CLINICAL STUDY

Utility of P300 auditory event related potential latency in detecting cognitive dysfunction in growth hormone (GH) deficient patients with Sheehan's syndrome and effects of GH replacement therapy

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Abstract

Objective: Impaired cognitive function has been demonstrated in adults with growth hormone (GH) deficiency (GHD) by using different neuropsychological tests. Despite several studies, present knowledge about the impact of GHD and GH replacement therapy (GHRT) on cognitive function is limited. P300 event-related potential (ERP) application is a well-established neurophysiological approach in the assessment of cognitive functions including the updating of working memory content and the speed of stimulus evaluation. GHD is a well-known feature of Sheehan's syndrome and cognitive changes due to GHD and the effects of GHRT remain to be clarified. The present study was designed to investigate the effects of GHD and 6 months of GHRT on cognitive function in patients with Sheehan's syndrome by using P300 latency.

Design and methods: The study comprised 14 patients with Sheehan's syndrome (mean age, 49.5 ± 7.8 years) and 10 age-, education- and sex-matched healthy controls. With hormone replacement therapy, basal hormone levels other than GH were stable before enrollment and throughout the GHRT. The diagnosis of GH deficiency was established by insulin-tolerance test (ITT), and mean peak level of GH in response to insulin hypoglycemia was 0.77 ± 0.35 mIU/L. Treatment with GH was started at a dose of 0.45 IU (0.15 mg)/day in month 1, was increased to 0.9 IU (0.30 mg)/day in month 2 and was maintained at 2 IU (0.66 mg)/day. Initially baseline auditory ERPs in patients and controls were recorded at frontal (Fz), central (Cz), and parietal (P3 and P4) electrode sites. In the patient group, ERPs were re-evaluated after 6 months of GH replacement therapy. During each session P300 amplitude and latency were measured.

Results: Mean serum insulin-like growth factor-I (IGF-I) concentration in the patient group before GHRT was 23 ± 13 ng/ml. After 6 months of GH therapy mean IGF-I significantly increased to an acceptable level, 234 ± 71 ng/ml ($P < 0.05$). The mean latencies (at all electrode sites) of the patients before GHRT were found to be significantly prolonged when compared with those of normal controls ($P < 0.05$). After 6 months of GHRT mean P300 latencies (at all electrode sites) were decreased significantly when compared with latencies before treatment ($P < 0.05$).

Conclusions: The present study, using P300 ERP latencies, therefore suggests an impairment of cognitive abilities due to severe GHD in patients with Sheehan's syndrome and an improvement of cognitive function after 6 months of physiological GHRT. Moreover, this was a novel application of P300 ERP latencies in cognitive function detection in patients with GHD. Further studies with different patient groups need to be done to assess the clinical use of this electrophysiological method in the diagnosis of cognitive dysfunction due to GHD.

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Introduction

Growth hormone (GH) deficiency (GHD) in adulthood is associated with adverse changes in exercise tolerance, body composition, bone mineral density, cardiovascular function and lipid profile (1). GH also appears to effect psychological functioning (2–4). In recent years much

interest has been expressed, and effort expanded, about the possibility that cognitive function is related to insulin-like growth factor-I (IGF-I) and GH. Indeed, impaired cognitive function has been demonstrated in adults with childhood-onset GHD (CO GHD) (2) and in adult-onset GHD (AO GHD) (5). In addition, a few studies have demonstrated that GH replacement

therapy (GHRT), in both adults with CO GHD and AO GHD, has beneficial effects on cognitive deficits (3, 5). In all of these studies, neuropsychological tests (questionnaires) have been used to assess cognitive performance. Despite these studies, present data about the impact of GHD and GHRT on cognitive function is limited. This is due to the absence of sufficient numbers of studies with homogenous patient groups and relevant control groups, and to a lack of uniformity in the psychological tests (6).

Event-related potentials (ERPs) are cerebral responses associated with various psychological events or cognitive functions such as recognition of certain stimuli, and are an objective parameter reflecting cognitive functions (7). Previous studies have demonstrated that the P300 amplitude is related to the updating of working memory content, and the P300 latency is related to the speed of stimulus evaluation (8, 9). P300 is one of the most prominent positive peaks occurring around 300 ms after the infrequently presented target stimulus to which the subject is requested to respond by a certain task in the 'odd-ball paradigm' (10). Abnormally prolonged P300 latencies have been reported in Parkinson's disease (11), Alzheimer's disease, dementias (12) and depression (7). Although P300 latency is a well-established parameter in cognitive function assessment in several disorders, electrophysiological changes in adults with GH deficiency have not yet been studied.

