Assessment of brainstem auditory evoked potentials (BAEPs) in patients with acromegaly

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Abstract

OBJECTIVES: Acromegaly is associated by various systemic complications, involving also the nervous system. Other studies revealed peripheral but not central nervous system impairment with somatosensory evoked potentials examinations in acromegaly. Aim of the present study was to assess whether brainstem transmission in acromegaly is disturbed.

MATERIAL AND METHODS: The study was carried out in 37 patients. The control group consisted of 47 healthy persons. In all of the subjects, peripheral transmission, reflected by peak I latency, and brainstem transmission, tested by interpeak latency I-V (IPL I-V), were examined.

RESULTS: Peak I latency was delayed in 6 out of 37 patients (1 – bilaterally, 2 – right side, 3 – left side). The group-mean latency of peak I was 1.53 msec and 1.56 msec, for the right and left side, respectively. There were found no statistically significant differences between the right and left side, likewise in comparison with control group. In turn, as compared with the controls, IPL I-V was disturbed in 25 out of 37 patients: in most of the cases IPL I-V prolongation was observed (8 – bilateral prolongation, 11 – right side, 6 – left side). Moreover, the statistically significant difference between the brainstem sides (4.27 vs. 4.11 msec; $p<0.05$) was observed.

CONCLUSION: In the examined patients with acromegaly, there was no peripheral disturbance in transmission, as examined by BAEPs registrations. Conversely, in nearly half of the patients with acromegaly, brainstem transmission was found to be delayed, and significant difference between responses from the both sides of the brainstem were noted.

ORIGINAL ARTICLE

Abbreviations:
BAEPs – brainstem auditory evoked potentials
DM – diabetes mellitus
GH – growth hormone
IGF-1 – insulin-like growth factor-1
IPL – inter-peak latency

INTRODUCTION

Acromegaly is a rare generalized disease caused by a pituitary growth hormone (GH) secreting tumor. Soft tissue enlargement and enhanced skeletal growth represent typical signs of the disease. Insulin-like growth factor-1 (IGF-1) is a GH peripheral mediator and it is responsible for the majority of systemic and metabolic effects of GH overproduction [1, 2].

In addition to numerous metabolic complications, like arterial hypertension, atheromatosis, diabetes mellitus and skeletal deformities, impairments of nervous system also appear [3, 4, 5]. Patients suffering from active acromegaly manifest the increased mortality rate, which returns to a population level if only a normalization of GH and IGF-1 secretion is achieved using successful therapy [3, 6]. Up to now, in patients with acromegaly, only few studies have revealed peripheral nerves involvement in somatosensory evoked potentials examination, but no central nervous system disturbances were documented [7, 8, 9].

There is a well-known relation between occurrence of acromegaly and diabetes mellitus (DM) [3, 5]. Up to 25% of patients with acromegaly have a decreased glucose tolerance or manifest evident symptoms of DM [10]. Some authors reported abnormalities of brain evoked potentials (EPs) found in diabetes mellitus, however, there is a scarcity of data concerning EPs changes in patients with clinical evidence of acromegaly [11, 12, 13].

A purpose of our study was to assess whether brainstem transmission in patients with acromegaly is disturbed.

MATERIAL AND METHODS

Subjects

A group of 37 consecutive patients (22 women and 15 men) treated because of acromegaly was enrolled in the present study. The mean age of the patients was 51.7 years, with a range between 21.1 and 77.8 years. In 12 of the 37 patients analyzed, the active stage of acromegaly was ascertained, whereas the remaining ones were in inactive phase of the disease, following successful surgery or somatostatin analogs chronic therapy.

Methods

Examinations of brain-stem auditory evoked potentials (BAEPs) were performed using monaural stimulation with a click sound of 70 dB intensity administered with a frequency of 10 Hz. Analysis of BAEPs tracings obtained from the patients concerned two crucial parameters, i.e., peak I latency and inter-peak latency I-V (IPL I-V). The results were referred to the data collected from the 47 age- and gender-matched normal subjects serving as a control group. Furthermore, the study results were compared to the BAEPs normative values established in our laboratory basing on the results of the over 20-year examinations. In our laboratory, the normal range for peak I latency is between 1.26 and 1.76 msec, and IPL I-V ranged from 3.85 to 4.20 msec.

