60. Jahrestagung
der Österreichischen Gesellschaft
für Kinder- und Jugendheilkunde
Altes AKH Wien 6. bis 8. Oktober 2022
AUF DEN SCHULTERN
VON RIESEN
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ÖGKJ

P01-03

ORAL FUCOSE REPLACEMENT THERAPY IN LEUKOCYTE ADHESION DEFICIENCY TYPE II/SLC35C1 CONGENITAL DISORDER OF GLYSOSYLATION (CDG) SYNDROME – LESSONS FROM A SINGLE CASE STUDY

Steurer L.[1], Konstantopoulou V.[2], Janecke A.[3], Repa A.[4], Grabmeier-Pfistershammer K.[5], Körmöczi G.[6], Schönbacher M.[6], Körmöczi U.[7], Kratzer B.[7], Pickl W.[7], Förster-Waldl E.[8], Vodopiutz J.[9]

[1]Division of Neonatology, Pediatric Intensive Care & Neuropediatrics, Department of Pediatric and Adolescent Medicine, Medical University of Vienna, 1090 Vienna, Austria; Vienna Bone and Growth Center and ERN BOND
[2]Division of Pediatric Pulmonology, Allergology and Endocrinology, Department of Pediatrics and Adolescent Medicine, Comprehensive Center for Pediatrics, Medical University of Vienna, 1090 Vienna, Austria
[3]Department of Pediatrics I and Division of Human Genetics, Medical University of Innsbruck, 6020 Innsbruck, Austria
[4]Division of Neonatology, Pediatric Intensive Care & Neuropediatrics, Department of Pediatric and Adolescent Medicine, Medical University of Vienna, 1090 Vienna, Austria
[5]Institute of Immunology, Centre of Pathophysiology, Infectiology and Immunology, Medical University of Vienna, 1090 Vienna, Austria
[6]Department of Blood Group Serology and Transfusion Medicine, Medical University Vienna, 1090 Vienna, Austria
[7]Institute of Immunology, Centre of Pathophysiology, Infectiology and Immunology, Medical University of Vienna, 1090 Vienna, Austria
[8]Division of Neonatology, Pediatric Intensive Care & Neuropediatrics, Department of Pediatric and Adolescent Medicine, Medical University of Vienna, 1090 Vienna, Austria; Center for Congenital Immunodeficiencies with Viennese Jeffrey Modell Diagnostic and
[9]Division of Pediatric Pulmonology, Allergology and Endocrinology, Department of Pediatrics and Adolescent Medicine, Comprehensive Center for Pediatrics, Medical University of Vienna, 1090 Vienna, Austria, Vienna Bone and Growth Center and ERN BOND

Einleitung: Leukocyte adhesion deficiency type II (LAD II), also known as SLC35C1-CDG, is a rare autosomal recessive inborn error of metabolism and of immunity caused by biallelic mutations in the Golgi transporter gene for GDP-fucose (SLC35C1) resulting in impaired generation of fucosylated glycans including CD15s, required for selectin binding. The disease is clinically characterized by leukocytosis, primary immunodeficiency with recurrent bacterial infections, short stature, facial dysmorphism and neurocognitive deficits. Oral fucose therapy was shown to improve the clinical course in some yet not all LAD II patients.
Patienten und Methoden: Herein, we report the case of a girl of Syrian consanguineous parents who presented with intrauterine growth retardation (IUGR), hypoplastic pulmonary arteries, muscular hypotonia, massive leukocytosis (> 60 G/L) with severe febrile bacterial infections, Bombay blood group phenotype and dysmorphic features. Immunological workup revealed a complete lack of CD15s expression on granulocytes. Exome sequencing revealed a novel homozygous variant in SLC35C1: NM_018389.4:c.391_393del(p.Asn131del) which confirmed the diagnosis of LAD II.
Next, we attempted to overcome the apparent Golgi enzyme defect by amplifying a scavenger pathway. For that purpose, the patient was treated with increasing doses of food-grade L-fucose. The initial dose of 100 mg/kg/day was increased by weekly doubling to a maximum dose of 1500 mg/kg/day.
Ergebnisse: Already 7 days after treatment initiation leukocyte counts significantly decreased and granulocytes started to express CD15s. Moreover, the functional activity of the patients' granulocytes, evaluated as PMA-induced respiratory burst activity, clearly improved. Antibiotic prophylaxis was discontinued. Additionally, there was a marked improvement of vigilance and muscular hypotonia, as well as growth within weeks. Neurodevelopmental improvement was dynamically measured using appropriate scores. No side effects were noted, especially no signs of hypoglycemia or hemolysis.
Schlussfolgerungen/Diskussion: LAD II is a rare inborn error of metabolism which might be potentially treatable with oral fucose therapy. Early diagnosis and a standardized monitoring of treatment outcome is important to evaluate oral fucose therapy in LAD II.