Permanent neonatal diabetes mellitus: clinical presentation and epidemiology in Oman

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Abstract

Aim—To estimate the accurate incidence and prevalence of permanent neonatal diabetes mellitus, and to determine the clinical profile of this condition in the Sultanate of Oman.

Methods—All children diagnosed as having permanent neonatal diabetes mellitus between 1991 and 1995 in Oman were included in the study.

Results—The mean incidence was 2.2 per 100 000 live births/year and the prevalence among under 5s during 1995 was 2.0/100 000. Intrauterine growth retardation was noted in all (mean birthweight 1.86 kg), and diabetic ketoacidosis (mean plasma glucose 34.4 (SD 8.7) mmol/l, mean pH 7.17 (SD 0.09) in 80%. Hypertriglyceridaemia (mean serum triglyceride 19.06 (6.13) mmol/l) was constant. No infant had clinical or immunological evidence of congenital viral infections. None had C-peptide excretion or circulating islet cell antibody during diagnosis or follow up. The other important features were parental consanguinity in all, HLA DR3/DR4 association in 80%, development of autoimmune hypothyroidism in one and observation of autoimmune disorders (insulin dependent diabetes mellitus and Hashimoto’s thyroiditis) in family members.

Conclusions—These findings strongly suggest an immune mediated aetiology for diabetes mellitus. The reported incidence of permanent insulin dependent neonatal diabetes mellitus in Oman is the highest in the world.

Keywords: permanent neonatal insulin dependent diabetes mellitus; epidemiology; Oman

Neonatal diabetes mellitus is a rare form of insulin dependent diabetes mellitus (IDDM) that presents within the first four weeks of life and persists for more than two weeks. The clinical picture includes evidence of intrauterine growth retardation (IUGR), failure to thrive, dehydration, fever, hyperglycaemia, acidosis with or without ketonuria. The aetiology and pathogenesis remain unclear. The rarity of the disease and lack of characteristic symptoms can often delay diagnosis. The outcome of neonatal diabetes is varied, as some infants develop permanent IDDM of neonatal onset (PNIDDM), others have transient remission with subsequent recurrence, and yet others may have apparently permanent remission.

There are no accurate epidemiological data on neonatal IDDM in different populations. Transient diabetes mellitus is not reported uniformly. The reported incidence of PNIDDM is around 1 in 400 000 live births, or 1 in 500 000 neonates, as noted in various regions. Two cases of PNIDDM diagnosed in our hospital within a year prompted us to undertake this study. This study aimed to estimate the accurate incidence and prevalence rates of PNIDDM and to determine the clinical profile of this condition in the Sultanate of Oman.

Methods

All children with PNIDDM studied were native Omani. They were treated and regularly followed up in the paediatric endocrinology clinic at the Royal Hospital, Muscat, which is the nation’s tertiary hospital. All complex and rare diseases are referred, as a rule, to this federal centre and new cases reported.

The clinical profiles of children with PNIDDM were analysed. The criteria for diagnosis of PNIDDM were defined earlier. Children under the age of 5 years with IDDM diagnosed during 1991–95 were also evaluated to calculate the prevalence among under 5s. IDDM was diagnosed according to WHO criteria. The date of the first insulin injection was taken as the date of diagnosis. Children with secondary diabetes were excluded. Incidence and prevalence rates were calculated by using the final results of the general census of population published yearly by the Ministry of Health, Sultanate of Oman; 95% confidence intervals were calculated as described by Armitage and Berry and Pearson correlation coefficients were calculated for clinical variables.

The results of the following investigations carried out during the initial presentation and admission were analysed: venous blood gas analysis, serum concentrations of glucose, cholesterol, triglycerides, electrolytes, urea, and creatinine were carried out using standard laboratory methods. Blood was screened for the presence of IgG and IgM antibodies against toxoplasma, cytomegalovirus, and other viruses—rubella, Coxsackie, and herpes. Indirect immunofluorescence technique (Serono laboratories, Cambridge, UK) on human pancreatic sections was done for detecting the presence of islet cell antibody. Plasma C-peptide concentration was estimated by radioimmunoassay. Glycated haemoglobin was determined using Abbott IMX glycated haemoglobin assay test kits. HLA typing of the...
Table 1  Baseline characteristics of the children with PNIDDM

<table>
<thead>
<tr>
<th>Case No</th>
<th>Gestational age (weeks)</th>
<th>Weight (kg)</th>
<th>Length (cm)</th>
<th>Head circumference (cm)</th>
<th>Age at diagnosis (days)</th>
<th>Symptoms duration (days)</th>
<th>Weight gain (g/day)</th>
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<tbody>
<tr>
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<td>39</td>
<td>1.85</td>
<td>47</td>
<td>32</td>
<td>20</td>
<td>2</td>
<td>1.92</td>
</tr>
<tr>
<td>2</td>
<td>38</td>
<td>1.52</td>
<td>40</td>
<td>32</td>
<td>18</td>
<td>8</td>
<td>1.63</td>
</tr>
<tr>
<td>3</td>
<td>37</td>
<td>2.1</td>
<td>47</td>
<td>32</td>
<td>14</td>
<td>4</td>
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<td>1.5</td>
<td>37</td>
<td>37</td>
<td>19</td>
<td>5</td>
<td>1.65</td>
</tr>
<tr>
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<td>38</td>
<td>2.35</td>
<td>48</td>
<td>35</td>
<td>6</td>
<td>3</td>
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</table>

