Brain-stem auditory evoked potentials in children and adolescents with anorexia nervosa

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Abstract

OBJECTIVE: In the course of anorexia nervosa (AN), the central nervous system (CNS) undergoes both anatomic and functional changes that may cause disturbances of stimulation transmission in the sensory areas of CNS. Method of brain-stem auditory evoked potentials (BAEPs) was used in the children with AN to test the auditory pathway transmission.

MATERIALS AND METHODS: The study included 37 children and adolescents, aged 10–18 years, with clinically diagnosed AN. BAEPs were recorded after a click stimulation of 75 dB intensity. Then, wave I latency (response from the auditory nerve) and inter-peak latency I–V (IPL I–V; response from the brain-stem) were analyzed.

RESULTS: Abnormalities of the BAEPs recordings were noted total in 32.4% of the study patients. Predominantly (in 24.3%), a decreased transmission within the brain-stem, expressed as the IPL I–V prolongation, was observed. It was also found that the percentage of the abnormal BAEPs results and the degree of IPL I–V prolongation were increasing together with enhancing AN severity.

CONCLUSIONS: IPL I–V prolongation observed in the AN children reflects a disturbed neural transmission in the brain-stem section of the auditory pathway and can be ascribed to impairments in the nerves myelin sheath.

Abbreviations :

AN	- anorexia nervosa
BAEPs	- brain-stem auditory evoked potentials
IPL I–V	- inter-peak latency I–V
CNS	- central nervous system

ORIGINAL ARTICLE

INTRODUCTION

The pathological condition called 'anorexia nervosa' (AN) was very rarely recognized before 1960. According to Bryant-Kush, a prevalence of anorexia nervosa in the population was about 0.06/100,000 at that time (Bryant-Kush 1992). Nielsen estimated a prevalence of AN as 1.9/100,000 in women and 0.17/100,000 in men (Nielsen 1990). In the subsequent years, the condition was recognized more and more often. Hoek stated that the incidence of AN was around 8.0/100,000 persons per year, and the average prevalence rate for AN among young females was 0.3% (Hoek 2006).

Although AN is seen primarily in girls and women, about 5–10% of cases occur in boys and men (Barry & Lippman 1990). It was also observed that the age at which the disease is recognized is going down (Rybakowa 1994). According to Keski-Rahkonen *et al.* (Keski-Rahkonen *et al.* 2007), the prevalence of AN in women aged 15–19 was 270/100,000 with the disease recurrence within 5 years about 66.8%.

Efficacy of the AN treatment is a complex problem depending on various predictive factors, and a body mass gain is a crucial treatment goal (Bulik *et al.* 2007; Nogal *et al.* 2009).

Numerous authors have analyzed factors determining the appearance of AN. Some of them suggest a psychogenic background of this pathologic condition (Higgs *et al.* 1989; Popielarska 1989; Roberts 1992; Olesti Baiges *et al.* 2008) while the others suggest environmental (Hill *et al.* 1990; Lucas 1991; Bryant-Kush 1992) or genetic (Strober 1991; Rybakowski *et al.* 2007) influences, as well as primary disorder of the hypothalamic –pituitary axis with secondary hormonal deficit (Baranowska *et al.* 2001). Endocrine disorders in AN refer not only to the hypothalamus – pituitary – adrenal axis, but also to gonads, thyroid and the GH-IGF-1 axis (Baranowska *et al.* 2003). Such neuropeptides as β-endorphin, neuropeptide-Y, galanin, orexin and leptin play an important role in thirst regulation, through their influence on the hypothalamic food centre. Lowered blood leptin and neuropeptide-Y levels and disorders in circadian rhythm of β-endorphin release have been observed in subjects with anorexia nervosa (Baranowska *et al.* 2003, Oświecimska *et al.* 2005). In recent years, much attention has been directed towards the above-mentioned genetic component related to the polymorphism of the BDNF-270 C/T gene (Brain Derived Neurotrophic Factor Gene), which occurs in women with a personality type predisposing to increased risk of AN (Rybakowski *et al.* 2007).