Sheehan's syndrome is a clinical condition due to postpartum necrosis of the anterior pituitary gland. It is still a serious health problem in some developing countries. GH is one of the earliest hormones lost and it was reported that GHD was neither variable according to the degree of hypopituitarism nor related to the number of additional anterior pituitary hormone deficiencies in Sheehan's syndrome (13, 14). Changes in cognitive function due to GHD and the effects of GHRT in Sheehan's syndrome remain to be clarified.

The present study was therefore designed to use ERPs to investigate the effects of GHD and 6 months of GHRT on cognitive function in patients with Sheehan's syndrome.

Subjects and methods

Subjects

The study comprised 14 patients with Sheehan's syndrome (mean age, 49.5 ± 7.8 years; range, 30–58 years) and 10 age-, education- and sex-matched healthy controls (mean age, 48.1 ± 7.6 years; range, 29–56 years). This study was approved by the Ethics Committee and the Institutional Review Board of Erciyes University Medical School, and informed consent was obtained from each patient.

The patients were previously diagnosed with Sheehan's syndrome and the mean duration of the disease

(time interval between the last labor and the diagnosis of the hypopituitarism) was 14.7 ± 5.5 years (range, 6–25 years). The mean body mass index of the patients was 28.9 ± 1.5 kg/m². Criteria for the diagnosis of Sheehan's syndrome included: (i) history of postpartum haemorrhage and/or history of postpartum failure of lactation and/or secondary amenorrhea; (ii) varying grades of loss of pituitary hormone reserve; (iii) good clinical response to hormone replacement therapy; and (iv) exclusion of pituitary mass lesion. In all cases, hormone deficiencies other than GH (Table 1) had been replaced with levothyroxine, adrenal steroids (prednisolone), sex steroids (ethinyl estradiol 20 µg and degestrol 150 µg, orally) and desmopressin acetate. With conventional hormone replacement therapy, basal hormone levels had been stable for at least 6 months before enrollment and during GHRT.

The diagnosis of GH deficiency was established by an insulin-tolerance test (ITT) and was defined as a peak GH level < 10 mIU/l after the test. After an overnight fast, the ITT was performed using i.v. regular insulin (0.1 U/kg) and serum glucose, cortisol, and GH levels were measured before and after 30, 45, 60 and 90 min. Patients with a history of current diabetes mellitus, any sign of neuropathy, atrial fibrillation, bundle branch block, history of myocardial infarction, heart failure, hypertension, seizure disorders or who were receiving any medication that might interfere with autonomic regulation were excluded. Serum GH levels were measured using immunoradiometric assay with a commercial kit (Immunotech, Marseille, France) intra- and interassay coefficients of variation were

Table 1 Peak GH response to ITT, IGF-I levels before and after GHRT, and clinical descriptions of patients with Sheehan's syndrome.

Patient	Age (years)	Duration ^a (years)	Other hormones ^b	GH ^c	IGF-I ^d	IGF-I ^e
1	50	16	G, T	0.8	17	364
2	52	16	G, T, A	0.3	11	203
3	54	17	G, T, A	0.3	18	200
4	54	16	G, T	0.8	9	277
5	35	6	G, T	0.6	18	228
6	57	11	G, T, A	0.7	22	160
7	50	20	G, T, A	0.3	12	147
8	58	17	G, T, A	0.6	12	199
9	50	14	G, T, A, ADH	1.1	41	290
10	48	15	G, T, A	1.3	35	190
11	54	25	G, T, A	1.3	14	249
12	50	6	G, T, A	1.2	51	166
13	51	20	G, T, A	1.0	25	221
14	30	7	G, T, A	0.6	45	382

^a Duration of the disease; time interval between the last labor and the diagnosis of the hypopituitarism.

^b Hormone deficiencies other than GH: G, gonadotropins; T, thyroid-stimulating hormone; A, adrenocorticotropin hormone; ADH, anti-diuretic hormone.

^c Peak GH response to ITT (mIU/l).

^d IGF-I levels (ng/ml) before GHRT.

^e IGF-I levels (ng/ml) after 6 months of GHRT.

0.66 and 13.45% respectively. All patients had serum glucose levels < 2.2 mmol/l at ITT.