Table 2  Laboratory data of children with PNIDDM at initial presentation

<table>
<thead>
<tr>
<th>Case No</th>
<th>Blood glucose (mmol/l)</th>
<th>Venous pH</th>
<th>Urinary ketones</th>
<th>Serum triglycerides (mmol/l)</th>
<th>Serum cholesterol (mmol/l)</th>
<th>Serum creatinine (mmol/l)</th>
<th>Serum potassium (mmol/l)</th>
<th>Blood urea (mmol/l)</th>
<th>Serum creatinine (mmol/l)</th>
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<td>1.7</td>
<td>128</td>
<td>5</td>
<td>10.2</td>
<td>63</td>
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<tr>
<td>2</td>
<td>34</td>
<td>7.22</td>
<td>1+</td>
<td>20</td>
<td>4</td>
<td>123</td>
<td>4.8</td>
<td>9.6</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>38</td>
<td>7.12</td>
<td>2+</td>
<td>22</td>
<td>2.5</td>
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<td>78</td>
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<tr>
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<td>8.9</td>
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<td>134</td>
<td>4.2</td>
<td>5.1</td>
<td>64</td>
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</table>

Mean (SD) 34.4 (8.7) 7.12 (0.09) 19.41 (4.87) 3.08 (1.04)
hypoglycaemia, in all the patients studied. Serial C-peptide estimations did not reveal any evidence of endogenous insulin secretion. The common HLA loci associated with IDDM (DR3 and/or DR4) were found in 80% of the patients studied (n = 5). Autoimmune hypothyroidism was diagnosed in one infant by the presence of thyroid antibodies and biochemical evidence of hypothyroidism.

One child died at the age of 2.5 years after aggressive hepatitis and liver failure following transfusion.

Discussion
IDDM in neonates is very rare. The incidence of IDDM increases with age and the highest incidence is seen around adolescence. The epidemiological aspects of PNIDDM have not been studied. The mean yearly incidence of PNIDDM per 100 000 live births in Oman from 1991 to 1995 was 2.2/year. During 1995, the prevalence of PNIDDM in the age group 0 to 5 years was 2.0/100 000. The incidence of PNIDDM during the five years of the study is the highest reported in the world. This could be related to the high degree of consanguinity in the Omani population, as noted earlier. Interestingly, there was a significant history of consanguinity in all the four families studied.

As noted in earlier reports, all our patients had IUGR with a mean birthweight of 1.9 kg. Insulin secreted by the fetal pancreas has a significant role in growth and metabolism of the fetus during the last half of gestation. Knip et al. suggested that intrauterine insulin deficiency could be the cause of IUGR in these patients.

Diabetes diagnosed in older children seems to present much less acutely than in neonates. Ketoadosisis was the initial presentation in 80% of infants with PNIDDM. This figure is much higher than that of older children. In a series reported by Salman et al. 70.8% of children below 5 years and 65.8% of children above 5 years presented with ketoadosisis. The duration of symptoms before diagnosis in our study ranged from 2 to 8 days, with a median of 4.4 days. The shorter duration of symptoms in neonates compared with older children might reflect either a faster deterioration of their β cell function, higher requirement of insulin/kg, and/or their increased susceptibility to dehydration compared to older infants and children.

Complete remission occurs in 3% of children with IDDM and partial remission (insulin requirement less than 0.5 unit/kg/day) occurs in around two thirds of children with IDDM. None of our patients with PNIDDM experienced partial or complete remission during the first year of life. This may be explained by the severity of β cell destruction. None of them had detectable circulating C-peptide concentration at presentation or during the first year after diagnosis, supporting the view of total destruction of their β cell mass. Two children developed autoimmune thyroiditis at the age of 1.5 and 3 years with raised antimicrosomal thyroid antibodies and high thyroid stimulating hormone activities.

The cause of β cell destruction in PNIDDM is not yet known. In general, in IDDM the process of β cell destruction in a genetically predisposed host by environmental agents (virus, toxins) is relatively slow. It may take many months or years for the overt diabetes to present itself. For diabetes to occur in the neonatal period the pathological process causing islet cell damage or destruction should clearly start in utero. In general, more than 80% of islet cells do not show β cells when IDDM unfolds clinically. At present, there are no studies to indicate whether the process of islet cell destruction in PNIDDM starts in utero. In the case reported by Dodge et al. no islet cells were seen in the neonate who died of diabetes at the age of 3 days. In all our cases the C-peptide secretion was absent at presentation (as early as the 8th day of life), concomitant with evidence of intrauterine growth retardation due to lack of the anabolic effect of insulin. These findings support the view that the β cell destruction starts in utero.

There was no historical, clinical, or immunological evidence of congenital infection at birth in any of the cases studied. However, we found a significant number of autoimmune mediated diseases in the affected neonates and their families including a high incidence of IDDM in siblings and their parents. PNIDDM has been reported in a mother and her son, and among siblings. We also found Hashimoto’s thyroiditis in one mother and autoimmune hypothyroidism in one child. IDDM and PNIDDM have occurred in the members of the same family.

The absence of islet cell antibodies in all our patients at presentation might point to a different mode of immune reaction in this age group. Non-islet cell antibody against interstitial tissue among the acinar cells was shown in two HLA DR3 and/or DR4 positive siblings. The common HLA loci associated with IDDM (DR3 and/or DR4) were found in 80% of the patients studied. This finding, in addition to the high degree of parental consanguinity (100%), high prevalence of IDDM, and other autoimmune disorders in the patients and their parents and siblings, strongly supports an immune aggression aetiology for their diabetes.

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