementary studies were analyzed. A next-generation sequencing panel including the seven most frequent NCL-related genes was designed. The 966 base deletion in the CLN3 gene was analyzed by allele-specific PCR in one case.

RESULTS: In the INCL group the mean age at onset was 3 years. The children presented with seizures (3) or cognitive decline (1). Two cases with classical INCL showed reduced activity of tripeptidyl-peptidase 1; both carried the same homozygous variant (p.Asp276Val) on the TPP1 gene (CLN2). A curvilinear pattern was identified on skin electron microscopy (EM) in one of them. Two cases with variant INCL disclosed compound heterozygous mutations in the MFSD8 gene (CLN7). Skin EM showed a curvilinear pattern in one, while it was normal in the other patient. Both patients with JNCL presented with visual impairment at a mean age of 6 years. They developed seizures and cognitive decline. Biallelic variants in the CLN3 gene were confirmed in one of them, who showed vacuolated lymphocytes and a mixed histopathological pattern on skin EM. Finally, in the second patient, biallelic variants were identified in the CLN5 gene.

CONCLUSION: This new methodological approach allowed to confirm the diagnosis in all cases. These results highlight the impact of an NGS panel as an efficient and non-invasive tool for accurate and early NCL diagnosis. Recognition of the molecular defects improves disease classification, therapeutic strategy, and genetic counseling, optimizing the comprehensive management of these patients.