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Abstract

***Aim*—To determine if children born to mothers with diabetes mellitus during pregnancy, who subsequently developed neonatal hypoglycaemia, experienced long term neurological dysfunction.**

***Methods*—Thirteen children with, and 15 without, neonatal hypoglycaemia (blood glucose < 1.5 mmol/l) were randomly selected from a larger cohort and investigated at the age of 8 years. They were also compared with 28 age matched healthy controls.**

***Results*—Children with neonatal hypoglycaemia had significantly more difficulties in a validated screening test for minimal brain dysfunction than controls and were also more often reported to be hyperactive, impulsive, and easily distracted. On psychological assessment, they had a lower total development score than normoglycaemic children born to diabetic mothers, and control children.**

***Conclusions*—Neonatal hypoglycaemia in diabetic pregnancy was associated with long term neurological dysfunction related to minimal brain dysfunction/deficits in attention, motor control, and perception.**

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Keywords: hypoglycaemia; diabetic pregnancy; neurological development

Pregnancy in women with diabetes mellitus is associated with a high incidence of neonatal mortality and morbidity in the offspring.[1] Close monitoring of pregnant diabetic women, including frequent blood glucose measurements and aggressive insulin treatment, has markedly reduced this.[2 3] However, the incidence of postnatal asymptomatic hypoglycaemia remains high in newborns born to mothers with insulin dependent (IDDM) and gestational diabetes mellitus.[4]

Some authors believe that asymptomatic neonatal hypoglycaemia has no effect on neurodevelopment.[2 3 5 6] On the other hand, Lucas has shown that moderate asymptomatic hypoglycaemia (blood glucose < 2.6 mmol/l) may be associated with reduced mental and motor development scores at 18 months of age.[7] Symptomatic and long lasting hypoglycaemic episodes in neonates can cause permanent central nervous system damage.[5 6 8–11]

Agreement has not been reached on the blood glucose concentration which defines neonatal hypoglycaemia.[12–15] Neural brainstem dysfunction has been shown at blood glucose concentrations below 2.6 mmol/l.[16] Many neonatal units diagnose neonatal hypoglycaemia at concentrations exceeding 1.5 mmol/l.[15]

Earlier follow up studies in children of diabetic mothers indicated a high incidence of cerebral dysfunction syndromes associated with complications during pregnancy, including poor glycaemic control of the mothers.[17–19]

In more recent studies, with better prenatal and perinatal management, normal IQ scores have been found at follow up.[2 3 20–22] However, early growth retardation during diabetic pregnancy and disturbances in maternal lipid metabolism in mid and late pregnancy have been associated with impaired psychomotor development.[21 23 24]

We wished to determine whether neonatal hypoglycaemia is associated with symptoms related to minimal brain dysfunction and/or deficits in attention, motor control, and perception (DAMP), other neurological dysfunction or changes in the EEG at the age of 7–8 years, in children born to mothers with diabetes mellitus during pregnancy that was treated with insulin.

Patients

Seventy six mothers with treated diabetes mellitus were identified in Örebro County, Sweden, during 1986 and 1988 (18 with IDDM and 58 with gestational diabetes mellitus). Gestational diabetes was diagnosed if the blood glucose concentration was > 8 mmol/l two hours after a 75 g oral glucose load. All women monitored their blood glucose concentrations and were seen every week or fortnight to adjust their insulin. Preprandial injections of fast acting insulin and intermediate acting insulin at bedtime aimed to restore normal glycaemic control.

During the study, 76 children were born and admitted to the neonatal intensive care unit. They were fed orally with formula every three hours from 2 hours of age and observed for at least 24 hours. Preprandial capillary blood glucose measurements (glucose oxidase method, YSI AM 23, Yellow Spring Inc, Yellow Springs, OH, USA) were carried out during the first 24 hours after birth.

