Letters

Approaching St Vincent

Working towards the St Vincent targets

Diabetes mellitus is the most prevalent chronic medical disease in the pregnant population [1,2] and is associated with less satisfactory pregnancy outcomes for both the mother and infant than the non-diabetic population [3,4]. The St Vincent declaration (1989) set as one of its main aims [5] the achievement of pregnancy outcome in diabetic women similar to that in non-diabetic women, and perinatal mortality (PMR) (that is stillbirths (SBR) and early neonatal deaths (ENND)) are widely used as a summary statistic for evaluating pregnancy outcome). When comparing outcomes it is more realistic to compare results to those of the local background population as SBR, PMR, and ENND rates differ in regions of the country because of inter-population differences. This study was carried out to look at the PMR before (1980–1989) and after (1990–1998) St Vincent to establish if positive progress is being made towards the aim proposed in St Vincent.

The study was carried out in a university teaching hospital serving a multicultural population of 2.5 million but also receiving referrals from a population of 5.2 million. A computerized database contains information (mother/infant) on all pregnancies complicated by diabetes since 1990, and this was used for the period 1990–1998. Information before St Vincent (1980–1989) was obtained from a paper-based system. By cross-referencing between obstetric diabetes and neonatal records, the information as far as we can ascertain is complete. SBR, ENND and PMR were calculated for each time-period per thousand births and compared with rates in the background population. Statistical analysis was with a two-sample test of proportions and \( P < 0.05 \) was taken as significant.

During the 10-year period 1980–1989, 444 pregnancies occurred in women with diabetes, 360 with pre-gestational disease. There were 51 526 deliveries in the background population. The SBR in women with diabetes was 15.7 rising to 16.6 in pre-gestational disease, compared to 5.8 in the background population, illustrating an almost threefold difference between groups. The ENND rate was 22.5 in those with diabetes rising to 27.7 in pre-gestational disease compared to 9.2 in the background population, again an almost threefold difference. Finally the PMR was 38.2 in those with diabetes increasing to 44.4 with pre-gestational disease, showing a threefold difference when compared to 15 in the background population (Table 1).

During the 8-year period between 1990 and 1998, there were 496 pregnancies in women with diabetes, 260 with pre-gestational disease. A total of 61 516 deliveries were recorded in the background population. The SBR in the diabetes cohort was 6 which was less than the background rate of 9. The rate increased to 11.5 when corrected for pre-gestational disease, but remained comparable to the background rate. The ENND rate was 14.1 in diabetes overall, comparable to a background rate of 12.3, but rising to 23 when corrected for pre-gestational disease, a twofold difference compared to background. The PMR was 20.1 in the diabetes group comparable to the background rate of 21.3 but increased to 34.6 when corrected for pre-gestational disease, a 1.6-fold difference. (Table 1)

Over the study period there has been a change in the referral pattern to the hospital. Women from the region with known or suspected fetal abnormality on ultrasound, or with a maternal obstetric problem necessitating early delivery are often transferred. The rate of in utero transfer has risen from 0.89% in the first period to 2% in the second period. This has resulted in an increase in SBR, ENND and PMR in the background population despite a fall in national and regional figures. Despite a similar change in the pattern of diabetes referrals (0.83% in utero transfers in period 1, 1.7% in period 2), we have observed a decrease in these rates. The SBR has fallen significantly from 16 to 6/1000 \( (P < 0.05) \) overall and from 17 to 11/1000 when corrected for pre-gestational disease which is clinically important. The difference in the rate compared to background has fallen from a 2.5 to 1.2-fold difference. The ENND rate has fallen from 23 to 14/1000 overall and from 28 to 23/1000 when corrected for pre-gestational disease. The difference compared to background has fallen from a 3.1 to 1.9 fold difference. The PMR has fallen significantly from 38 to 20/1000 \( (P < 0.05) \) overall and from 44 to 34/1000 when corrected for pre-gestational disease. The difference compared to background has fallen from a 3.0 to 1.6-fold excess. When compared to regional figures there is a downward trend in rates but the difference remains unacceptably high with a 2–4-fold excess (Table 1). The differences highlighted by this study emphasize the importance of comparable populations when examining outcomes.