In the course of anorexia nervosa, the CNS undergoes both anatomic changes and functional disorders (Wagner *et al.* 2006; Mühlau *et al.* 2007). Basing on our earlier observations regarding acromegaly, we assumed that since white substance of the brain is composed of cells having myelin sheath, it is possible that a decrease of white substance mass may influence a speed of transmission in the auditory pathway, which may caused abnormalities in BAEPs recordings (Pilecki *et al.* 2008).

MATERIAL AND METHODS

The study included 37 children and adolescents (35 girls and 2 boys) presenting clinically defined anorexia nervosa, aged 10–18 years (mean: 15.2 ± 1.6). The study had been approved by the local Ethics Committee, and the informed consents were collected from the all participants or their parents.

The patient population was divided into four subgroups of varying clinical course of AN – from mild through moderate to severe and very severe, which is displayed in Table 1. The control group was constituted by the age- and sex-matched children with no clinical evidence of AN.

Body weight loss observed in the study group, as compared to the baseline, was between 25% and 54% (mean 35.6%, SD=7.51).

Brain-stem auditory evoked potentials (BAEPs)

The BAEPs examinations were performed using a click stimulation of 75 dB intensity and of 80 μs duration that were delivered through stereophonic earphones at the frequency of 10/s.

The following selected BAEPs parameters were analyzed:

- Wave I latency: enables evaluation of the peripheral section of the auditory pathway and the Corti's organ sensitivity to sound stimuli. Reference values set for this parameter by our laboratory are ≤1.75 ms latency.
- Inter-peak latency I–V (IPL I–V): enables evaluation of the brainstem section of the auditory pathway. Reference values set for this parameter by our laboratory are within the range of 3.85 ms to 4.20 ms.

Responses evoked from both sides (right and left) of the brainstem (so called 'unilateral responses') were evaluated and their symmetry was also analyzed.

The above-mentioned parameters are commonly accepted criteria used in evaluation of the BAEPs examination results.

The results were analyzed with regard to the two following aspects: (1) comparison of abnormalities observed in patients with anorexia nervosa with reference values of our laboratory set for the particular parameters. (2) statistical analysis comparing the results of the anorexia nervosa group with the control group and comparison of results within the patient group with regard to clinical course.

Statistical analysis

The data concerning wave I latency and IPL I–V were analyzed statistically using the Student's t-test (for comparing normally distributed groups) as well as the non-parametric Mann-Whitney's test for the others. The assumed level of significance was set at $p<0.05$.

RESULTS

Response symmetry

BAEPs waveforms were symmetrical in the almost all examinations. Only in one boy, asymmetry in wave I latency and inter-peak latency I–V was observed.

Wave I latency

The abnormal result (beyond the reference range of the laboratory) was observed in one case. The deviation was unilateral and very small, i.e., 1.82 ms.

The data in Table 2 showed that the mean wave I latency in the control group was 1.53 ms (right-sided responses – 1.53 and left-sided responses – 1.52), and 1.50 ms in the study group (right-sided responses – 1.49 and left-sided responses – 1.51). Statistical analysis revealed no differences in wave I latency between the study group and the control group.

Further analyses were also meant to establish if there was a correlation between the wave I latency and the clinical course. The results are shown in Table 3.

Statistical analysis did not reveal differences between the subgroups of varying clinical course, as well as compared to the control group.

Since wave I latency is related to sound sensitivity tested on the level of the auditory nerve, results obtained for right- and left-sided responses should be considered independently. On making this assumption, further statistical analysis may be conducted for wave I latency after the results are combined into one set.

Results concerning a correlation between clinical presentation and wave I latency following the above-mentioned combination are shown in Table 4.

The analysis of the influence of anorexia clinical course on wave I latency showed that the correlation was statistically significant while comparing subjects with anorexia nervosa of a very severe clinical course with the control group, but only with combined results of right- and left-sided stimulation. In the remaining cases, no statistically significant correlation between the clinical course of the disease and wave I latency were observed.

