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SHORT COMMUNICATION

Quantitative EEG in type 1 diabetic adults with childhood exposure to severe hypoglycaemia: a 16 year follow-up study

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Abstract
Aims/hypothesis In diabetic children and adolescents, a history of severe hypoglycaemia (SH) has been associated with increased slow EEG activity and reduced cognition, possibly due to harmful effects of SH on the developing brain. In a group of type 1 diabetic patients with early exposure to SH, who had EEG abnormalities and reduced cognition in childhood, we have recently demonstrated that the reduced cognition may persist into adulthood. We have now assessed whether the reduced cognition was accompanied by lasting EEG abnormalities.
Methods In 1992–1993, we studied EEG and cognition in 28 diabetic children and 28 matched controls. 16 years later, we re-investigated the same participants, with 96% participation rate. Diabetic participants were classified as with (n=9) or without (n=18) early SH, defined as episodes with convulsions or loss of consciousness by 10 years of age. For each EEG band (delta, theta, alpha and beta) and cerebral region (frontocentral, temporal, and parietooccipital), we calculated relative amplitudes and amplitude asymmetry. We also calculated occipital alpha mean frequency, alpha peak frequency at maximum amplitude, alpha peak width, and theta regional mean frequencies. We examined whether these EEG measures, relative to age- and sex-matched controls, differed between diabetic participants with and without early SH.
Results We found no association of early SH with any of the EEG measures.
Conclusions/interpretation Childhood SH was not associated with EEG abnormalities in young type 1 diabetic adults. Our findings suggest that the reduced adulthood

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cognition associated with childhood exposure to SH is not accompanied by lasting EEG abnormalities.

Keywords EEG · Hypoglycaemia · Type 1 diabetes mellitus

Abbreviation
SH Severe hypoglycaemia

Introduction

Harmful effects of severe hypoglycaemia (SH) on the developing brain may explain why early-onset diabetes and exposure to SH have been associated with reduced cognition [1], structural brain alterations and EEG abnormalities [2–5] in diabetic children and adolescents [6]. Recent studies suggest that reduced cognition associated with childhood SH may persist into adulthood [7], but it is not known if the reduced cognition is accompanied by lasting EEG changes. In a group of type 1 diabetic patients with early exposure to SH, we have previously reported EEG abnormalities [2] and reduced cognition [1] in childhood and persistently reduced cognitive function after 16 years of follow-up [7]. We have now assessed whether these diabetic patients with childhood exposure to SH have EEG abnormalities in adulthood.

Methods

Study population In 1992–1993, we studied EEG [2] and cognitive function [1] in diabetic children. Among 73 diabetic children attending Trondheim University Hospital, the only referral centre for childhood diabetes in the region, we included all 15 children with prior SH and 13 diabetic children of similar age without prior SH. Each patient was matched with a control child of same sex and age.

In 2008, the participants were invited to a follow-up study [7] approved by the regional ethics committee. Twenty-seven of the 28 diabetic participants and all the original controls gave their informed consent prior to participation.

Assessment of metabolic control and medical history All diabetic participants attended Trondheim University Hospital during childhood and adolescence, and 19 of them also in adulthood. Medical history, including assessment of hypoglycaemic episodes, was obtained from hospital records and by personal interview. For participants who had moved from the region, additional information was obtained from local physicians.

SH was defined as episodes with convulsions or loss of consciousness. We categorised the diabetes–control pairs into two groups according to the diabetic patient's exposure to early SH (≤10 years of age, n=9) or not (n=18).

All HbA_{1c} measurements since diagnosis were recorded. HbA_1 (measured until 1989) was recalculated as HbA_{1c} following a method comparison at the hospital's Department of Clinical Chemistry. HbA_{1c} was measured more frequently in childhood than in adulthood. For each diabetic patient, we therefore computed mean HbA_{1c} for intervals of 4 years, from which we computed an overall weighted mean HbA_{1c}.

Quantitative EEG analysis EEG was recorded (Viasys NicOne Nervus 5.11) and digitised (256 Hz sample rate) from 16 scalp electrodes according to the 10–20 system, with the participants lying relaxed and supine with closed eyes. The participants were asked to open and close their eyes every minute. Eye movements were recorded. Blood glucose was measured in diabetic patients and snacks given if glucose was low. No participants had symptomatic hypoglycaemia during the recording.

