ESID-0638 FLH Type 5 Caused by a Novel Mutation in STXBP2 Gene: An Unusual Cause of Failure to Thrive and Diarrhea in Infancy

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Familial hemophagocytic lymphohistiocytosis (FHL) is caused by genetic defects in cytotoxic granule components or their fusion machinery, leading to impaired natural killer cell and/or T lymphocyte degranulation and/or cytotoxicity.

STXBP2, also known as MUNC18-2, has recently been identified as the disease-causing gene in FHL type 5 (FHL-5). We represent a 9-month old boy with a previous history of recurrent infections, failure to thrive and chronic diarrhea and an acute presentation of irritability, fever, hepatosplenomegaly, ascites, pancytopenia, low fibrinogen, elevated ferritin and triglycerides and increased soluble CD25 (24200 pg/ml) compatible with hemophagocytic lymphohistiocytosis (HLH). No haemophagocytosis was seen on bone marrow and brain MRI showed demyelinisation of the white matter. Further diagnostic work-up revealed slightly decreased NK cell activity and normal expression of perforin. According to the history of failure to thrive, intractable diarrhea, hypogammaglobulinemia and HLH, a mutation analysis of *STXBP2* and *UNC13D* genes was performed: two mutations were identified in STXBP2 gene: 902+5G>A mutation in intron10 affecting RNA splicing and a novel mutation c.421 del G in exon 6 (p.Glu141ArgfsX68) leading to a frame shift. Treatment was started following HLH-2004 protocol and finally, the patient underwent hematopoietic stem cell transplantation (HSCT) with good immunological response. However, diarrhea continues requiring parenteral nutrition. FLH-5 should be considered in the differential diagnosis of a child presenting with HLH in a context of chronic diarrhea and failure to thrive. In FLH-5, partial conservation of NK cell function can be observed, as is seen in our proband.