Before our follow up investigation, all children were numbered and divided into two groups. In one group the children had experienced blood glucose concentrations < 1.5 mmol/l as neonates while the other group had not. To obtain comparable groups, we stratified with respect to gender and type of maternal diabetes. We selected a proportional number of children from each group, with respect to the sizes of the groups within the total cohort. Thus follow up involved 15

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Table 1 Clinical characteristics of insulin treated diabetic mothers and their infants, with or without hypoglycaemia, in the neonatal period, mean (SD)

	Mean (SD) neonatal hypoglycaemia (n=13)	*Mean (SD) neonatal normoglycaemia (n=15)*
Mothers		
Type of diabetes, IDDM, white class	3 (B, C, F)	4 (2B, 2C)
GDM	10	11
Age (years)	31.3 (5.6)	30.6 (4.8)
Length of gestation (weeks)	38.2 (1.4)	38.6 (1.0)
Weight at delivery (kg)	78.7 (14.1)	66.2 (9.7)
$HbA1_c$* % (last trimester)	6.9 (1.5)	7.5 (1.6)
Caesarean section	3/13	2/15
Infants		
Birth weight (g)	3484 (758)	3445 (526)
Length at birth (cm)	49.0 (2.8)	49.6 (2.5)
Head circumference at birth (cm)	35.2 (1.1)	34.2 (1.3)
Haemoglobin concentration (g/l)	201.2 (27.0)	194.1 (19.4)
Haematocrit (%)	63.6 (8.1)	62.1 (6.9)
Apgar < 7 at 1 min	0/13	1/15
Apgar < 7 at 5 min	0/13	0/15
Hyperbilirubinaemia	3/13	1/15
Neonatal respiratory disturbance	2/13	2/15

* Glycosylated haemoglobin concentrations were measured with an affinity chromatography method. Local reference values for healthy adults were 4.0–6.5%.

Table 2 Clinical characteristics of children, with or without postnatal hypoglycaemia, of diabetic mothers and control children at follow up at 7-8 years of age

	Mean (SD) children with postnatal hypoglycaemia (n=13)	*Mean (SD) children without postnatal hypoglycaemia (n=15)*	*Mean (SD) control children (n=28)*
Age (years)	7.9 (0.7)	7.7 (0.6)	7.8 (0.4)
Male:female	4:9	5:10	14:14
Weight (kg)	30.3 (8.2)	28.4 (6.2)	28.4 (4.4)
Height (cm)	127.7 (9.0)	127.8 (5.9)	130.2 (5.3)
Head circumference (cm)	52.7 (1.4)	52.8 (1.6)	53.6 (1.7)
Left handed	1/13	4/15	1/28

children with, and 15 without, postnatal hypoglycaemia. Eight had been children born to mothers with IDDM and 22 had been born to mothers with gestational diabetes.

Data about the neonatal period, reported elsewhere,[4] are presented in table 1 and show the clinical characteristics of the mothers. The lowest blood glucose concentrations in the hypoglycaemic group ranged from 0–1.4 mmol/l (mean 1.1) compared with 1.6–2.9 mmol/l (mean 1.9) in the normoglycaemic group. Four children with neonatal hypoglycaemia had been described as "jittery," but none had any other obvious symptom associated with hypoglycaemia.

At follow up, the children's neurological development was investigated. Table 2 shows their clinical characteristics at follow up. A boy with asymptomatic hypoglycaemia declined to participate in the study and a girl with symptomatic hypoglycaemia, cyanosis, hypertension and a blood glucose value of 0.9 mmol/l, was excluded because she developed severe mental retardation, autism, left sided hemiplegia and intractable epilepsy. None of the investigated children had a history of neurological, neurodevelopmental, or behavioural problems before follow up.

The children of diabetic mothers were compared with 30 control children in the same age group, randomly chosen from 10 school classes in four parts of the county (table 2). The control children were studied by the same investigators and by the same procedures, excluding the EEG recordings. Two children in the control group could not participate because of acute respiratory illness at the time of follow up.

The study was approved by the local hospital medical ethics committee and all parents gave informed consent to participation in the study.

FOLLOW UP METHODS

The follow up study had four parts and took place during one day in the outpatient clinic. Each child was accompanied by one parent. All children were tested blind according to their status in the neonatal period and by the same investigators.

General and neurological examination

One author (ES) performed a standardised physical examination, including measurements of height, weight, and head circumference, neurological examination, vision and hearing evaluation; this aimed to detect major or minor neurological deficits. We used a validated screening test for minimal brain dysfunction.[25–27] with six highly discriminative examination items, to detect neurological and neurodevelopmental abnormalities. This test has a false negative rate for minimal brain dysfunction of less than 10%, if the cutoff is set at two abnormalities out of six possible items in girls and three abnormalities out of six items in boys.[25 26] The specific items are described in table 3.