EEG sequences without artefacts were selected and analysed using Harmonie software (Stellate systems, Quebec, Canada) by a clinical neurophysiologist who was blinded with respect to the participants' clinical status. Recordings from frontopolar (Fp1, Fp2) and frontotemporal (F7, F8) electrodes were excluded because of proximity to the eyes.

A Fast-Fourier transform was applied to average-referenced 4-s sections after cosine tapering (no overlap). For each EEG band, i.e. the delta (0.75–3.75 Hz), theta (4.00–7.75 Hz), alpha (8.00–12.75 Hz) and beta bands (13.00–30.00 Hz), we calculated the average relative amplitude (from the square root of the power in μV) within the frontocentral (EEG locations F3, F4, C3 and C4), temporal (T3, T4, T5 and T6), and parietooccipital (P3, P4, O1 and O2) regions. We also calculated occipital (O1 and O2) alpha mean frequency, alpha peak frequency at maximum amplitude, alpha peak width, and theta regional mean frequencies. Occipital spectra were seven-point smoothed before peak frequency and width were calculated.

Differences in amplitudes between the hemispheres may indicate increased EEG variability. For each EEG band and region, we calculated an amplitude asymmetry variable as the absolute value of the difference between amplitudes at right and left locations, divided by the sum of amplitudes of the right and left locations.

Statistical analyses For each relative amplitude and EEG frequency measure, we estimated mean values among diabetic participants with and without early SH and their respective controls. Alpha peak width was analysed after $\log_e$-transformation. Using a mixed linear model, we compared each diabetic participant with his/her control and estimated the effect of early SH, as expressed by the

interaction term between having diabetes and being part of a diabetes–control pair in which the diabetic patient was exposed to early SH. In separate analyses, we adjusted for the diabetic patients' blood glucose at EEG recording, but this adjustment did not substantially influence the estimates. Also, the results remained similar after exclusion of two pairs in which the diabetes patient (one with and one without early SH) experienced SH within 1 month prior to EEG recording.

To examine whether early SH was associated with amplitude asymmetry, we assessed whether the difference in each asymmetry variable between diabetic participants and controls differed between diabetic participants with and without early SH, using the Mann–Whitney *U* test.

In additional analyses, we categorised the diabetes–control pairs according to total number of SHs experienced by the diabetic patient since diabetes onset (≤2, $n=6$; 3–5, $n=10$; or ≥6, $n=11$) and assessed whether the number of SHs was associated with regional mean relative amplitudes or EEG frequency measures, as expressed by p for interaction between diabetes and number of SHs, using the categories of number of SHs as a continuous variable. Similarly, we examined whether overall mean HbA_{1c} (≤8.0%, $n=7$; 8.1–9.0%, $n=12$; or ≥9.1%, $n=8$) was associated with relative amplitudes or EEG frequencies. We used Kruskal–Wallis one-way analysis of variance by ranks to assess amplitude asymmetry in relation to number of SHs and overall HbA_{1c}.

The data were analysed using SPSS version 17.0 for Windows (SPSS, Chicago, Illinois, USA).

Results

Characteristics of the participants are given in electronic supplementary material (ESM) Table 1. Epileptiform activity was not observed.

We found no association of early SH with regional mean relative amplitudes or amplitude asymmetry in any EEG band or cerebral region (Table 1), nor with occipital alpha mean frequency, alpha peak frequency at maximum amplitude, alpha peak width, or theta regional mean frequencies (Table 2).

