Best Practice & Research Clinical Endocrinology & Metabolism
Vol. 22, No. 1, pp. 17–40, 2008
doi:10.1016/j.beem.2007.08.003
available online at http://www.sciencedirect.com

2

Neonatal hyperglycaemia and abnormal development of the pancreas

Isabelle Flechtner MD, MSc
Pediatric Endocrinologist
Clinique des Maladies du Développement, Unité d'Endocrinologie, Diabétologie et Gynécologie Pédiatrique, Hôpital Necker-Enfants Malades, Paris, France

Martine Vaxillaire Dpharm, PhD
Researcher in the Field of Genetics
Centre National de la Recherche Scientifique UMR 8090, Institute of Biology and Pasteur Institute, Lille, France

Hélène Cavé Dpharm, PhD
Biochemist Involved in the Diagnosis of Genetic Disorders
Genetic biochemistry, Hôpital Robert Debré, Paris, France

Raphael Scharfmann PhD
Researcher in Developmental Biology
Unité INSERM U845, University Paris V, Paris, France

Philippe Froguel MD, PhD
Geneticist, Professor of Genetics
Genetic biochemistry, Hôpital Robert Debré, Paris, France
Imperial College, Hammersmith Hospital (PF), London, UK

Michel Polak* MD, PhD
Pediatric Endocrinologist, Professor
Clinique des Maladies du Développement, Unité d'Endocrinologie, Diabétologie et Gynécologie Pédiatrique, Hôpital Necker-Enfants Malades, 149 rue de Sèvres, Paris, France
Unité INSERM U845, University Paris V, Paris, France

* Corresponding author. Tel.: +33 1 44 49 48 02; Fax: +33 1 44 38 16 48.
E-mail address: michel.polak@nck.aphp.fr (M. Polak).

1521-690X/$ - see front matter

Transient and permanent neonatal diabetes mellitus (TNDM and PNDM) are rare conditions occurring in around 1 per 300,000 live births. In TNDM, growth-retarded infants develop diabetes in the first few weeks of life, only to go into remission after a few months with possible relapse to permanent diabetes usually around adolescence or in adulthood. In PNDM, insulin secretory failure occurs in the late fetal or early postnatal period. The very recently elucidated mutations in *KCNJ11* and *ABCC8* genes, encoding the Kir6.2 and SUR1 subunits of the pancreatic K_{ATP} channel involved in regulation of insulin secretion, account for a third to a half of the PNDM cases. Molecular analysis of chromosome 6 anomalies and the *KCNJ11* and *ABCC8* genes encoding Kir6.2 and SUR1 provides a tool for distinguishing transient from permanent neonatal diabetes mellitus in the neonatal period. Some patients (those with mutations in *KCNJ11* and *ABCC8*) may be transferred from insulin therapy to sulphonylureas.

Key words: neonatal diabetes mellitus; pancreatic insufficiency; β-cell function; insulin secretion; insulin therapy; newborns; genetic mechanisms; imprinting; diabetes mellitus genes; potassium channel; SUR1; kir6.2.

Mathis was hospitalized in June 1999 for the onset of diabetes mellitus at 3 months of age. He was described by his parents as a thirsty toddler whose diapers had to be changed often. Upon arrival, his blood glucose was elevated 10 g/L (55 mmol/L) and ketoacidosis had occurred. He was initially treated in the intensive care unit and then transferred to the endocrine ward for the continuation of the insulin therapy, administered by continuous subcutaneous insulin injection. Subsequently, questions which at that time did not have an answer were raised by the parents: why such diabetes when no such case had ever been present in their family? Will the insulin therapy be for life? What is the risk of his brother developing diabetes? In 2004 Mathis was found to have a potassium channel neomutation (subunit Kir6.2) which led to a radical change in his life. Indeed, he could be successfully switched from insulin injections to sulphonylureas; insulin was stopped 17 days after introduction of the sulphonylureas, and he is now free of the need for insulin injections and has superb metabolic control. His brother, who does not have the mutation, will not develop diabetes mellitus. It is the willingness to believe in a better future for those children by a small group of physicians and researchers, and by the families of these children, that made Mathis's story possible.

Neonatal diabetes mellitus (NDM) is a rare (around 1/300,000 newborns) but potentially devastating condition. Two main groups have been recognized on clinical grounds: transient NDM (TNDM) and permanent NDM (PNDM); these differ in the duration of insulin dependence early in the disease. Recently advances have been made in the understanding of the molecular mechanisms of pancreatic development that are relevant to PNDM and of TNDM (Table 1). This review focuses on the clinical features and the molecular causes of these varied conditions. It also underlines how the molecular understanding of some forms of neonatal diabetes led to the transfer of patients from insulin injections to oral sulphonylureas in a spectacular example of a pharmacogenomic approach.

CLINICAL DESCRIPTION (TABLE 2)

Clinical description of 'transient' neonatal diabetes mellitus

TNDM is a developmental disorder of insulin production that resolves in the postnatal period. TNDM contributes 50–60% of cases of neonatal diabetes.[1,2] Intrauterine