Motor development assessment

An experienced physiotherapist carried out a test devised by Henderson and Sugden—the Movement Assessment Battery for Children aged 6 to 12 years (Movement ABC)—to identify gross or fine motor retardation, coordination, and concentration difficulties.[28] The test had three parts: manual dexterity, ball skills, and static and dynamic balance. A total score of less than 10 points is considered normal; 10–13 points means borderline; and more than 13 points definite motor problems.

The test included a questionnaire to parents regarding subjective evaluation of behavioural

Table 3 Screening test for evaluation of minimal brain dysfunction (MBD)

Selected items	*Marked abnormality*
1 Hop on one leg 20 times	12 seconds or longer or 2 or more interruptions with both feet on the ground (2p). Minor abnormality: 9-11 seconds and 1 interruption (1p)
2 Stand on one leg for 20 seconds	Manages 10 seconds or less (2p). Minor abnormality: 11-19 seconds (1p)
3 Associated movements when walking on lateral sides of feet for 10 seconds	Elbow flexion of 60° or more with abduction of arms or movements of lips and tongue (2p). Minor abnormality: elbow flexion < 60° with abduction of arms or movements of lips and tongue (1p)
4 Diadochokinesis for 10 seconds	Manages ≤ 10 pro-supinations for "worst" hand or awkward pro-supination and elbow moving over a distance of 15 cm (2p). Minor abnormality: 11-19 pro-supination for "worst" hand or awkward pro-supination and elbow moving < 15 cm (1p)
5 Cut out a paper circle with a diameter of 10 cm	≥ 120 seconds to cut out a circle or 1/5 or more of circle area included extra or excluded in end-result (2p). Minor abnormality: 60-120 seconds to cut the circle and ≤ 1/5 circle area included extra or excluded in end-result (1p)
6 WISC labyrinth test in accordance with description in manual	Score < 2 SD below mean of comparison group (8 or less of 21 possible points) (2p). Minor abnormality: 9-12 of 21 possible points (1p)

difficulties. If children were considered by their parents to be overactive (squirming and fidgeting, unable to keep still when listening to instructions, fiddling with clothes), impulsive (starting before instructions/demonstrations are complete, impatient about details) and distracted (looking around, responding to noises/movements outside the room), we regarded them as having behavioural difficulties.

Psychological assessment

An experienced psychologist used Griffiths' mental developmental scales (2–8 years), standardised for Swedish children, to test cognitive, mental, and perceptual functions.[29] We excluded the locomotion part of this test as it is included in the Movement ABC. Each of the remaining five parts was concluded with a developmental quotient (DQ) and in stanine units, 1–9 (equivalent to DQ < 73–>127). A total developmental quotient was also given.

EEG

A standardised EEG recording (Walter Graphtek GmbH, PL-EEG, version 2.1) using the 10-20 system was carried out, including both hyperventilation and photo activation. We selected individual parts of the EEG, without artefacts, with the child awake and with his/her eyes closed, without knowing anything about the child's status in the neonatal period. From these, we sampled 20 epochs of 3 seconds each of which was analysed by frequency distribution, fast Fourier transformed. Having performed the transformation, the absolute values of the transformed Fourier signals were averaged.

The total frequency band power at each electrode position was calculated by summation within the defined frequency band limits (δ 1.0–3.5 Hz, θ 3.5-8.0 Hz, α 8.0–12.5 Hz and β 12.5–40 Hz). Maximal power frequency (area under the curve), relative power frequency, distribution of δ, θ, and α activity as well as a quotient of δ and θ activity divided by α activity was calculated from the recordings obtained with 12 surface electrodes, F7/F8, C3/C4, P3/P4, O1/O2, T3/T4, T5/T6. Because of possible interference from eye movements in the analysis of recordings from the frontal lobe, we excluded Fp1/Fp2, F3/F4 derivatives.

STATISTICAL ANALYSES

Student's *t* test for independent samples was used for comparisons between children, with or without hypoglycaemia, of diabetic mothers for continuous outcome variables. For possible non-normal distribution of continuous outcome variables, log transformation was carried out before analysis. Group comparisons with nominally and ordinally scaled variables were done using Pearson's χ^2 test with calculation of p values adapted to small samples (StatXact 3, statistical software for exact nonparametric inference. Cytel Software: MA, 1996). Three group comparisons for hypoglycaemic, "normoglycaemic," and control children with respect to continuous outcomes were done using analysis of variance (ANOVA), with posthoc tests, according to Fisher's PLSD method. The level of significance was set at 0.05.