GH administration protocol

GH treatment was given according to the recommendations of the Growth Hormone Research Society Workshop (15). The patients were not previously treated with GH. GH was self-administered at night (s.c.) and drug compliance was assessed by vial count. Treatment with GH (Genotropin, Pharmacia & Upjohn AB, Stockholm, Sweden) was started at a dose of 0.45 IU (0.15 mg)/day in month 1, was increased to 0.9 IU (0.30 mg)/day in month 2 and was maintained at 2 IU (0.66 mg)/day until the end of month 6. With a similar maintenance dose adequate IGF-I levels for each patient were achieved. After baseline measurement, patients were seen at 3 and 6 months and IGF-I levels were measured. IGF-I in serum was measured by immunoradiometric assay after formic acid-ethanol extraction (BC1010, Biocode SA, Liege, Belgium); intra- and interassay coefficients of variation were 3.4 and 8.4% respectively. The minimum detectable concentration of IGF-I was 5 ng/ml; the reference ranges for the relevant ages were 83–570 ng/ml (30–45 years) and 61–430 ng/ml (46–60 years).

ERP recording techniques Baseline auditory ERPs in patients with Sheehan's syndrome and controls were recorded initially. In the patient group, ERPs were re-evaluated after 6 months of GHRT. The reproducibility and reliability of the P300 latency measurements have been clearly established by short- and long-term studies in normal controls after repeated recordings (16, 17). On each session P300 amplitude and latency were measured. In all patients, the P300 recordings were taken before breakfast (at 0830 h) after an optimal overnight sleep. All measurements were performed by the same physiologist at the Department of Physiology Brain Dynamics Center and the physiologist was unaware of the patients' treatment status (18, 19).

Recording conditions Electronencephalogram (EEG) activity was recorded at the frontal (Fz), central (Cz) and parietal (P3 and P4) electrode sites of the 10/20 international system using Ag/AgCl electrodes, affixed with electrode paste and tape, with an impedance of 10 k Ohm or less. The reference electrode was attached to the right earlobe and the ground electrode was attached to the left earlobe. The signals from the electrodes were amplified and band-passed between 0.3 and 100 Hz by bioelectric amplifiers (AB-621 G, Nihon Kohden). EEG was digitized at 1000 Hz with a 1024 ms pre-stimulus baseline. Wave forms were collected and averaged off-line by a Pentium 100 computer, which also controlled the stimulus presentation (Brain Data acquisition station). Automatic artifact

rejection was used, based on signal amplitude ($> 50 \mu\text{V}$ or $< -50 \mu\text{V}$) in Fz.

Stimuli The 'odd-ball paradigm' was applied to all subjects. In this paradigm, standard (2000 Hz) and target (1000 Hz) auditory stimuli with a duration of 1000 ms were presented to the subject binaurally over headphones. The deviant tone was designated as target and was counted by the patient. The target tone occurred regularly with a 0.20 probability. The rise and fall time of each tone was 5 ms.

Procedure On arrival, the subject was familiarized with the procedure in a dimly lit room. The experiment started with a 5 min adaptation period during which the EEG was calibrated. After the electrodes were attached, the subject was provided with an adjustable chair in an isolated room adjacent to the recording room. Subjects were instructed to sit quietly with open eyes, follow the stimuli carefully and to try to count rare tones of 1000 Hz frequency. Prior to the experiments 20 tones with altering frequencies (2000 and 1000 Hz) were demonstrated to the subjects. Subjects were also asked not to move, speak or blink too much, and were instructed to look at a fixed point. Twenty responses to standard or target stimuli were averaged at each location. The amplitudes were measured with respect to peak-to-peak. The amplitude and latency measurements obtained in patients before and after GHRT were compared with control values.

Statistical methods

Statistical analysis was performed using the SPSS 10.0 program. All results are presented as means $\pm$ s.d. The results of the study were analyzed using two-sided Mann-Whitney and Wilcoxon ranked tests for unpaired and paired data. $P < 0.05$ was considered significant.

Results

Biochemical results and side-effects

The mean peak level of GH in response to insulin hypoglycemia was 0.77 ± 0.35 mIU/l. The peak GH response in all patients was < 6 mIU/l, which is accepted as severe GH deficiency. Clinical characteristics of the patients and peak GH responses to ITT are summarized in Table 1.

The mean serum IGF-I concentration in the patient group before GHRT was 23 ± 13 ng/ml. After 6 months of GH therapy, mean IGF-I level significantly increased to 234 ± 71 ng/ml ($P < 0.05$). In all cases IGF-I concentrations were within the age-dependent normal reference ranges after 6 months of GHRT (Table 1). Three patients receiving GH developed mild arthralgia which resolved without dose reduction. All patients tolerated the maintenance dose well.