Statistical analysis

Standard statistical Student *t*-test was applied for comparison of the two variables. The values are presented as the mean ± SD, and a level of statistical significance was set at $p < 0.05$.

RESULTS

Evaluation of peak I latency

The mean latency of BAEPs peak I noted in the control group was 1.54 ± 0.11 msec for the right-sided responses and 1.53 ± 0.11 msec for the left-sided responses. In turn, peak I latency observed in the examined patients with acromegaly fell in a range from 1.20 to 2.08 msec. Totally, a delay of peak I latency was observed in 6 out of 37 examined patients (16.2%), including 1 patient with a bilateral delay. Of these 6 delayed responses, 2 was right-sided, 3 left-sided, and in 1 case a bilaterally delay of peak I was observed. In 50% of the cases with a delayed latency of peak I, a prolongation was rather slight – the mean latency was 1.76 msec – however, in 4 patients (28.6%) a delay appeared to be longer than 1.90 msec.

For right-sided responses, the mean latency was 1.53 ± 0.19 msec, whereas for left-sided ones, it was 1.56 ± 0.21 msec. In the patient group, the Student *t*-test did not reveal any statistically significant differences between the values of peak I latency recorded for the right- and left-sided evoked responses. There were also no significant differences in relation to the group-mean value of peak I latency when the acromegaly group and the control group were compared.

The results concerning latency values of BAEPs peak I obtained from the two considered groups are depicted in Table I.

Considering possible divergences between the patients with active phase of acromegaly and those who were successfully cured, peak I latency did not show any significant differences between the individual patient groups, i.e., with DM, with prediabetes, and without disturbances of glucose tolerance.

Evaluation of inter-peak latency I-V

In the examined patients with acromegaly, IPL I-V was found to range from 3.68 msec to 4.88 msec. Comparison of the results with the laboratory normative values is depicted in Tab. II.

Table I. Peak I latency in the acromegaly group and in the control group

	Latency of peak I [msec]					
	Mean ± SD		Minimal value		Maximal value	
	Right-sided	Left-sided	Right-sided	Left-sided	Right-sided	Left-sided
Acromegaly - entire group	1.53 ± 0.19	1.56 ± 0.21	1.28	1.20	2.08	2.08
Acromegaly with DM	1.46 ± 0.18	1.63 ± 0.33	1.28	1.20	1.68	2.08
Acromegaly with prediabetes	1.53 ± 0.17	1.51 ± 0.18	1.36	1.28	2.00	1.76
Acromegaly without DM	1.56 ± 0,20	1.57 ± 0.19	1.28	1.36	2.08	2.00
Control group	1.54 ± 0.11	1.53 ± 0.11	1.26	1.28	1.75	1.75

Table II. Comparison of the IPL I-V values between the patients with acromegaly and the controls

Result	No. of cases	Percentage
Bilaterally normal IPL I-V	10	27.0%
Bilaterally delayed IPL I-V	8	21.6%
Right-sided IPL I-V prolongation with:		
- left-sided IPL I-V shortening	5	13.5%
- left-sided normal IPL I-V	6	16.2%
Left-sided IPL I-V prolongation with:		
- right-sided IPL I-V shortening	0	0%
- right-sided normal IPL I-V	6	16.2%
Right-sided IPL I-V prolongation with left-sided normal IPL I-V	1	2.7%
Left-sided IPL I-V shortening with right-sided normal IPL I-V	1	2.7%
Total	37	100%

Table III. Presentation of IPL I-V results recorded separately from the right and the left side of the brainstem

BAEPs tracings IPL I-V	No. of cases	Percentage
Right side: normal	17	23.0%
prolongation	20	27.0%
shortening	0	0.0%
Left side: normal	17	23.0%
prolongation	14	18.9%
shortening	6	8.1%

When analyzing the all 74 BAEPs tracings (without differentiating the right- and left-sided responses), the normal results were found in 34 cases (45.9%), IPL I-V prolongation in 33 cases (44.6 %), and IPL I-V shortening in 7 cases (9.5%).

Considering the BAEPs tracings obtained separately from the either side of the brainstem can be the other approach to presentation of the IPL I-V results (see Tab. III).