Interpeak latency I–V (IPL I–V)

Evaluation of abnormalities concerning IPL I–V

With regard to the IPL I–V parameter, the results were more diversified as compared to the wave I latency data. In most cases, the IPL I–V values were within the reference range. However, there were some values lower or higher than the reference range. The latter occurred more often, i.e. in almost one fourth of the subjects. With regard to symmetry of response obtained from particular brain sides, the results were symmetrical except for one subject. In that patient, brainstem transmission was bilaterally inhibited (which means that the IPL I–V value was prolonged), but the inhibition was different depending on the side: 4.48 ms for right-sided response and 4.27 ms for left-sided response. More detailed analysis of the results is shown in Table 5.

Tab .1. Subgroups of patients with varying clinical course.

Clinical course	Patients no.
Mild	3
Moderate	17
Severe	10
Very severe	7

Tab. 2. Wave I latency in subjects with anorexia nervosa compared to the control group, according to reference values set by our laboratory.

Response tested	Wave I latency In the study group (ms)			Wave I latency In the control group (ms)		
	Values	Mean	±SD	Values	Mean	±SD
Right-sided	1.33–1.75	1.49	0.10	1.26–1.75	1.53	0.10
Left-sided	1.33–1.82	1.51	0.10	1.26–1.75	1.52	0.10
Total	1.33–1.82	1.50	0.10	1.26–1.75	1.53	0.10

Tab. 3. Wave I latency in subjects with anorexia nervosa of varying clinical course.

Clinical course	Wave I latency in the study group (ms)		Wave I latency in the control group (ms)	
	Right-sided responses	Left-sided responses	Right-sided responses	Left-sided responses
Mild	1.47±0.07	1.54±0.07	1.53 (SD±0.10)	1.52 (SD±0.10)
Moderate	1.52±0.11	1.54±0.13		
Severe	1.48±0.10	1.51±0.09		
Very severe	1.46±0.07	1.46±0.09		

Tab. 4. Wave I latency in subjects with anorexia nervosa of various intensity compared to the control group, after combination of the results obtained from the particular brainstem sides.

Clinical course	Wave I latency in the study group		Wave I latency in the control group		Comparison with the control group (*p*-value)
	Mean	±SD	Mean	±SD	
Mild	1.51 ms	0.07	1.53	0.10	NS (0.63)
Moderate	1.53 ms	0.12			NS (1.00)
Severe	1.49 ms	0.10			NS (0.23)
Very severe	1.46 ms	0.08			*p*=0.03*

* statistically significant difference

Comparison of IPL I–V values between the study group and the control group

Statistical analysis aimed to establish if there were any differences between the study group and the control group with regard to IPL I–V values and if there were differences if the analysis of the study group was performed after subdivision into groups of varying clinical symptom intensity. The IPL I–V values in the study group and the control group are shown in Table 6.

Tab. 5. Evaluation of IPL I-V values in subjects with anorexia nervosa.

	Side tested			
	Right		Left	
IPL I-V shortening	3	(8.1%)	3	(8.1%)
IPL I-V normal value	25	(67.6%)	25	(67.6%)
IPL I-V prolongation	9	(24.3%)	9	(24.3%)
Total	37	100 %	37	100 %

Tab. 6. IPL I-V values in subjects with anorexia nervosa compared to the control group, according to reference values set by our laboratory.

Response tested	IPL I-V in the study group (ms)			IPL I-V in the control group (ms)		
	Reference range	Mean	±SD	Values	Mean	±SD
Right-sided	3.78–4.48	4.10	0.19	3.85–4.20	4.04	0.09
Left-sided	3.78–4.48	4.09	0.19	3.85–4.20	4.05	0.08
Total	3.78–4.48	4.10	0.19	3.85–4.20	4.04	0.07

Tab. 7. Evaluation of IPL I-V abnormalities in subjects with anorexia nervosa of varying clinical intensity.

Clinical course	Group size	Evaluation of abnormalities concerning IPL I-V In relation to reference values		
		Shortening	Prolongation	Total
Mild	3	0	0	0
Moderate	17	1 (5.9%)	2 (11.8%)	3 (17.6%)
Severe	10	0	2 (20%)	2 (20.0%)
Very severe	7	2 (28.6%)	5 (71.4%)	7 (100%)
Total	37	3 (8.1%)	9 (24.3%)	12 (32.4%)

Tab. 8. Comparison of the IPL I-V value between the study group and the control group with regard to the clinical course of the disease.

