Prevalence of monogenic obesity among Polish children and adolescents with severe obesity – biochemical and genetic study of leptin-proopiomelanocortin pathway – Polish-German Study

The obesity epidemic has become important medical and socioeconomic issue in many countries as excessive body weight is the leading cause of increased morbidity and mortality. The leading cause of obesity is reduced daily physical activity with increased calories consumption enhanced by polygenic background. However, there is a group of patients in whom the mutation in the single gene can lead to excessive body weight (monogenic obesity). This group is usually characterized by extreme appetite and severe obesity with the origin before the age of 6 years (severe early onset obesity, SEOO). In subjects with SEOO, depending of country, population studied, ethnicity and number of genes tested, the prevalence of monogenic obesity could vary between 3-10% of cases. Additionally, population-specific mutations in obesity-related genes exist. Nowadays mutations in at least 50 genes are known to be related to monogenic obesity, and many others are tested. Based on the rarity of monogenic gene variants as the cause of obesity the question has to be posed whether there is a justification to search for them. Aside from purely scientific reasons - finding new, population-specific mutations related to SEOO, the justification is given by the fact that during the past years mutation-specific treatments have been developed, e.g. leptin deficiency can be treated by administration of recombinant human leptin. Unfortunately there is no data about the prevalence of severe obesity in Polish children as well as about the prevalence of monogenic obesity in Polish SEOO children. If we assume that in Poland, as in Czech Republic, there is 2.2% of children with severe obesity and the prevalence of monogenic obesity among them we estimate at the level of 3%, it means that about 4500 children in Poland can be obese due to the mutation in a single gene. In some of them, more than lifestyle intervention and diet can be offered, and specific treatment can be used.

The primary aim of the project is to establish the Polish database of severely obese children and adolescents, to characterize them clinically and biochemically and to evaluate the prevalence of monogenic forms of obesity in this cohort. The secondary project aim is to identify new population-specific mutations in obesity-related genes in severely obese Polish children and adolescents.

The first two objectives were partly met between 2015 and 2019 when Polish-German consortium was established to implement the “Early-onset Obesity and Leptin – German-Polish Study (EOL-GPS)” project. In February 2020 our main findings were published (J Pediatr Endocrinol Metab. 2020 Feb 25;33(2):255-263. doi: 10.1515/jpem-2019-0469). In order to further explore this important topic the Polish-German consortium decided to continue its cooperation. The current study will be the first to focus on monogenic obesity in SEOO Polish children, to establish prevalence of the most common monogenic lesions as a cause of severe obesity and to identify new mutations in obesity-related genes, specific for the Polish population.

In this population study, we plan to recruit 500 children (1-18 years of age) with SEOO defined according to their body mass index (BMI). The patients will be recruited in four Polish centers of Pediatric Endocrinology (Katowice, Cracow, Rzeszow, Szczecin) from inpatient and outpatient departments. In each patient we are going to take the medical history regarding the obesity duration in the patient and obesity and its complication existence in the family. Next the questionnaire regarding the symptoms characteristic for specific mutations, which we are going to test, will be performed. Extreme appetite will be assessed on the basis on age-specific questionnaires (CEBQ - Children’s Eating Behavior Questionnaire by Wardle for children below the age of 8 years, TFEQ - Three-Factor Eating Questionnaire – for children above 8 years of age)**.** The physical examination with weight, height, head and waist circumference measurement will be performed, basic biochemical and hormonal parameters as well as the concentration of total leptin and bioactive leptin will be measured. Finally genetic analysis will be done using Next Generation Sequencing (NGS) with sequencing libraries prepared to include 11 target genes (*LEP, LEPR, MC4R, SIM1, KSR1, POMC, PCSK1, NTRK2, MRAP2, SH2B1, BDNF*), in addition further analysis of other, less frequent, obesity-related genes (*UCP1, UCP3, CARTPT, DYRK1B, NROB2, PCSK2, PPARG, PPP1R3A, PPARGC1A, CCK, SLC2A4, TUB, ADCY3, SREBF1, ADRB2, ADRB3, AGRP, MC3R, ENPP1, PPARGC1B, PYY, SDC3, ADIPOQ, NAMPT, CFD, RETN, NPY, ADD1, PTPN1, IRS-1, GHRL, NEGR1, GIPR, TMEM18, FTO, SLC22A1*) will be done. The NGS findings will be confirmed with the use of classic sequencing (the Sanger's method). Clinical, biochemical and genetic results will be analysed and the conclusions will be drawn. In the future the pathogenicity of new mutations in obesity-related genes identified in our cohort is planned to be confirmed by functional testing in vitro.