In Fig. 1 a comparison between the pair of BAEPs tracings (right- and left-sided; *upper and lower*) with normal IPL I-V values (Fig. 1a) and the other one showing a prolongation of IPL I-V (Fig. 1b) is presented.

In turn, in Fig. 2, the interesting case of BAEPs result obtained from the patient with acromegaly showing right-sided prolongation of IPL I-V (4.56 msec) and left-sided shortening of IPL I-V (3.68 msec) is presented.

The analysis using Student *t*-test showed in the patient group a statistically significant difference ($p< 0.05$) between the mean values of the right-sided and the left-sided evoked responses, which were of 4.27 ± 0.24 msec and 4.11 ± 0.23 msec, respectively.

It is worth noting that a comparison of the IPL I-V values acquired for each of the examined groups revealed a strong statistically difference ($p< 0.00001$) with regard to the right-sided responses, which was 4.27 msec in the patients *vs* 4.06 msec in the controls. On the contrary, there wa s no significant difference found for the left-sided responses, where the mean IPL I-V value was 4.11 msec for the patients, and 4.05 msec for the controls ($p = 0.1$).

In addition, analysis of the IPL I-V results was performed in relation to disturbances of carbohydrates metabolism occurring in the examined patients with acromegaly. In this regard, the acromegaly patients were divided to three subgroups: with diabetes mellitus, prediabetic status, and without any glucose impairments.

The results concerning IPL I-V results acquired in the all analyzed subgroups are presented in Tab. IV.

Statistical analysis concerned possible BAEPs differences between the acromegaly patient subgroups demonstrating various level of glucose metabolism disturbances.

It was shown that as severity of glucose disturbances grows, IPL I-V was more prolonged in the BAEPs responses obtained from the right side of the brainstem, although there were no significant differences between the patient subgroups with various stage of diabetes mellitus. However, there were significant differences concerning IPL I-V between the all acromeg-

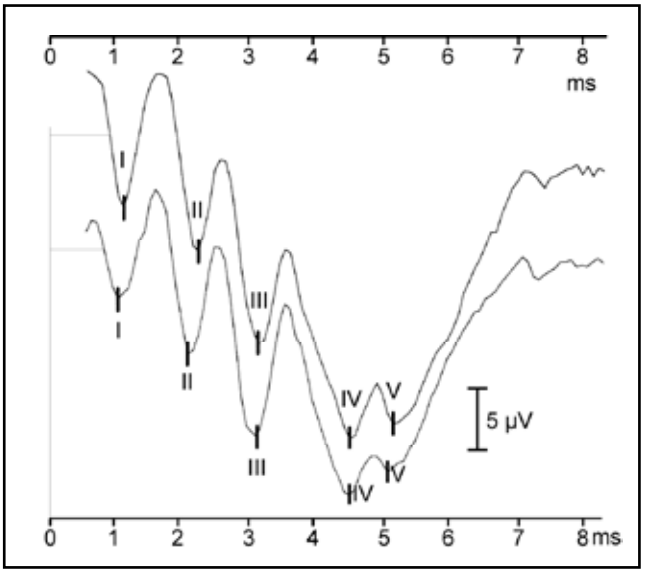

Figure 1(a). The pair of BAEPs tracings with normal IPL I-V values (both sides: 4.04 msec)

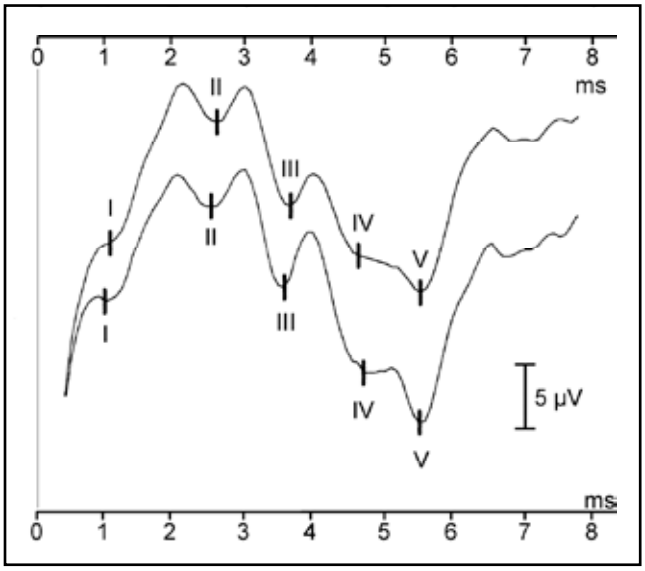

Figure 1(b). The pair of BAEPs tracings with prolonged IPL I-V values (both sides: 4.48 msec)