Total number of SHs and overall HbA_{1c} were not significantly associated with regional mean relative amplitudes or EEG frequencies (data not shown). Also, the

Table 1 Mean relative amplitudes in diabetic participants and controls, by early[a] exposure to SH, and the association of early SH with mean relative amplitudes and amplitude asymmetry

Location	Mean relative amplitudes (%)							Amplitude asymmetry: p value for association with early SH
	Diabetes with early SH		Diabetes without early SH		Association with early SH			
	Diabetic participants	Controls	Diabetic participants	Controls	Difference[b]	95% CI	p value[c]	
Frontocentral region								
Delta	17.1	18.1	18.9	20.6	0.7	(−3.4, 4.8)	0.73	0.30
Theta	16.9	16.6	17.7	18.5	1.1	(−2.9, 5.2)	0.57	0.10
Alpha	26.8	28.3	25.6	24.1	−3.0	(−10.0, 4.0)	0.39	0.24
Beta	39.2	37.0	37.7	36.8	1.2	(−6.4, 8.8)	0.76	0.08
Temporal region								
Delta	17.6	18.8	18.6	20.0	0.2	(−3.5, 4.0)	0.90	0.92
Theta	17.6	17.2	16.8	17.8	1.4	(−2.6, 5.4)	0.48	0.57
Alpha	28.6	29.7	27.4	24.7	−3.9	(−10.4, 2.6)	0.23	0.12
Beta	36.2	34.2	37.2	37.4	2.2	(−5.2, 9.6)	0.54	0.80
Parietooccipital region								
Delta	16.6	16.5	18.0	19.1	1.1	(−3.6, 5.7)	0.64	0.88
Theta	15.7	15.2	16.1	16.8	1.2	(−3.0, 5.5)	0.55	0.64
Alpha	33.3	35.4	32.6	30.4	−4.3	(−12.5, 3.8)	0.28	0.38
Beta	34.5	32.9	33.3	33.7	2.0	(−4.6, 8.7)	0.53	0.76

[a] By 10 years of age

[b] Difference in relative amplitude (percentage points) associated with early exposure to SH, calculated as (difference between diabetic participants with early SH and controls) − (difference between diabetic participants without early SH and controls)

[c] p value for interaction between having diabetes and being part of a diabetes–control pair in which the diabetic participant was exposed to early SH

Table 2 Mean EEG frequencies (Hertz) in diabetic participants and controls, by early[a] exposure to SH

Variable	Diabetes with early SH		Diabetes without early SH		Association with early SH		
	Diabetic participants	Controls	Diabetic participants	Controls	Difference[b]	95% CI	*p* value[c]
Alpha mean frequency at occipital electrodes	10.20	10.05	10.15	10.05	0.05	−0.55, 0.65	0.86
Alpha peak frequency at maximum amplitude	10.17	9.78	10.00	9.75	0.14	−1.16, 1.44	0.83
Alpha peak width at 50% amplitude[d]	1.42	1.29	1.06	1.04	8[e]	−42, 99	0.81
Frontocentral theta regional mean frequency	5.93	5.96	5.88	5.89	−0.01	−0.16, 0.14	0.87
Temporal theta regional mean frequency	5.95	5.95	5.89	5.90	0.01	−0.15, 0.17	0.91
Parietooccipital theta regional mean frequency	5.96	5.99	5.90	5.95	0.02	−0.16, 0.21	0.80

[a] By 10 years of age

[b] Difference in frequency (Hz) associated with early exposure to SH, calculated as (difference between diabetic participants with early SH and controls) − (difference between diabetic participants without early SH and controls)

[c] *p* value for interaction between having diabetes and being part of a diabetes–control pair in which the diabetic participant was exposed to early SH

[d] Geometric means

[e] Percentage increase associated with early exposure to SH

number of SHs and overall HbA_{1c} were not consistently associated with amplitude asymmetry. However, a high number of SHs was associated with asymmetry of frontocentral alpha amplitudes (p=0.046). High HbA_{1c} was associated with asymmetry of frontocentral delta amplitudes, whereas low HbA_{1c} was associated with asymmetry of frontocentral and temporal alpha amplitudes (all p=0.04).

Discussion

Quantitative EEG analysis and neuropsychological testing are two approaches to study potential cerebral damage from early SH. When the present participants were investigated at about 13 years of age, participants with prior SH had increased frontocentral theta activity and reduced alpha activity [2]. After 16 years of follow-up, however, childhood SH was not associated with persistent EEG abnormalities.