When compared to the background hospital population, we are approaching, although have not reached, the aim of
Association of the T14709C mutation of mitochondrial DNA with maternally inherited diabetes mellitus and/or deafness in an Italian family

A maternal effect in the transmission of non-insulin-dependent diabetes mellitus (NIDDM) has been recognized for many years and suggests the involvement of a genetic factor encoded by mitochondrial DNA (mtDNA) in its pathogenesis [1]. Recently, several authors have reported pedigrees with maternal transmission of NIDDM and identified mitochondrial mutations, linking with the disease. In several cases, a sensorineural deafness, which is frequently observed in mitochondrial diseases, accompanied the maternally inherited diabetes mellitus [2].

In this report the nucleotide position (np) 3243 [3,4], np 7445 [5] and np 14709 [6] mt mutations, and the 10.4-kb [2] deletion in 10 families with maternally inherited diabetes mellitus and/or deafness have been analysed. The 10 families were identified through patients attending the Departments of Paediatrics of the University in Messina and of the II University in Naples (Italy).

The study was approved by the committee for ethics in medical research and was therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All the subjects gave their informed consent prior to their inclusion in the study.

From these families, four children affected by neurosensory deafness and by insulin-dependent diabetes mellitus (IDDM), six affected by deafness and seven affected by NIDDM were selected. Their median age was 13 years (range 6–16 years). All patients had a mother affected by NIDDM and at least one relative of the first degree with MIDD or with maternally inherited NIDDM. The pedigrees are illustrated in Fig. 1.

Blood was collected from the probands, from the mothers and 19 available affected relatives. Thus, the total number of subjects studied in this group was 52 (median age 55 years, range 48–65 years).
Figure 1  The pedigrees of the families. Roman numerals indicate generations. The arrows indicate the subjects with the mitochondrial T14709C mutation.
Total DNA was extracted from the patients’ blood and amplified by polymerase chain reaction (PCR) in order to analyse the incidence of np 3243, np 7445 and np 14709 mutations.

Several pairs of primers were used to amplify the regions of mtDNA comprised between the nucleotides 4705 and 15497 in order to detect the 10.4-kb deletion. All studied subjects underwent several audiometrical, neurological and metabolic check ups.

The np 3243, np 7445 mutations and the 10.4-kb heteroplasmic deletion were not found in any of the subjects of our study. Instead, in the D pedigree (Fig. 1) the mutation T14709C was found in the probands III-1, III-2, III-5 and in their diabetic mother.

In this pedigree the proband III-1 was a 16-year-old boy and became deaf at the age of 12.

The proband III-2 was a 12-year-old female who was diagnosed as having deafness at the age of 6. She was affected by a severe myopathy and complained of progressive muscle weakness and exercise intolerance. Weakness affected especially the neck and limb muscles. Gait was normal except for a slight difficulty of walking on heels. Tendon reflexes were hypoactive in the arms but brisk in the legs, with a bilateral Babinski reflex. Electromyography was abnormal and resting serum creatine kinase was increased to 1590 U/dl (normal < 250). There was no family history of neuromuscular disorders. A diagnosis of mitochondriopathy was based on a deltoid muscle biopsy that showed a large number of ragged-red fibres (RRF).

The patient III-5 was a 10-year-old boy who became deaf and developed diabetes at the age of 5 and 8 years, respectively. Diabetes was treated with insulin and diet.

The 60-year-old female (II-2) in the second generation was diagnosed as having Type 2 diabetes at the age of 57 years and was treated with oral hypoglycaemic therapy.

The clinical phenotypes of our subjects carrying the T14709C mitochondrial mutation are different. This apparent confusing pattern may be explained by the fact that the patient with severe myopathy and deafness may still become hyperglycaemic. The absence of the mitochondrial T14709C mutation in subjects III-3 and III-4 is not surprising. Similar findings were observed in previous studies [7]. The transmission of mutant mtDNA from an affected mother to her offspring is variable, and can range from no affected progeny to all the children inheriting the mutant gene. During embryogenesis, only a small proportion of total mtDNA contained in the oocyte is replicated and transmitted to the developing tissues. Thus, some children might not inherit the mutation, and those who do may exhibit a variable expression of mutant mtDNA in different tissues, a phenomenon called ‘heteroplasmy’ [1,7].