Results

We detected no differences between the mothers of infants in the test groups in prenatal and perinatal risk factors, including type of diabetes, age and weight at delivery, length of gestation, $HbA1_c$ during last trimester or type of delivery (table 1); nor were there any other differences in neonatal morbidity or growth characteristics at birth between the children in each group (table 1).

At follow up, measurements of height, weight, and head circumference did not differ between children in the test groups and control children, although a tendency towards a larger head circumference was noted in controls (table 2).

We found no difference in the neurological examination between children in the test groups and control children. The examination included evaluation of tendon reflexes, muscle strength, deep and superficial sensibility, gross assessment of movement, balance and coordination, as well as of hearing and vision. Five children born to diabetic mothers were left handed compared with one child in the control group.

Children with neonatal hypoglycaemia had a significantly higher total score in the minimal brain dysfunction screening test than controls, as did "normoglycaemic" children of diabetic mothers; $p < 0.05$ (table 4). In subtests children with neonatal hypoglycaemia had more difficulties than did control children when standing on one leg ($p < 0.05$) and cutting out a circle ($p < 0.01$). The same tendency was seen for three of the other four investigated items although they were not significant (table 4).

In the movement ABC test, we found no significant differences in the total score or in the three subtests between children in the test groups and control children, although the hypoglycaemic children tended to have a higher mean score than the controls in all subtests (table 4).

The parents' questionnaire identified four children of diabetic mothers with neonatal hypoglycaemia who were considered by the parents to be hyperactive, impulsive, and easily distracted, but none in the control group, $\chi^2 = 10.5$; $p = 0.004$ (table 4).

No child had a test result consistent with mental retardation. Those with neonatal hypoglycaemia had a lower total developmental quotient than those without and the control children ($p < 0.05$). Their score was significantly lower on the personal and social developmental scale ($p = 0.024$), compared with controls. The same tendency was seen on the hearing and speech scale ($p = 0.06$) (table 4). Six children of mothers with diabetes (four with, and two without, neonatal hypoglycaemia) had a markedly irregular test pattern compared with none in the control group.

Computerised analysis of the EEG frequency distribution showed no significant difference between children with or without neonatal hypoglycaemia in maximal power fre-

Table 4 MBD screening test, Movement ABC, and Griffiths' developmental test comparisons between children with or without hypoglycaemia in the neonatal period of diabetic mothers, and control children (number, abnormal : normal)

Test	*Hypoglycaemic (n=13)*	*Non-hypoglycaemic (n=15)*	*Controls (n=28)*
MBD screening test (number)			
1 Hop on one leg 20 times (abnormal : normal)	4:9	2:13	2:26
2 Stand on one leg for 20 seconds (abnormal : normal)	4:9*	4:11	1:27
3 Associated movements when walking on lateral sides of feet for 10 seconds (abnormal : normal)	5:8	2:13	4:24
4 Diadochokinesis for 10 seconds (abnormal : normal)	4:9	4:11	2:26
5 Cut out a paper circle with a diameter of 10 cm (abnormal : normal)	6:7*	7:8	3:25
6 WISC labyrinth test in accordance with description in manual (abnormal : normal)	3:10	2:13	1:27
Total score (points)	2.5 (2.8)*	1.6 (1.9)*	0.5 (0.6)
Screening test abnormal in ⩾ 3 items	5**	2	0
Movement ABC (points)			
Manual dexterity	1.96(2.4)	1.33 (1.7)	0.93 (1.0)
Ball skills	2.12(2.0)	2.13 (2.2)	1.75 (1.9)
Static and dynamic balance	1.50(2.4)	0.83 (1.3)	0.59 (1.2)
Total score	5.58(6.0)	4.30 (3.90)	3.27 (2.4)
Movement ABC > 13p	1	0	0
Movement ABC 10-13p	1	2	1
Parents' questionnaire			
Behavioural difficulties	4**	1	0
Griffiths' test (stanine units)			
Scale, personal and social development	4.8 (0.9)*	5.8 (1.3)	6.1 (1.6)
Scale, hearing and speech	6.4 (1.7)	7.0 (1.6)	7.7 (1.6)
Scale, eye and hand coordination	5.9 (2.4)	7.2 (1.7)	6.6 (1.6)
Scale, test of performance	5.1 (2.1)	5.8 (2.2)	5.9 (1.2)
Scale, practical reasoning	4.4 (1.6)	5.6 (1.4)	5.4 (1.8)
Total score (DQ)	94.9 (7.9)*	100.5 (5.7)	99.8 (5.4)

* p<0.05, ** p<0.01, compared to control children.

