**P-074 - MILD LATE INFANTILE MULTIPLE SULFATASE DEFICIENCY: CLINICAL DESCRIPTION AND PRELIMINARY FUNCTIONAL ANALYSIS OF TWO BRAZILIAN CASES**

Silva TO\(^1\), De Souza CFM\(^1\), Brusius-Facchin AC\(^1\), Michelin-Tirelli K\(^1\), Burin MG\(^1\), Giugliani R\(^2\), Schlotawa L\(^3\), Dierks T\(^4\), Radhakrishnan K\(^4\), Schwartz IVD\(^2\)

\(^1\) Hospital de Clínicas de Porto Alegre. \(^2\) Universidade Federal do Rio Grande do Sul. \(^3\) University of Göttingen. \(^4\) University of Bielefeld. Porto Alegre - Brazil. thiagooliveira272@gmail.com

**INTRODUCTION:** Multiple Sulfatase Deficiency (MSD) is a rare lysosomal disease caused by biallelic loss-of-function mutations in the SUMF1 gene, which encodes the formylglycine-generating enzyme (FGE), involved in the post-translational activation of all sulfatases. The clinical presentation includes symptoms of the individual sulfatase deficiency disorders, with variable severity. **OBJECTIVES:** to describe and perform functional analysis in two mild MSD cases. **MATERIALS AND METHODS:** case reports and gene expression plasmid construction. **RESULTS:** Patient 1 was referred to the medical geneticist at 17 months of age, presenting mild developmental delay and minimal dysmorphic features (flat face, bifid uvula, long fingers), with parental consanguinity and one male sibling prematurely deceased. Initial workup (neuroimaging and basic metabolic screening; not including tests for lysosomal diseases) had normal results. At subsequent evaluations, dry skin was observed. After a follow-up break, she returned when 8 years old, presenting neurological regression, aggressive behavior, ichthyosis and short stature. Neuroimaging showed dysgenesis of the corpus callosum, white matter hyperintensities and cerebral-cerebellar atrophy. Analysis of urinary glycosaminoglycans was requested and presented abnormal results, leading to enzyme assays, which confirmed MSD. Sanger sequencing detected a previously reported variant c.1A>G (p.Met1Val) in SUMF1, in homozygous state. Our biochemical studies indicated that, although p.Met1Val is as active as the wild type (WT), a reduced expression level (≤ 20% of WT) contributes to the loss-of-function that results in MSD. Patient 2 was referred to the medical geneticist at 10 years of age, presenting mild developmental delay, hepatomegaly and hypercholesterolemia since infancy. No conclusive diagnosis at the previous investigation. We found deficient activity of Arylsulfatase A and other sulfatases. A novel pathogenic variant p.Arg224Gln (c.671G>A) in SUMF1 was detected by next-generation sequencing, in heterozygosis. In-silico analysis and 3-D modelling indicate that this mutation is pathogenic. Our biochemical findings revealed that mutation-induced misfolding and reduced intracellular stability of FGE contribute to its loss-of-function. The second variant has not been detected yet. **CONCLUSIONS:** Those two cases demonstrate how MSD diagnosis may be a real challenge, mainly when presentation is mild, and the importance of a comprehensive investigation. RNA studies from these cases are ongoing.