Identification of all the mtDNA alterations is required for the correct evaluation of the pathogenic mechanism in MIDD. In pancreatic β cells mitochondria are presumably involved in the mechanism of glucose sensing and it is plausible that mitochondria with the mutations will affect the glucose sensing mechanism as they are not functional. Another explanation is that the presence of mutant mitochondria might reduce β cell mass and so impair insulin secretion. In muscle, the main site of peripheral glucose disposal, glucose is metabolized by glycolysis and mitochondrial oxidation. Impaired mitochondrial function may increase glycolytic flux and peripheral production of lactate which can be converted back into glucose by hepatic gluconeogenesis. Alternatively, a mitochondrial dysfunction in muscle might impair the function of hexokinase II, resulting in insulin resistance.

The study of mitochondrial diseases continues to yield novel defects of mtDNA and further studies will be aimed at investigating the prevalence of these in NIDDM. Pathophysiological and molecular biological studies of mitochondrial function may significantly advance our understanding of this challenging metabolic disease.

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Long hypoglycaemic periods detected by subcutaneous continuous glucose monitoring in toddlers and pre-school children with diabetes mellitus

In spite of frequent blood glucose monitoring by finger pricks, asymptomatic and nocturnal hypoglycaemia may often remain undetected, particularly in children [1]. As subcutaneous glucose readings are closely related to blood glucose values [2], a subcutaneous Continuous Glucose Monitoring System (CGMS; MiniMed Inc., Sylmar, CA, USA) providing measurement of glucose concentration in subcutaneous interstitial fluid (2.2–22.4 mmol/l) has been developed [3]. However, up to now there has been little information regarding the feasibility of CGMS in very young children, who are at highest risk of severe hypoglycaemia [4].

We therefore investigated the feasibility of continuous glucose monitoring in very young toddlers and pre-school children with Type 1 diabetes (five boys, 10 girls; age (years), 3.6 (0.1–6.0); diabetes duration (years), 1.5 (0–3.5); HbA1c (%), 8.1 (5.7–9.4); median (range)) volunteering for the investigation. Moreover, we examined whether CGMS gave more information about glucose fluctuations and hypoglycaemic episodes compared with periodic measurements from a blood glucose meter. Parents were instructed to assess capillary blood glucose measurements by finger pricks according to their usual routine with a calibrated Accutrend® Sensor blood glucose meter (Roche Diagnostics, Mannheim, Germany) at least five times per day (prerandial before the main meals, 22 h and 2 h) and additionally when hypoglycaemic symptoms were suspected. Furthermore, they kept an activity protocol caused by the sensor. Eleven out of 15 children carried the CGMS during out-patient conditions. Patients living too far from the hospital to reach it in short time in the case of monitor malfunction were encouraged to simulate regular daytime activities in a hospital setting.

The median duration of CGMS application was 72 h (55–90 h). The mean sensor number used was 1.4 (1–3) per patient and the mean sensor function time 49 h (18–90 h), which is comparable to the experience in adults [3]. Parents reported carrying the CGMS during normal daily activities without significant pain or discomfort in spite of the high activity level and long sleeping time typical for this age. After applying local anaesthesia the sensor-needle insertion was painless and well tolerated by the children as judged by the parents.

Thirty-six hypoglycaemic episodes (glucose concentration < 60 mg/dl) were documented by CGMS in 11 patients, resulting in 0.02 (0.0–0.13) hypoglycaemic events per hour. Nine of these patients had one or more nocturnal (i.e. between 20 h and 8 h) hypoglycaemic events. The duration of hypoglycaemias varied (10–480 min) with a median of 58 min (Fig. 1). There was a tendency towards longer episodes during the night compared with those during the day time (n = 19, 110 (10–480) min vs. n = 17, 45 (10–310) min), but this did not reach statistical significance (P = 0.167). In contrast, capillary blood glucose monitoring detected hypoglycaemia in only 13 of 36 events. In those 13 cases the fall of interstitial glucose levels preceded the detection of low blood glucose values with the meter [5]. In the 20 episodes undetected by blood glucose testing the parents had not suspected hypoglycaemia and had therefore not performed an additional test.

The present study documents for the first time that continuous glucose monitoring is feasible and useful in young children with diabetes. Low glucose levels seem to last far longer than previously believed and remain undetected even by frequent finger prick monitoring. Thus information gathered by occasional CGMS may allow a better assessment of rapid fluctuating glucose levels in very young pre-school children, potentially leading to better adjustment of therapeutic regimens.

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