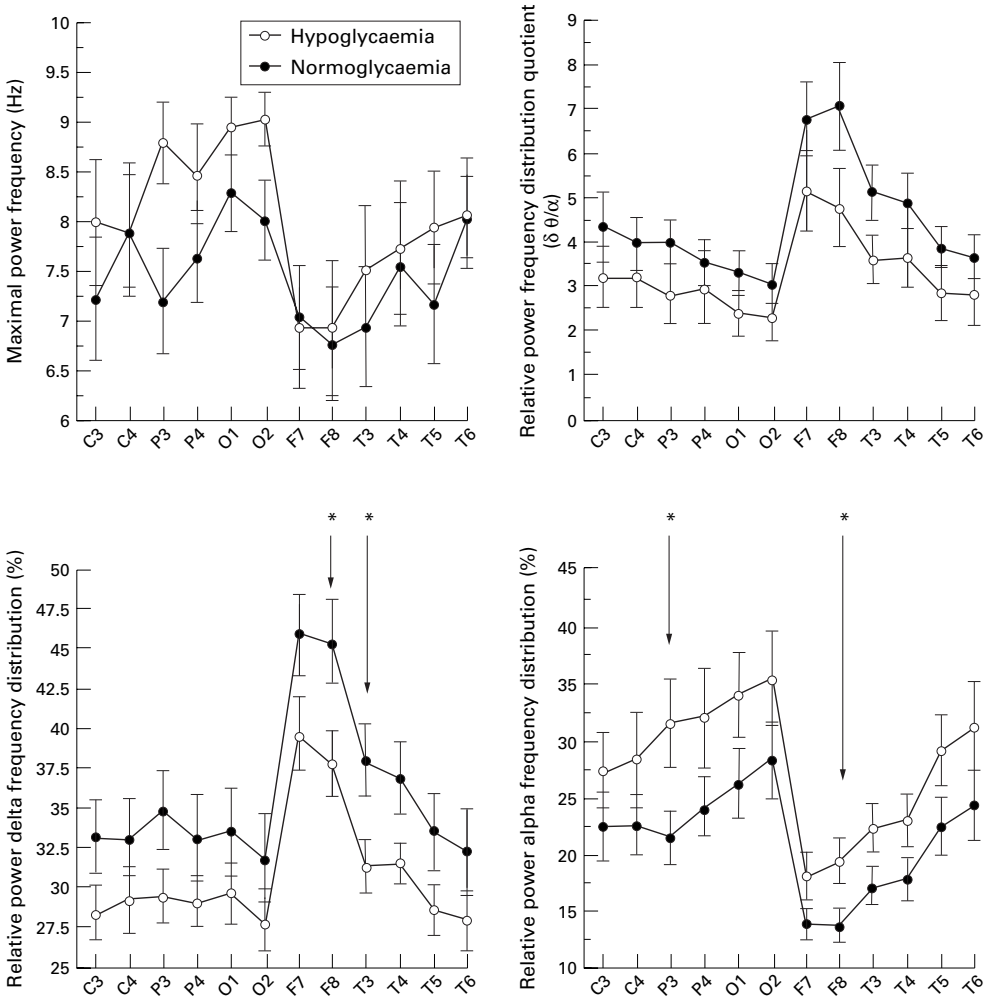

Figure 1 EEG maximal power frequency and relative power frequency distribution from 12 surface electrodes (horizontal axis) in children with (open circles) and without (closed circles) postnatal hypoglycaemia born to diabetic mothers: figures are mean (SEM).

quency or the relative power frequency distribution quotient in any of the 12 surface electrodes (fig 1). A lower relative δ power frequency distribution, in the fronto-temporal region (F8, T3), ($p = 0.03$), together with a higher relative α power frequency distribution in frontal and parietal regions (F8, P3), ($p = 0.03$) was found in children with neonatal hypoglycaemia than in those without (fig 1).

