Rare disease

Neonatal hyperglycaemia: a challenging diagnosis

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Summary

Neonatal diabetes mellitus (NDM) is a very rare disorder occurring between 1:400 000 and 1:500 000 live births and, until recently, little was known about this disease. The authors report a case of transient NDM in a 2-day-old female infant admitted in an intensive care unit with a blood glucose level greater than 400 mg/dl, glycosuria, ketonuria and with no evidence of autoimmunity. Treatment with insulin was necessary until the 51st day of life and many difficulties were found in the management of metabolic control because of the need for tiny quantities of insulin. Hyperglycaemia is sometimes routinely treated with insulin by neonatologists but after excluding the common causes of hyperglycaemia, NDM should be considered as a diagnostic possibility with clinical, genetic and therapeutic implications.

BACKGROUND

Neonatal hyperglycaemia is a common finding, especially in intensive care units, and major causes should be excluded, such as low birth weight, drugs (corticosteroids, theophylline, caffeine, dopamine and diazoxide), overinfusion of glucose and stress.¹ Neonatal diabetes mellitus (NDM) is a rare disease and two main groups have been recognised: transient NDM (TNDM) and permanent NDM (PNDM), which differ in the duration of insulin dependence early in the disease.

The authors present a case which highlights the difficulty in the management of this disorder, especially in what concerns the treatment with insulin, determination of the correct dose and best method of delivery in this age group, sensitivity of neonates to insulin and risk of hypoglycaemia. A brief review of the clinical, therapeutic and genetic aspects will be focused.

CASE PRESENTATION

We report the case of TDMN in a 2-day-old female infant, born at 38 weeks gestation with birth weight of 2179 g and Apgar score of 9 at 1 min and 10 at 5 min. No history of gestational diabetes or consanguinity between her parents was noted, but there was a family history of type II diabetes mellitus in her grandmother.

She was admitted in our neonatal intensive care unit with blood glucose level above 400 mg/dl, glycosuria and ketonuria, with no acidosis on blood gas analysis and no electrolyte disturbances. Her physical examination was normal except for low birth weight. There were no dysmorphic features.

INVESTIGATIONS

Investigations revealed negative sepsis screen, low C-peptide (0.20 ng/ml), normal pancreatic anatomy by abdominal ultrasound and evidence of intraventricular

haemorrhage (IVH) grade I on cranial ultrasound scan. There was no evidence of autoimmunity (negative insulin antibodies, glutamic acid decarboxylase antibodies and islet cell antibodies).

TREATMENT

She started on continuous intravenous rapid acting insulin therapy (≈ 0.5 U/kg/day) with strict blood glucose monitoring by bedside capillary glucose testing, and ketonuria ceased in 24 h. High caloric intake was maintained and satisfactory weight gain and growth was accomplished. On the 38th day of life insulin therapy was changed from intravenous infusion to diluted (with isotonic saline solution NaCl 0.9%) subcutaneous rapid acting insulin (Actrapid), with progressive metabolic control.

OUTCOME AND FOLLOW-UP

During hospital stay, her glucose concentration ranged from 84 to 410 mg/dl (mean 190 mg/dl), with a mean total insulin dose of 0.16 U/kg/day – figure 1 demonstrates the difficulty in stabilising glucose values. After the 39th day of life, only tiny amounts of insulin were required (<0.003 U/kg/day). Although there weren't significant episodes of hypoglycaemia, slow increments or adjustments of insulin were needed to achieve satisfactory glucose levels with adequate caloric intake. Exclusive enteric nutrition with breast feeding was achieved on 10th day.

The newborn insulin requirement has continued thereafter and after parental education, the child was discharged home on the 51st day of life with small doses of subcutaneous rapid insulin but, at home, she no longer needed insulin therapy. Genetic profiles were programmed for outpatient follow-up. The subsequent cranial ultrasound scan showed resolution of IVH. She is currently 2 years old and has had a good clinical evolution.

Figure 1 Metabolic evolution and insulin requirements.

DISCUSSION

NDM was first described by Kitzelle in 1852. Since then, there has been a great evolution in clinical, therapeutic and genetic aspects but still without a clear understanding of this disorder.

NDM is defined as hyperglycaemia occurring in the first 6 weeks of life.^{2 3} Clinically this condition can be divided in two categories (TNDM and PNDM) which differ from each other in the resolution or persistence by 18 months of age. Both entities are extremely rare with an incidence estimated of 1 per 400 000–500 000 live births.^{1 3 4} Between 50% and 60% of neonatal diabetes cases are transient but there is a predisposition for relapse during adolescence or early adult life.^{2 3} These data suggest a permanent defect in β cell function expressed variably throughout growth and development and emphasise the need for a prolonged follow-up.