P300 event-related potentials

The grand means of the ERPs at all electrode sites for the three groups (control group, women with Sheehan's syndrome before GHRT and women with Sheehan's syndrome after 6 months GHRT) are presented in Fig. 1.

The latencies of the P300 component measured at the Fz, Cz, P3 and P4 electrode sites were assessed separately. Mean latencies (at all electrode sites) of the patients before GHRT were found to be significantly prolonged when compared with those of normal controls ($P < 0.05$, Table 2). After 6 months of GHRT, mean P300 latencies (at all electrode sites) were decreased significantly when compared with latencies before treatment ($P < 0.05$, Table 2). There was no difference between the latencies of the patients after GHRT and normal control values ($P > 0.05$). The mean P300 latencies are summarized in Table 2. We could not demonstrate any significant difference between P300 amplitudes of the three groups at all sites ($P > 0.05$, Table 3).

When individual data before and after GHRT in 14 patients were analyzed, the number of patients with

decreased P300 latencies at Fz, Cz, P3 and P4 were 10, 11, 11 and 10 respectively.

Discussion

Using ERP recordings, the present study clearly indicates the prolongation of P300 latencies in Sheehan's syndrome patients with severe GHD. Furthermore, 6 months of GHRT significantly normalizes the P300 ERP latencies at all electrode sites. P300 ERP application (especially P300 ERP latency) is a well-established neurophysiological approach in any disease where cognitive functions are impaired (20). In addition it has been found to be relatively simple, non-invasive, reproducible and safe to implement as compared with other brain metabolic and structural studies (16, 21, 22). P300 latency is reported to reflect the duration of the evaluation process for an event or stimulus (23). In brief, P300 latency has been related to the speed of stimulus evaluation (9). Moreover, P300 latency is reported to exhibit good correlation with the neuropsychological tests conventionally used to assess cognitive performance; for example, the

Figure 1 The grand means of the event-related potentials at Fz, Cz, P3 and P4 electrode sites in: control group (trace a); subjects with Sheehan's syndrome after 6 months GHRT (b); subjects with Sheehan's syndrome before GHRT (c). The heavy line at 0 ms represents the stimuli and all traces have 128 ms pre-stimulus baseline. Numbers under traces (on the peak of the P300 wave) represent mean P300 latencies (in ms) in subjects with Sheehan's syndrome before (trace c) and after treatment (trace b).

Table 2 Mean P300 latencies (in ms) in control group and in subjects with Sheehan's syndrome before and after GHRT.

Groups	Electrode sites			
	Fz	Cz	P3	P4
Control	335.60±14.56	334.30±11.57	334.55±9.85	333.50±13.89
Before GHRT	357.78±23.18*	351.07±20.93*	353.30±18.43*	350.78±19.49*
After GHRT	337.58±11.52†	336.78±12.55†	335.00±12.92†	334.45±13.69†

Data are expressed as means±s.d. * $P < 0.05$ before treatment vs control. † $P < 0.05$ before treatment vs after treatment. Fz, frontal; Cz, central; P3 and P4, parietal; GHRT, growth hormone replacement therapy.

Table 3 Mean P300 amplitudes (in mv) in control group and in subjects with Sheehan's syndrome before and after GHRT.

Groups	Electrode sites			
	Fz	Cz	P3	P4
Control	8.66±5.28	8.98±3.74	9.47±4.55	9.19±3.16
Before GHRT treatment	9.31±5.98	9.27±2.44	8.19±3.78	8.86±3.92
After GHRT treatment	10.72±5.81	9.95±4.27	9.71±4.55	11.09±4.2

Data are expressed as means±s.d. $P > 0.05$ between the three groups at all electrode sites. Fz, frontal; Cz, central; P3 and P4, parietal; GHRT, growth hormone replacement therapy.

Wechsler Adult Intelligence Scale (WAIS) score (24) and the Wechsler memory scale (25). The latency of the P300 wave has been studied in various conditions (such as hepatic encephalopathic patients (26), major depression (7) and dementia (12)) where cognitive ability is affected. Whereas previous findings indicate the clinical usefulness of P300 latency prolongation as an objective parameter in several disorders with impaired cognitive function, further placebo-controlled trials with sufficient numbers of patients need to be done for the clinical application of this parameter in GHD. By using our preliminary observations with a restricted number of patients and normal controls it is difficult to define a pathological cut-off P300 latency for clinical interpretation.

