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Evans syndrome, immunodeficiency and phenotypic heterogeneity due to SASH3 germline loss-of-function mutations in children

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Einleitung: "Evans syndrome (ES)" describes a heterogeneous group of benign hematologic conditions, defined by two or more autoimmune cytopenias, due to mostly unknown pathogenic mechanisms. However, ES may represent the initial disease in patients with inborn errors of immunity (IEIs), and pathogenic variants in CTLA4, STAT3, TNFRSF6, PIK3CD, and KRAS have been identified in this context. Loss-of-function mutations in SASH3, which encodes a signalling adapter protein in lymphocytes, have recently been reported as a novel IEI entity in four patients with X-linked combined immunodeficiency with immune dysregulation including immune cytopenias.
Patienten und Methoden: We studied a now 16-year-old patient with ES and his 8-year old brother, and performed whole exome sequencing, deep clinical phenotyping and immunophenotyping. We further investigated T cell receptor signalling of isolated patient and healthy donor T-cells. This study aimed to dissect aberrant immune cell functionality in SASH3-deficient patients to enhance the understanding of pathogenic mechanisms in ES.
Ergebnisse: We discovered a germline nonsense variant in SASH3 (c.862C>T;p.Arg288Ter) in our index patient. The maternally inherited variant was also identified in his yet asymptomatic brother. This variant was described in two patients in the discovery cohort of SASH3 deficiency as a novel type of IEI. Our patient initially presented with AIHA at the age of 8 years, later developed ITP and suffered from a severe SARS-COV2 infection. Immune phenotyping showed transient CD4+ T- and B-cell lymphopenia and reduced T-cell proliferation upon PHA and SEB stimulation. Furthermore, the patient had hypogammaglobulinemia, and 'transitory CD21 low B-cells' were significantly increased, reflecting impaired lymphocyte maturation possibly causing the autoreactive phenotype of the disease. Interestingly, the patient developed large haemorrhagic splenic cysts during ITP associated bleeding diathesis, and thus underwent splenectomy, which led to a complete remission of ES. Divergently, the now 8-year-old brother carrying the same variant has no clinically apparent phenotype until now.
Schlussfolgerungen/Diskussion: We present the 5th and 6th patient with hemizygous variants in SASH3. Thus, this study expands the clinical phenotype and suggests marked phenotypic heterogeneity in patients bearing the same mutation.