MODY 2 presenting as neonatal hyperglycaemia: a need to reshape the definition of "neonatal diabetes"?

Dear Sir,

Neonatal diabetes mellitus is defined as a rare condition (1:400.000 live births) of unknown origin, characterised by hyperglycaemia occurring in the first month of life that requires exogenous insulin therapy [1, 2]. The derangement of glucose metabolism in newborns affected by this condition could be permanent (permanent neonatal diabetes mellitus, PNDM) or could (or could not) recur after remission of hyperglycaemia (transient neonatal diabetes mellitus, TNDM) [1, 2]. In a pedigree with maturity onset diabetes of the young (MODY) harbouring the glucokinase (GK, MODY 2) mutation Q38P, we followed a new pregnancy of the non-mutant mother of the index case. We found that 15 days after delivery her child presented hyperglycaemia (11.7 mmol) with dehydration and mild ketosis (Table 1, patient No. 1); intravenous insulin therapy was started on the same day. The presence of the Q38P mutation in the newborn was subsequently confirmed by DNA sequencing. Investigation of the clinical records of the Italian MODY collection showed three additional GK mutants with neonatal hyperglycaemia (1–26 days after birth) but no insulin treatment during the first six months of life (Table 1). Two infants (Table 1, patient No. 1, No. 2) met the criteria for the diagnosis of diabetes (i.e. 2-h post-meal plasma glucose values > 11.1 mmol/l; twice). We also observed two patients (No. 1, No. 4) whose periods of hyperglycaemia exacerbated and were associated with infections. We found MODY 2 presenting with neonatal hyperglycaemia, previously the earliest diagnosis was 12 months [3, 4].

Protean criteria are adopted to define neonatal diabetes [1, 2]. In particular, TNDM applies to "those infants with neonatal diabetes who developed non-insulin dependent diabetes within the first year of life" [2]. Thus, according to the current definition(s), our patient No. 1, who is now 36 months old and diabetic, could have been classified as TNDM [1, 2]. The absence of insulin therapy within the first 4 weeks from birth, however, would have left the remaining three in a diagnostic limbo. Moreover, extremely low birth weight is also a feature of "typical", but not all, patients with TNDM [2] and cannot be considered a stringent criterium for selecting patients. We observed that the moderate low birth weight of patients No. 1 and No. 3 was probably influenced by a mutation of paternal origin and subsequent low fetal insulin secretion.

Mutations in the GK represent the more frequent cause of MODY in some series [3] and it has been calculated that up to 6% of familial Type II (non-insulin-dependent) diabetes mellitus could bear a MODY 2 allele [3]. We and others have frequently observed that the mutation-carrying parent of children with MODY 2 is unaware of his or her hyperglycaemia. As a consequence, some previously described cases of permanent neonatal diabetes of unknown origin might be linked to GK mutations in both alleles, even in the absence of consanguineity loop (i.e. compound heterozygous). Neonatal, insulin-requiring, permanent diabetes mellitus is the main feature of GK knock-out mice models [5].

We believe that the definition of neonatal diabetes currently in use [1, 2] needs to be revised in order to: firstly, permanently incorporate the concept that TNDM (in some cases linked to paternal uniparental disomy of chromosome 6) [2, 6] and PNDM should be considered as separate entities [7] and secondly, include those cases with known causes (e.g. MODY 2, IPF-1) [8].

Yours faithfully,

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Table 1. Clinical features of four patients with GK mutation presenting with neonatal hyperglycaemia

Patient No., date of birth, GK mutation	Weeks of gestation	Birth weight (kg)	Plasma glucose (mmol/l)	Days from birth[a]	Insulin dose (U/kg/body weight)	Age at start	Duration of therapy
No. 1 (NA-1) 27/02/1997 Q38P	36	2.580	11.7 (after meal)	15	0.1/hr/i.v.	15 days	2 days
No. 2 (NA/B-1) 08/09/1997 K39del	42	3.000	11.5 (after meal)	1	0.4/day/s.c.	6 months	2 weeks
No. 3 (MI-5) 21/09/1993 G261R	42	2.370	8.9 (random)	8			
No. 4 (RM-4) 04/11/1987 L122-1G > A	42	3.550	7.6 (fasting)	26	0.2/day/s.c.	5 years	5 years

[a] Days of life at the first observation of hyperglycaemia

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No evidence of rapid onset (Japanese) Type I diabetes in Caucasian patients