Discussion

Except for the excluded girl, we found no gross neurological abnormalities, including ophthalmological[30] or hearing impairments, in children of diabetic mothers at follow up. Despite the relatively small size of the study groups, children with neonatal hypoglycaemia had higher scores in the minimal brain dysfunction screening test than control children of the same age. Subtests, emphasising concentration, coordination, perception and fine motor function were most decisive, which is expected in children with minimal brain dysfunction/DAMP.[31] We also found a lower total developmental quotient with an irregular test pattern, including low scores on personal and social, hearing and speech scales, in children with neonatal hypoglycaemia. These findings indicate a lesion rather than a diffuse dysmaturation of the brain, but they may also be influenced by disturbances in auditory perception and concentration. The test pattern was similar to that found in early growth retarded children born to diabetic mothers,[23] which might indicate influences of the same origin related to the episodes of hypoglycaemia. In minimal brain dysfunction/DAMP, eye–hand coordination and performance scales are most frequently affected, but retardation in the development of speech and language is also common in this group.[31] Children with neonatal hypoglycaemia were also more often reported to be overactive, impulsive, and easily distracted, which agrees with observations in the minimal brain dysfunction screening test and in the psychological test, where concentration and tendency to distraction have an important role. None of the previous follow up studies has emphasised minimal brain dysfunction/DAMP related problems, although a recent study by Rizzo focused on behavioural problems related to child obesity in children of diabetic mothers.[32] Before 1960, studies mainly focused on survival rates and descriptions of malformations.[33 34]

Cerebral palsy, mental retardation, and minor neurological disorders, like language and behavioural problems, were reported earlier,[1] as well as a lower IQ, at the age of 4 to 5, in diabetic pregnancy complicated with acetonuria or amniotic infections, and in children with low birthweight.[17–19] These findings are primarily related to maternal vascular complications and poor metabolic control. With better antenatal treatment of diabetic pregnancies, the outcome for children has improved markedly with normal IQ scores, no relation to asymptomatic neonatal hypoglycaemia,[2 3] and no significant psychomotor impairment.[35] However, infants of diabetic mothers with early growth retardation are reported to have very low scores for personal and social development, gross motor function, and especially in language and speech, when tested at the age of 4.[23] An association has also been found between IQ, cognitive function,and disturbed maternal lipid metabolism in diabetic pregnancy.[20 21 24]

As far as we are aware, there has been no follow up in such children that has involved spectral analysis of EEG activity. Previous studies in children with IDDM have reported conflicting results regarding increased amounts of slow EEG activity.[36–38] Episodes of severe hypoglycaemia may affect fronto-central cerebral function in diabetic children.[38] Although the number of children investigated was small, we found no effect on the maximal power frequency or the relative power frequency distribution in children born to diabetic mothers with hypoglycaemia, as an indication of permanent neuronal damage. However, in children with neonatal hypoglycaemia we noted a lower δ and a higher α relative power frequency distribution in the fronto-temporal and fronto-parietal regions. This is consistent with findings in children with attention deficit hyperactivity disorders (ADHD) and attention deficit disorders (ADD), compared with control children and implies overarousal in the former groups.[39]

In contrast to previous studies, we found no difference in height or weight between children of diabetic mothers and control children at follow up. In earlier studies children of diabetic mothers were shorter,[33 40–42] taller,[24 34 34] or heavier[2 24 33 34 40 44] than control children. Nor did we find any significant difference in head circumference, although a tendency towards smaller head circumferences was noted in children born to diabetic mothers, which agrees with earlier observations.[2 45] The absence of differences between children born to diabetic mothers and controls could be due to small numbers in the study groups but probably reflects better management of diabetic pregnancy with fewer resulting vascular complications. The distribution of mothers was also dominated by those with gestational diabetes who had near normal $HbA1_c$ values during the third trimester.Our finding of no difference in other prenatal, perinatal, or postnatal characteristics between the children and their mothers, indicates that the observed differences between the groups is probably associated with neonatal hypoglycaemia. There is no consensus on the blood glucose concentration defining neonatal hypoglycaemia.[15] A critical concentration of 2.6 mmol/l has been suggested because of the neonatal neurophysiological findings[16] and psychological tests at follow up.[7] Long term studies in children born to diabetic mothers have used blood glucose concentrations of 1.1 mmol/l and 1.7 mmol/l, respectively, but no association has been detected between hypoglycaemia and unfavourable neurological outcome in the offspring.[2 3]

Our definition of hypoglycaemia was < 1.5 mmol/l for term infants. Most children were asymptomatic. Asymptomatic neonatal hypoglycaemia has previously been considered of

little importance for future neurodevelopment.[2 3 6 11] However, our findings indicate that even asymptomatic hypoglycaemia in children of diabetic mothers may be a risk factor for impaired neurodevelopment and must therefore be identified, prevented and treated.

