Role of chymotrypsin C (CTRC) mutations in idiopathic recurrent acute and chronic pancreatitis in children

Lásztity N. [1], Párniczky A.[1], Mosztbacher D. [2], Tóth A., Andorka Cs. [3], Veres G. [3], Czelecz J. [4], Szmola R. [5], Németh B. [6], Balázs A. [6], Hegyi E. [6], Hritz I. [6], Sahin-Tóth M. [7], Hegyi P. [6, 8]

[1]*Heim Pal Children's Hospital, Budapest, Hungary,* [2]*Children's County Hospital Tolna, János Balassa Hospital, Szekszárd, Hungary,* [3]*University of Szeged, Faculty of Medicine, Hungary, Semmelweis University, I. Department of Pediatrics, Hungary,* [4]*Bethesda Children's Hospital, Budapest, Hungary,* [5]*Department of Interventional Gastroenterology, National Institute of Oncology, Budapest, Hungary,* [6]*First Department of Medicine, University of Szeged, Hungary,* [7]*Department of Molecular and Cell Biology, Boston University Henry M. Goldman School of Dental Medicine, Boston, United States,* [8]*Hungarian Academy of Sciences, University of Szeged, Mon, Hungary*

Introduction: Children with idiopathic pancreatitis ofen carry one or more mutations in several disease-associated genes. It has been shown that loss-of-function alterations in chymotrypsin C (CTRC) predispose to pancreatitis by diminishing its protective trypsin-degrading activity.

Aims: The aim of this study was to investigate the incidence of CTRC mutations, their association with PRSS1, SPINK1and CFTR mutations and their effect on the age of onset in idiopathic pancreatitis in children.

Patients & methods: The national registry of the Hungarian Pancreatic Study Group (HPSG) contains 43 children. Idiopathic pancreatitis was found in 26/43 children,12/26 of them had genetic testing performed.Blood DNA was isolated from all patients. Mutations were detected in CTRC, the cationic trypsinogen gene (PRSS1), the serine protease inhibitor Kazal type 1 gene (SPINK1)and the cystic fibrosis transmembrane conductance regulator gene (CFTR) by direct DNA sequencing.

Results: 58% (7/12) of children had CTRC mutations.Four patients were homozygous and 3 patients heterozygous for the p.G60G mutation. 43% (3/7) of the patients having CTRC mutations had additional mutations in different genes. These included mutations in the CFTR gene (p.F508delta heterozygous), the SPINK1 gene (p.N34S heterozygous) and the PRSS1 gene (p.R122H heterozygous).Patients having two mutations had earlier disease onset (5.7 vs. 8 years), more attacks (12.6 vs. 5.3) and earlier development of chronic pancreatitis (9 vs 13.8 years) than patients with only a single mutation.

Conclusion: CTRC mutations are often detected in children with idiopathic pancreatitis and seem to cause the disease in combination with other genetic risk factors.Age of onset appears to be earlier in patients carrying multiple mutations in different risk genes.