Although it is not as extensively studied as P300 latency, a relationship between P300 amplitude and memory processing has been demonstrated (27). In several studies, alterations in both P300 latency and P300 amplitude in patients with cognitive dysfunction have been reported (20, 21). In the present study, we could not demonstrate any significant difference in P300 amplitudes between the GH-deficient patients (before and after treatment) and normal controls. The underlying mechanisms of prolongation of P300 latencies, but without significant change in P300 amplitudes, in GH-deficient patients with Sheehan's syndrome remain to be clarified. Consistent with our findings, prolonged P300 latencies without significant differences in amplitude have recently been demonstrated in Behcet's patients with cognitive impairment (28).

Impaired cognitive function has been determined in adults with CO GHD (2, 29). Forty-eight men with CO GHD have been evaluated in a comprehensive study and impaired memory performance as well as lower

intelligence scores have been demonstrated in men with either isolated GHD or multiple pituitary hormone deficits, including GHD (2). In adults with CO GHD the effects of GH replacement on cognitive performance have been evaluated in several studies. There are contradictory results from two earlier studies. Improved recognition memory has been reported in five individuals with multiple pituitary hormone deficits who were treated with GH for 4 weeks (30). In contrast, Degerblad *et al.* (31) performed a placebo-controlled cross-over study using GH for 12 weeks in a small number of patients but improvements in cognitive function were not demonstrated. In another study in adults with CO GHD, 6 months of GHRT has been reported to be associated with an improvement of the WAIS score (29). Recently, Deijen *et al.* (3) reported an improvement in memory function after 2 years of GHRT in 48 males with CO GHD.

The cognitive function in AO GHD has not been as extensively studied as in CO GHD. Burman *et al.* (5) have documented the effects of GHD and GHRT on quality of life and on cognition by the use of self-rating tests (psychological parameters, including cognition, have been assessed by a subscale of the Hopkins Symptom Check List) and by a partner questionnaire which are not formal tests on cognition. When compared with healthy controls, more problems in cognitive function in patients with AO GHD (15 females and 21 males) have been reported. Moreover, compared with placebo, 21 months of GH treatment has been shown to improve quality of life and cognitive ability (5). Consistent with previous findings both in CO and AO GHD, we have observed impaired cognitive function due to severe GHD in patients with Sheehan's syndrome when compared with age- and sex-matched healthy women.

In a recent contradictory study, Baum *et al.* (32) have evaluated cognitive function by using several neuropsychological questionnaires in 40 patients with AO GHD, and no changes in cognitive performance were observed after 18 months of GHRT (32). However, a limitation of Baum's study was that no significant differences in cognitive function between the GH-deficient patients and normal controls were demonstrated at baseline. These controversial results, in different studies, may be due to the heterogeneity of the etiology of the pituitary diseases, a lack of uniformity in the psychological tests, and differences of treatment modalities which may interfere with cognitive function (6). All the patients in the present study had the same etiology of GHD and none of them had had any surgery and/or radiotherapy. After 6 months of GHRT, mean P300 latencies (at all electrode sites) were decreased significantly when compared with latencies before treatment. Moreover, when individual data of all patients were evaluated, P300 latencies decreased in the majority of patients at all electrode sites after GHRT. As shown in our results, only a few patients did not demonstrate the similar latency decrease at all electrode sites (but they showed a P300 latency decrease at at least one site). The different GH-induced effects at different electrode sites in this minority of patients might be due to the short duration of GHRT. We have therefore clearly demonstrated, using P300 ERP latencies, that after 6 months of physiological GHRT there was an improvement of cognitive function; and an improvement in the duration of the evaluation process for an event or a stimulus in particular.

While the neurotransmitters and the molecular mechanisms playing a role in the generation of the P300 component have not yet been elucidated, to our knowledge, observations in the present study provide the first evidence for electrophysiological changes due to GHD and/or low IGF-I levels. Normalization of P300 latencies after physiological doses of GHRT suggests that the underlying disturbances in neural cell metabolism are normalized by either direct or indirect central effects of GH and/or IGF-I. Further experimental and clinical data are warranted to clarify the basic mechanisms of the effects of the GH-IGF-I axis on cognition.

In summary, the present study used P300 ERP latencies to evaluate cognitive function in patients with GHD; the results suggest an impairment of cognitive abilities due to severe GHD in patients with Sheehan's syndrome and an improvement of cognitive function after 6 months of physiological GHRT. Moreover, this was a novel application of P300 ERP latencies in cognitive function detection in patients with GHD. Further studies with different patient groups are needed to assess the clinical use of this electrophysiological method in the investigation of cognitive dysfunction in patients with GHD.

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