The present results contrast with the persistently reduced cognition that we have recently demonstrated in these participants with early SH [7]. Possibly, EEG abnormalities as markers of cortical dysfunction may normalise with time [8], even if subtle cerebral damage persists. This could explain why reduced cognition, but not EEG abnormalities, persisted into adulthood. Alternatively, the lack of association between childhood SH and adulthood EEG could support the hypothesis that impaired learning conditions in childhood [6], rather than lasting damage from SH on cerebral tissue, may explain the association of early SH or early-onset diabetes with reduced adulthood cognition.

In several, but not all [9] studies, prior SH has been associated with EEG abnormalities in diabetic children, adolescents [2–5], and adults [10], and particularly with globally [4, 10] or frontocentrally [2] increased slow (i.e. delta and theta) activity. In some studies, recurrent SH or poor metabolic control has been associated with EEG abnormalities [3, 4, 9], but we could not reproduce these findings. We found some evidence to suggest that number of SHs and HbA_{1c} were associated with amplitude asymmetry, but these findings did not display consistent patterns and were of borderline statistical significance, and may be due to chance.

A strength of this study is the nearly complete follow-up of diabetic patients and matched controls. The participants were selected in childhood and thus, subsequent events that may have influenced cerebral function did not bias the selection. Recall bias is not likely to have influenced the results, since all early SHs were contemporarily documented in the hospital records. The small sample size may have prevented us from detecting minor EEG abnormalities. Participants with early SH were younger at diabetes onset than participants without early SH (mean age 5 vs 10 years). However, it seems unlikely that this difference may explain why we found no association of childhood SH with adulthood EEG, unless early-onset diabetes could induce EEG changes that are opposite to those associated with SH.

In summary, this 16 year follow-up study of type 1 diabetic participants suggests that the reduced adulthood cognition related to childhood exposure to SH is not accompanied by lasting EEG abnormalities.

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B.O.Å. participated in the study design, analysed and interpreted the data, and drafted the manuscript. T.S. designed the study, analysed and interpreted the data, and revised the manuscript. K.A.H. participated in the study design, interpreted the data, and revised the manuscript. M.R.B. designed the study, interpreted the data, and revised the manuscript. All authors have approved the final version of the manuscript.

Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

References

1. Bjorgaas M, Gimse R, Vik T, Sand T (1997) Cognitive function in type 1 diabetic children with and without episodes of severe hypoglycaemia. Acta Paediatr 86:148–153
2. Bjorgaas M, Sand T, Gimse R (1996) Quantitative EEG in type 1 diabetic children with and without episodes of severe hypoglycemia: a controlled, blind study. Acta Neurol Scand 93:398–402
3. Haumont D, Dorchy H, Pelc S (1979) EEG abnormalities in diabetic children: influence of hypoglycemia and vascular complications. Clin Pediatr (Phila) 18:750–753
4. Hyllienmark L, Maltez J, Dandenell A, Ludvigsson J, Brismar T (2005) EEG abnormalities with and without relation to severe hypoglycaemia in adolescents with type 1 diabetes. Diabetologia 48:412–419
5. Soltesz G, Acsadi G (1989) Association between diabetes, severe hypoglycaemia, and electroencephalographic abnormalities. Arch Dis Child 64:992–996
6. Northam EA, Lin A (2010) Hypoglycaemia in childhood onset type 1 diabetes—part villain, but not the only one. Pediatr Diabetes 11:134–141
7. Asvold BO, Sand T, Hestad K, Bjorgaas MR (2010) Cognitive function in type 1 diabetic adults with early exposure to severe hypoglycemia: a 16-year follow-up study. Diabetes Care 33:1945–1947
8. Tupola S, Saar P, Rajantie J (1998) Abnormal electroencephalogram at diagnosis of insulin-dependent diabetes mellitus may predict severe symptoms of hypoglycemia in children. J Pediatr 133:792–794
9. Hauser E, Strohmayer C, Seidl R, Birnbacher R, Lischka A, Schober E (1995) Quantitative EEG in young diabetics. J Child Neurol 10:330–334
10. Howorka K, Pumprla J, Saletu B, Anderer P, Krieger M, Schabmann A (2000) Decrease of vigilance assessed by EEG-mapping in type I diabetic patients with history of recurrent severe hypoglycaemia. Psychoneuroendocrinology 25:85–105