As in the reported case, no evidence of autoimmunity has been found. It has been proposed that possibly all cases of diabetes mellitus diagnosed before 6 months are due to a mutation in a single gene whereas after 6 months autoimmune type I diabetes mellitus seems to be the major cause.⁴

In a cohort study of infants with a history of TNDM, Shield² showed that the median age of presentation was 3 days of life, the majority were born small for gestational age, the median requirement for exogenous insulin therapy was 12 weeks and islet cell antibodies were negative. All these findings are in consonance with our case report. Some associations with TNDM such as umbilical herniae and macroglossia were also reported.

In fact, TNDM neonates are usually diagnosed at a younger age, are more likely to have significant intrauterine growth retardation, require less insulin for metabolic control and present with less severe ketosis, when compared with PNDM.¹ However, significant overlap exists between the two forms of NDM, namely the temporal course, and its

transitory or permanent character is possibly only predicted by means of genetic analysis. Different molecular defects are recognised in TNDM and in PNDM.

Most of the patients (70%) with TNDM have anomalies in chromosome 6q24. Three types of anomalies were identified: (1) paternal uniparental isodisomy (UDP6) in which both copies of chromosome 6 are paternally inherited with no maternal contribution; (2) paternal duplications of 6q24 and (3) absent or defective methylation of the maternal copy of chromosome 6 originating a superexpression of the paternal allele.^{4–6} Two genes in that locus are candidates to the disease: *ZAC*, encoding the cellular cycle and apoptosis and *HYMAI* with unknown function.^{3 4}

In our patient no genetic analysis was performed since she was off insulin therapy by the time of first outpatient visit; moreover, it seems the genetic mechanism identified as the primary cause of TNDM has no influence in the outcome in terms of relapse later in life.² The risk of TNDM in further parental pregnancies is also minimal.²

In contrast to the transient form, the aetiology of PNDM is more heterogeneous. Causes identified include genetic conditions resulting in abnormalities of pancreatic development or function such as: (1) mutations in the gene encoding the ATP-sensitive potassium-channel subunit Kir6.2, being the most common cause of PNDM occurring in 32–64% of cases and also associated with a syndrome DEND (development delay, epilepsy and neonatal diabetes)^{7 8}; (2) mutations in the insulin gene accounting for 12% of patients with PNDM⁴; (3) severe pancreatic hypoplasia associated with an insulin promoter factor-1 mutation which in heterozygous cause mature onset diabetes of the young (MODY) 4 and in homozygous were reported in PNDM and in pancreatic agenesis^{4 5}; (4) homozygous glucokinase mutation, a rare cause of PNDM^{4 5}; (5) other clinical syndromes associated with PNDM including IPEX (immunodysregulation, polyendocrinopathy and enteropathy X linked syndrome),

Wolcott-Rallison syndrome (autosomal recessive disorder characterised by early-infancy insulin-dependent diabetes with epiphyseal dysplasias, hepatic, renal and cardiac alterations, exocrine pancreas dysfunction and neutropenia), and a severe syndrome with NDM and cerebellar hypoplasia.^{4 5}

Concerning treatment, the hallmark of management in the acute phase is to allow normal energy utilisation by tissues as well as the replacement of fluids and electrolytes, in order to achieve satisfactory weight gain and growth – high caloric intake and insulin therapy should be given. After stabilisation, newborns should initiate a chronic therapy. This is not an easy task and we needed the support of an endocrinologist to establish an appropriate regimen since few data are available on the methods of insulin delivery.⁹ Regardless of the type of insulin used, blood glucose levels should be strictly measured (every 3–4 h or anytime symptoms of hypoglycemia develop), given the extreme insulin sensitivity of newborns.¹ We initiated diluted subcutaneous rapid acting insulin but other possibilities could have been insulin glargine and continuous subcutaneous insulin infusion (CSII) (insulin pump), perhaps with better results in metabolic control.^{1 5 6} CSII is the treatment modality of choice in many centres since it seems to be safe, more physiological, easier to manage than injections and offers the possibility of very low rates of insulin delivery, making it ideal for neonates.^{1 5 6} However, CSII has significant economic disadvantages, which may limit its use. Except for patients with detected mutations in the ATP potassium channels that may benefit with treatment with sulphonylureas, the remaining patients should be managed with insulin therapy.⁴

In spite of all the recent advances, neonatal diabetes is still challenging. The physician should be well aware of this, since a better knowledge of this clinical entity has important implications in the treatment and outcome of patients.

Learning points

- ▶ Since hyperglycaemia is not uncommon in the neonatal period, other causes should be excluded before assuming the diagnosis of NDM.
- ▶ Considerable overlap exists between the two groups and so TNDM and PNDM cannot be distinguished based on clinical features.
- ▶ Recurrent diabetes is common in TNDM demonstrating the need for prolonged follow-up
- ▶ Genetic analysis may be of crucial help in predicting the transient or permanent character, as well as in the orientation of some aspects of treatment.

Competing interests None.

Patient consent Obtained.

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