Dear Sir,
Type I (insulin-dependent) diabetes mellitus has been classified as an autoimmune (Type 1A) or idiopathic disease (Type 1B) [1]. The idiopathic group is poorly defined other than by its lack of islet cell antibodies including antibodies to glutamic acid decarboxylase (GAD). In a recent study of 56 consecutive Japanese patients with Type I diabetes, 20 did not have GAD antibodies. Of these 20 patients, 11 had glycated haemoglobin (HbA_{1c}) values (an index of preceding blood glucose values) less than 8.5 %, that is close to the upper limit of normal of 5.8 %. These 11 patients, compared with the other GAD positive and GAD negative patients, had a shorter duration of hyperglycaemic symptoms (mean 4 days), higher plasma glucose (mean 42.9 mmol/l), lower urinary C peptide (3.2 μg/day) and higher serum amylase (4.2 times upper limit of normal) [2]. The authors concluded that these Japanese patients with idiopathic Type I diabetes had a non-autoimmune, fulminant disorder characterised by an abrupt onset and high serum pancreatic enzyme concentrations. Because there are no similar analyses of Type I diabetic patients of Caucasian origin, we undertook an analysis of a consecutive series of Italian patients from a single region [3] who had been newly diagnosed with Type I diabetes. We studied 82 patients aged 5 to 35 years (mean age 19 years ± 8 SD), diagnosed according to the recent classification of the American Diabetes Association [1] with sufficient serum available to measure autoantibodies and pancreatic amylase. Of the 82 patients, 59 had GAD antibodies and 23 did not. The characteristics of each group are shown in Table 1. Contrary to the patients described in Japan [2], GAD positive patients at diagnosis had significantly lower HbA_{1c} and were older than GAD negative patients. Of the nine patients with HbA_{1c} less than 7.5 % (which is close to the normal range and suggests a relatively rapid onset of diabetes) only one was GAD negative. They differed from those 59 with higher HbA_{1c} values in that they had a lower blood glucose concentration at diagnosis ($p < 0.04$) and required less insulin ($p < 0.007$). Of note, serum amylase concentrations did not differ between patients with or without GAD antibodies (Table 1) or HbA_{1c} values more or less than 7.5 %. Only one patient had an increased amylase concentration and that patient was GAD antibody positive with an HbA_{1c} of 12.1 %. We observed that the age of our patients was considerably less than that of the Japanese subgroup of GAD negative patients with increased serum amylase concentrations.

Table 1. Characteristics of 82 patients with recent onset Type I diabetes, according to the presence or absence of GAD antibodies

	GAD + ve $n = 59$	GAD – ve $n = 23$	p value
HbA_{1c} (% ± SD)	9.4 ± 2.1	10.8 ± 2.3	< 0.01
Age (years ± SD)	20.1 ± 8.1	15.8 ± 7	< 0.02
Blood glucose (mg ± SD)	349 ± 147	408 ± 181	NS
Symptoms (days ± SD)	32.5 ± 31.6	37.9 ± 25.2	NS
Insulin (iU/kg) ± SD	0.51 ± 0.32	0.64 ± 0.33	NS
C Peptide (ng/ml) ± SD	0.96 ± 0.56	0.95 ± 0.73	NS
Amylase (unit/l) ± SD	47.4 ± 21.0	49.9 ± 18.6	NS

We were unable to identify a group of Type I diabetic patients of Caucasian origin at diagnosis with non-autoimmune fulminant disease associated with an increased amylase concentration. Therefore the new subtype of Type I diabetes mellitus reported in Japan [2] is specific to that population.

Yours faithfully,
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High fasting glucose and QTc duration in a large healthy cohort

Dear Sir,
Marfella et al. [1] reported the effects of acute hyperglycaemia on QTc duration in healthy men. They found that QTc duration increased from a basal 413 ± 26 to 442 ± 29 ms ($p < 0.05$) at the end of a hyperglycaemic clamp. As stated by the authors, the relevance of these short-term changes to the high mortality rates of diabetic patients is speculative. We provide data that support their findings in a large healthy cohort.

We studied the association between QTc duration, fasting glucose and cardiovascular risk factors in a population-based study of 6543 subjects without evidence of clinical or electrocardiographic cardiac abnormalities. Subjects with diabetes mellitus, defined as a fasting plasma glucose concentration of 7.8 mmol/l or more or the use of oral hypoglycaemic agents or in-

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