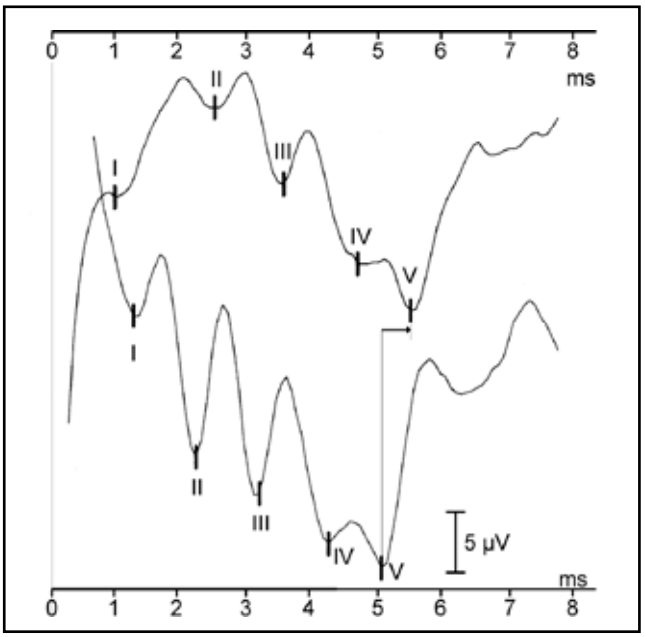

Figure 2. BAEPs result from the patients with acromegaly presenting right-sided prolongation of IPL I-V (*upper tracing*) and left-sided shortening of IPL I-V (*lower tracing*)

aly subgroups and the control group (for all $p \leq 0.001$): the most considerable difference was found for the subgroup with diabetes mellitus ($p = 3.5 \times 10^{-7}$), whereas for the subgroup without DM p was 4.0×10^{-4}.

As regards IPL I-V recorded from the left side of the brainstem, surprisingly, no prolongation was noted, even more, IPL I-V tended to be shortened, although there were no statistical differences both between the particular patient subgroups ($p = 0.052$), likewise in relation to the control group, e.g. for the patients with DM and for the patients with prediabetic status p was 0.16.

Relative assessment, using percentage, revealed that the number of acromegaly patients presenting prolonged IPL I-V increased along with a severity grade of glucose impairments. Interestingly, in the right-sided BEAPs, the number of prolonged IPL I-V was significantly larger, as compared with left-sided responses. Unfortunately, a quantity of the analyzed patient subgroups was low, which makes the observations inconclusive.

In Tab. V a prevalence of IPL I-V prolongation in the particular acromegaly subgroups with various stage of glucose disturbances is displayed.

DISCUSSION

To our best knowledge, the present paper is one of the first reports describing central nervous system disturbances in brainstem auditory evoked potentials in patients with acromegaly. Up to now, barely few studies have revealed peripheral nerves involvement in somatosensory evoked potentials examination [7, 8, 9]. Although, the study of brainstem auditory potentials and somatosensory potentials were carried out in acromegaly patients previously by Ozata et al, but they did not found any disturbances in the recordings [9]. In contrast to the quoted above authors, our study revealed abnormal results of BAEPs in patients with acromegaly. These differences in the assessment of acromegaly influence on the BAEPs results could be caused by longer disease duration and older age in our patients.

