Sessie: from MODY to hyperinsulinism

MODY and Mitochondrial diabetes: diseases with a genetic defect leading to beta cell dysfunction

J.A. (Ton) Maassen, dept of Molecular Cell Biology, LUMC and dept of Endocrinology, VU-MC, Monique Losekoot, dept. of Human Genetics, LUMC

A complex interplay between insulin secretion and insulin action contributes to maintenance of proper glucose homeostasis. Diabetes emerges in those cases in which insulin secretion is inadequate to meet the demand for insulin. Diabetes is a heterogeneous collection of diseases with contributions of life style factors and genetic predisposition in setting the individual risk for developing diabetes.

In a few % of cases, diabetes inherits as monogenetic disease with high penetrance. The diabetic subtypes involved are the various forms of Maturity Onset Diabetes of the Young. Currently 7 different forms of MODY have been identified with mutations in different genes belonging to the family of transcription factors. The disease shows dominant inheritance with high penetrance. Impaired insulin secretion is a main factor in the pathogenesis of the disease. In the Netherlands, we have identified gene defects in approximately 100 MODY patients. In approximately 60% of cases, MODY 3 mutations are found; the remaining cases are predominantly MODY-2 and MODY-1.

Another form of diabetes with monogenic involvement is Maternally Inherited Diabetes and Deafness (MIDD) due to mutations in the tRNA(Leu, UUR) gene in mitochondrial DNA. This mutation shows strict maternal inheritance with 90% penetrance . Also in this form of diabetes insulin secretion gets impaired.

Genetic diagnosis has implications for improvement of therapeutic intervention. This aspect will be discussed.

session 6