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1 Yssing M. Long-term prognosis of children born to mothers diabetic when pregnant. In: Camerini-Davalos RA, Cole HS, eds. *Early diabetes in early life: proceedings of the third international symposium, Funchal, Madeira, December 1974.* New York: Academic Press, 1975: 575-86.
2 Cummins M, Norrish M. Follow-up of children of diabetic mothers. *Arch Dis Child* 1980;**55**: 259-64.
3 Persson B, Gentz J. Follow-up of children of insulin-dependent and gestational diabetic mothers. Neurophysiological outcome. *Acta Paediatr Scand* 1984;**73**:349-58.
4 Stenninger E, Schollin J, Åman J. Neonatal macrosomia and hypoglycaemia in children of mothers with insulin-treated gestational diabetes mellitus. *Acta Paediatr Scand* 1991;**80**: 1014-18.
5 Fluge G. Neurological findings at follow-up in neonatal hypoglycaemia. *Acta Paediatr Scand* 1975;**64**:629-34.
6 Koivisto M, Blanco-Sequerios M, Krause U. Neonatal symptomatic and asymptomatic hypoglycaemia: a follow-up study of 151 children. *Dev Med Child Neurol* 1972;**14**:603-14.
7 Lucas A, Morley R, Cole TJ. Adverse neurodevelopmental outcome of moderate neonatal hypoglycaemia. *BMJ* 1988;**297**:1304-8.
8 Cornblath M, Odell GB, Levin EY. Symptomatic neonatal hypoglycemia associated with toxemia of pregnancy. *J Pediatr* 1959;**55**:545-62.
9 Brown RJ, Wallis PC. Hypoglycaemia in the newborn infant. *Lancet* 1963;**i**:1278-82.
10 Haworth JC, McRae KN. The neurological and developmental effects of neonatal hypoglycemia: a follow-up of 22 cases. *Can Med Ass J* 1965;**92**:861-5.
11 Griffiths AD, Bryant GM. Assessment of effects of neonatal hypoglycaemia. A study of 41 cases with matched controls. *Arch Dis Child* 1971;**46**:819-27.
12 Cornblath M, Schwartz R, Aynsley-Green A, Lloyd JK. Hypoglycemia in infancy: The need for a rational definition. *Pediatrics* 1990;**85**:834-7.
13 Schwartz R. Neonatal hypoglycemia: Back to basics in diagnosis and treatment. *Diabetes* 1991;**40 suppl 2**:71-3.
14 Ward Platt MP. Hypoglycaemia in the newborn. *Curr Med Lit* 1991;**4**:31-4.
15 Koh TH, Eyre JA, Aynsley-Green A. Neonatal hypoglycaemia - the controversy regarding definition. *Arch Dis Child* 1988;**63**:1386-8.
16 Koh TH, Aynsley-Green A, Tarbit M, Eyre JA. Neural dysfunction during hypoglycaemia. *Arch Dis Child* 1988;**63**:1353-8.
17 Churchill JA, Berendes HW, Nemore J. Neuropsychological deficits in children of diabetic mothers. *Am J Obstet Gynecol* 1969;**105**:257-68.
18 Stehbens JA, Baker GL, Kitchell M. Outcome at ages 1, 3 and 5 of children born to diabetic women. *Am J Obstet Gynecol* 1977;**127**:408-13.
19 Naeye RL. The outcome of diabetic pregnacies: a prospective study. *Ciba Found Symp* 1979; **63**:227-41.
20 Rizzo TA, Ogata ES, Dooley SL, Metzger BE, Cho NH. Perinatal complications and cognitive development in 2- to 5-year-old children of diabetic mothers. *Am J Obstet Gynecol* 1994;**171:**706-13.
21 Rizzo TA, Dooley SL, Metzger BE, Cho NH, Ogata ES, Silverman BL. Prenatal and perinatal influences on long-term psychomotor development in offspring of diabetic mothers. *Am J Obstet Gynecol* 1995;**173**:1753-8.
22 Sells CJ, Robinson NM, Brown Z, Knopp RH. Long-term developmental follow-up of infants of diabetic mothers. *J Pediatr* 1994;**125**:s9-17.
23 Petersen MB, Pedersen SA, Greisen G, Pedersen JF, Mølsted-Pedersen L. Early growth delay in diabetic pregnancy: relation to psychomotor development at age 4. *BMJ* 1988;**296**:598-600.