We have shown a relatively high prevalence of IPL I-V prolongation in the patients suffering from acromegaly. IPL I-V prolongation could suggest a decrease of myelinization status of auditory pathway in the brainstem. A suggested reason for this abnormality could be glucose metabolism disturbances occurring in acromegaly, since IPL I-V prolongation was documented also in diabetes mellitus type I [11]. What should be emphasized, in the patients with DM type II or with

Table IV. Inter-peak latency I-V (IPL I-V) in the acromegaly subgroups, considering various glucose disturbances, as compared with the control group

	IPL I-V [msec]					
	Mean ± SD		Minimal value		Maximal value	
	Right-sided	Left-sided	Right-sided	Left-sided	Right-sided	Left-sided
Acromegaly - entire group	4.27 ± 0.24	4.11 ± 0.23	3.84	3.68	4.88	4.72
Acromegaly with DM	4.43 ± 0.31	4.05 ± 0.30	4.00	3.68	4.88	4.32
Acromegaly with prediabetic status	4.29 ± 0.21	4.12 ± 0.25	4.00	3.68	4.56	4.40
Acromegaly without DM	4.21 ± 0.23	4.13 ± 0.20	3.84	3.76	4.72	4.72
Control group	4.06 ± 0.10	4.05 ± 0,11	3.78	3.78	4.27	4.20

Table V. Prevalence of IPL I-V prolongation in the patients with acromegaly with regard to glucose disturbances

Subgroup of the patients with acromegaly	Right-sided BAEPs		Left-sided BAEPs	
	Normal or shortened	Prolonged	Normal or shortened	Prolonged
Without DM	12 (60%)	8 (40%)	14 (70%)	6 (30%)
Prediabetic status	5 (42%)	7 (58%)	7 (58%)	5 (42%)
DM	1 (20%)	4 (80%)	2 (40%)	3 (60%)
Prediabetic status + DM	6 (35.3%)	11 (64.7%)	9 (52.9%)	8 (47.1%)

prediabetic status our results revealed the significantly higher extent of IPL I-V delay in comparison with the acromegaly patients without glucose metabolism disturbances. This outcome corresponds with the observations reported by Dolu et al, who reported significant prolongation of IPL I-V and IPL I-III in patients with DM type II, which was ascribed by the authors to central neuropathy occurring in long-term course of diabetes [14].

What can seem intriguing, in the present study a high variety of the results was observed. The prolongation of IPL I-V was documented in 16% of the all BAEPs examinations, whereas shortage in 22% of them. These results might suggest that disturbed brainstem transmission is due rather to diabetes than acromegaly.

Another cause of disturbances observed could be sleep-apnea, which is common in acromegaly, but this symptom was not extensively analyzed in our group of patients, and it requires further studies. A theoretical background of that point is a fact that respiratory centre is located within the brainstem [10].

It is noteworthy that we observed a significant difference between the IPL I-V values recorded from the right and the left side of the brainstem. Unfortunately, we cannot submit any reasonable explanation for this observation. Since no differences were recognized between the patients with active stage of disease and those cured, and between those after tumor surgery and those who underwent somatostatin analogs therapy, these factors seem to be of no influence on the results observed. Pituitary tumor surgery and somatostatin analogs are comparable methods regarding therapy efficacy in acromegaly [15, 16, 17].

Our results revealed some abnormalities in BAEPs examinations among patients with acromegaly. However, the answers to the questions why we observed a high prevalence of IPL I-V prolongation in acromegaly and why there was the right-sided domination of that phenomenon remain obscure, which obliges us to continue the study on the much numerous patient material.

The number of BAEPs tracings with normal transmission within brainstem portion of the auditory pathway (normal IPL I-V) is the same like those with delayed transmission (IPL I-V prolongation). Therefore, essential disturbance is demonstrated as slowing of brainstem transmission, although in some of the examined patients transmission was accelerated.

It seems interesting that in the examined patients with acromegaly, there was observed so high variety of the IPL I-V results. Firstly, assessing the entire patient group, we observed not only normal IPL I-V values, but shortened and prolonged ones, as well. This fact suggests that acromegaly does not influence brain functioning in homogenous manner. Secondly, when analyzing the individual patients, in five cases we found opposite reaction from the either side of the brainstem, i.e., IPL I-V shortening and prolongation in the same patient.

In conclusion, in the examined patients with acromegaly, there was no peripheral disturbance in transmission as observed in BAEPs registrations. Conversely, in nearly half of the patients with acromegaly brainstem transmission was found to be delayed, and significant difference between responses from the both brainstem sides were noted.

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