Outline concept of paediatric and genetic research in the Czech Republic for the period 2015-2020

The prenatal period and childhood belong to the most developmentally rapid and thus important biological periods of human life. During prenatal development broad and to a certain degree permanent epigenetic modifications are being established, thereby affecting multiple genes. The epigenetic modifications are due to the effect of maternal milieu on the embryo and fetus. A large number or severe diseases, which are both due to genetic and exogenous factors, and which contribute to substantial morbidity and mortality in childhood and later during adulthood, commence within early childhood. Therefore, the prenatal period and early childhood have a defining impact on the lifelong health of an individual, hence, medical research carried out in this period may have a significant role for the well being of future generations. Finally, development in childhood comprises not only "biology", but also psychosocial development, which together could markedly influence health later during life.

The life of a child and their health status is particularly threatened in prenatal, perinatal or early postnatal periods. Study and analysis of mechanisms, which lead to the development of serious diseases in early childhood, new therapeutic modalities and preventive measures, including screening, belong to core aims of medical research in this age period.

Although a small part of rare diseases could manifest in adulthood, their majority becomes clinically apparent in childhood. A sizeable part of these disorders is amenable to preventive and therapeutic interventions but early diagnosis and analysis of pathogenic mechanisms together with new therapies are very important topics. Rare diseases with a strong genetic component serve as optimal models for the analysis of chronic multi-factorial diseases in adulthood (i.e. monogenic rare forms of diabetes serve as models for diabetes type 1 and type 2, or cystic fibrosis for COPD). Rare diseases are defined by the European Commission as those affecting less than 5 in 10,000 individuals in the general population (EC 141/2000). Approximately 90% of all rare diseases have a defined genetic component and comprise for instance inborn errors of metabolism, rare cancers in children and adults, some infections, neurological, autoimmune, endocrine disorders as catalogued by the European portal – Orpha.net. Rare diseases consist of more than 7000 clinical entities. Despite their individually low prevalence they together constitute serious medical and socio-economic problem. It is estimated that about 6% of the EU populations is affected by one of these diseases. The overall number of rare diseases is not finite and with the gradual development of novel technologies, including for instance the next generation sequencing new clinical entities are being defined. Nevertheless, detection of genes and pathogenic mutations in a new disease research work only starts, whereby elucidation of novel pathogenic mechanisms requires genomics, metabolomics, proteomics, molecular and cell biology, including animal models. For untreatable rare diseases with a genetic component, development of preimplantation and prenatal diagnosis, which render effective primary and/or secondary prevention, is instrumental in affected families.
Patients with rare diseases do not have equitable access to diagnostics and care due to the limited number of experts, unspecific initial symptoms of their disease resembling common conditions, as well as, limited therapies (e.g. due to small market populations for the pharmaceutical companies or limited research in a confined domain). These shortcomings are one of the main reasons why the Czech government adopted the "National strategy for rare diseases for the period 2010-2020" based on Government Resolution n. 466 from 14.6.2010 and the „National action plan for rare diseases for the period 2012-2014" based on Government Resolution n. 633 from 29.8.2012). Both domestic resolutions reflect the EU

Council Recommendation on a field of action in rare diseases adopted during the Czech Presidency to the Council on June 8th, 2009 (2009/C151/02)", where research into rare disorders is clearly stipulated.

Although the substantial decrease in the neonatal mortality places the Czech Republic amongst the most advanced countries, the increasing number of children with low birth weight (from 5% 25 years ago to current 8.5%), in particular increase of extremely immature newborns, brought additional adaptation problems that necessitate pathogenic and therapeutic studies. The proportion of newborns surviving different birth defects and/or inherited conditions due to medical advances is increasing. Therefore, study of chronic diseases commencing in early childhood, including related negative social impact renders new research avenues. Moreover, nutritional issues of the infant period to the growth acceleration in adolescence also belong to key issues, impacting upon adulthood. Novel evidence suggests that many chronic diseases in adulthood already start in early childhood including cardiovascular disorders or gradual increase of allergic, autoimmune or metabolic disorders which influence morbidity and mortality in adults. In summary, without modern scientific approaches it will not be possible to improve the overall health status of children and adults in our country.

Finally, recently we have been witnessing increase in psychosocial and psychiatric disorders not only in adolescence but also in pre-school age period, termed "new morbidity in childhood". In this regard clinical pharmacology and pharmacotherapy are important topics.

Key aims:

The main aim of the research in this area is deepening of our understanding of the pathogenesis and pathophysiology of inborn disorders which manifest in prenatal period or in early childhood, including the long term consequences of the low birth weight, chronic diseases in childhood and rare diseases by implementation of novel diagnostic strategies. Outcomes of basic science research will be translated directly into clinical practice, applied to the development of novel diagnostic methods and algorithms, new therapeutic and preventive measures, including prenatal and preimplantation diagnostics.

The main priority is elucidation of diseases of unknown etiology, by molecular, biochemical and cellular mechanisms in defined rare diseases as a prerequisite for novel diagnostic strategies and therapeutic interventions. An additional priority is focused on phenotype ontology, epidemiology, methods for early prevention, screening and cost of illness studies in such diseases.

Secondary aims:

Study of the impact of genetic and non-genetic factors which are influencing the pathogenesis and pathophysiology of severe diseases in childhood;
development of novel diagnostic methods for chronic diseases in childhood;
establishment of new preventive measures and therapeutic interventions for the improvement of the quality of life in chronically ill children.