24 Silverman BL, Rizzo T, Green OC, *et al*. Long-term prospective evaluation of offsprings of diabetic mothers. *Diabetes* 1991;**40 (suppl 2)**:121-5.
25 Gillberg C, Carlström G, Rasmussen P, Waldenström E. Perceptual, motor and attentional deficits in seven-year-old children. Neurological screening aspects. *Acta Paediatr Scand* 1983; **72**:119-24.
26 Gillberg C, Rasmussen P. Studie i Göteborg: MBD hos sex- och sjuåringar kan spåras med enkla diagnoshjälpmedel. *Läkartidningen* 1982;**79**:4413-14, 4419.
27 Gillberg C, Rasmussen P. Perceptual, motor and attentional deficits in six-year-old children. Screening procedure in pre-school. *Acta Paediatr Scand* 1982;**71**:121-9.
28 Hendersson S, Sugden DA. *Movement Assessment Battery for Children*. Sidcup, Kent: The Psychological Cooporation Ltd, 1992.
29 Griffiths R. *The abilities of young children*. London: Child development research centre, 1970.
30 McKinna AJ. Neonatal hypoglycemia-some ophthalmic observations. *Can J Ophthalmol* 1966;**1**:56-9.
31 Rasmussen P, Gillberg C. Perceptual, motor and attentional deficits in seven-year-old children. Paediatric aspects. *Acta Paediatr Scand* 1983;**72**:125-30.
32 Rizzo TA, Silverman BL, Metzger BE, Cho NH. Behavioral adjustment in children of diabetic mothers. *Acta Paediatrica* 1997;**86**:969-74.
33 Hagbard L, Olow I, Reinand T. A follow-up study of 514 children of diabetic mothers. *Acta Paediatrica* 1959;**48**:184-97.
34 Bibergeil H, Godel E, Amendt P. Diabetes and pregnancy. Early and late prognosis of children of diabetic mothers. In: Camerini-Davalos RA, Cole HS, eds. *Early diabetes in early life: proceedings of the third international symposium, Funchal, Madeira, December 1974.* New York: Academic Press, 1975: 427-34.
35 Weintrob N, Karp M, Hod M. Short- and long-range complications in offspring of diabetic mothers. *J Diabetes Complications* 1996;10:294-301.
36 Eeg-Olofsson O, Petersen I. Childhood diabetic neuropathy. A clinical and neurophysiological study. *Acta Paediatr Scand* 1966;**55**:163-76.
37 Eeg-Olofsson O. Hypoglycemia and neurological disturbances in children with diabetes mellitus. *Acta Paediatr Scand* 1977; **(Suppl 270)**: 91-6.
38 Bjørgaas M, Sand T, Gimse R. Quantitative EEG in Type 1 diabetic children with and without episodes of severe hypoglycemia: a controlled blind study. *Acta Neurol Scand* 1996;**93**:398-402.
39 Kuperman S, Johnson B, Arndt S, Lindgren S, Wolraich M. Quantitative EEG differences in a nonclinical sample of children with ADHD and undifferentiated ADD. *J Am Acad Child Adolesc Psychiatry* 1996;**35**:1009-17.
40 Farquhar JW. Prognosis for babies born to diabetic mothers in Edinburgh. *Arch Dis Child* 1969;**44**:36-47.
41 Breidahl HD. The growth and development of children born to mothers with diabetes. *Med J Aust* 1966;**1**:268-70.
42 Haworth JC, McRae KN, Dilling LA. Prognosis of infants of diabetic mothers in relation to neonatal hypoglycaemia. *Dev Med Child Neurol* 1976;**18**:471-9.
43 Weitz R, Laron Z. Height and weight of children born to mothers with diabetes mellitus. *Israel J Med Sci* 1976;**12**:195-8.
44 Gerlini G, Arachi S, Gori MG, *et al*. Developmental aspects of the offspring of diabetic mothers. *Acta Endocrinol (Copenh)* 1986;**277 (Suppl)**:150-5.
45 Hod M, Rabinerson D, Kaplan B, *et al*. Perinatal complications following gestational diabetes mellitus how "sweet" is ill? *Acta Obstet Gynecol Scand* 1996;**75**:809-15.