Clinical course	IPL I-V value				*p*-value	Comparison of groups
	Study group		Control group			
	Mean	±SD	Mean	±SD		
Mild	4.05	0.05	4.04	0.07	0.87	NS
Moderate	4.04	0.16			0.93	NS
Severe	4.12	0.11			4.0×10^{-4}	$p \leq 0.001$*
Very severe	4.21	0.29			5.6×10^{-5}	$p \leq 0.001$*
Total	4.10	0.19	4.04	0.07	0.034	$p \leq 0.001$*

* statistically significant difference

Although differences in mean IPL I–V values between the study group and the control group were rather small, the statistical analysis revealed that the difference is statistically significant (p=0.034).

Analysis of correlation between the clinical symptom intensity in subjects with anorexia nervosa and the prevalence of abnormal results

Abnormal BAEPs results were observed in 12 out of 37 subjects (i.e., 32.4%). In the majority of these subjects (i.e. in 9/12), the abnormality was related to IPL I–V prolongation, which causes reduced transmission in the brainstem section of the auditory pathway (see Table 7).

As it was shown in Table 7, the number of abnormal results is growing together with increasing severity of clinical symptoms. This is especially apparent in the results concerning IPL I–V prolongation, which indicates a correlation between the clinical course and transmission disorder in the brainstem part of the auditory pathway.

Analysis of correlation between the intensity of clinical symptoms and the IPL I–V value

The analysis of the IPL I–V value in subgroups formed on the basis of the clinical course of anorexia nervosa revealed that mean IPL I–V values in subjects with severe and very severe clinical course were significantly different from results obtained in the control group and in the group of subjects with mild and moderate clinical course.

The results presented in Table 8 show that there are no differences in IPL I–V between subjects with mild and moderate clinical course and the control group (the results are almost identical), whereas in case of subjects with severe and very severe symptoms, the difference is statistically significant at $p \leq 0.001$.

DISCUSSION

Studies describing the method of brain-stem auditory evoked potentials to examine the activity of central nervous system in children with anorexia nervosa are very rare. Reports concerning evaluation of the function of the brain-stem in the auditory pathway with a use of BAEPs method are even rarer (Pilecki *et al.* 2008). Therefore, it is very difficult to compare the results of our studies performed with this method to the results of the other authors.

Rothenberger *et al.* (1991) conducted studies of BEAPs in adolescents with AN, but he registered evoked responses from the subcortical and cortical areas, not from the brain-stem section, as it occurred in our study. The quoted authors claimed that subjects with AN, even after putting on weight, might have had problems with proper modulation of the sound stimulus on the subcortical level, whereas they did not differ from healthy subject in this respect with regard to the cortical level. He also observed a difference between amplitudes of auditory potentials at subcortical and cortical level in the low body weight subjects with AN, which may suggest dissociation between the subcortical and cortical neural system. After weight stabilization the dissociation was reduced. No such phenomenon (dissociation

and further stabilization) was observed in healthy subjects. Moreover, Rothenberger *et al.* observed that the CT images were not correlated to the abnormalities seen in BAEPs recordings. He claims that the role of functional pseudoatrophy observed in CT studies of subjects with anorexia has not been explained so far (Rothenberger *et al.* 1991).

Studies of the CNS structures in patients with anorexia were also conducted by Kornreich *et al.* (1991). The authors observed in the brain, on the basis of studies using CT and MR in 13 girls with AN, the following anatomic changes: widening of the third ventricle, increased number of visible cortical sulci and the lack of pituitary overgrowth typical for puberty.

The most recent studies confirm that in the course of AN, the CNS undergoes both anatomic changes and functional disorders. According to Mühlau *et al.* (2007), anatomic changes refer both to cerebrospinal fluid and to white and grey substance. In turn, Wagner *et al.* (2006) claim that the cerebrospinal fluid volume is increased, whereas the volume of both types of 'solid tissues' is decreased.

Swayze *et al.* reported anatomic changes in morphology, depending on changes in patient weight and they claimed that weight stabilization was accompanied by an increase in white and grey substance volume together with a decrease in the fluid volume (Swayze *et al.* 2003). Results obtained in the present study, showing IPL I–V prolongation in the subjects with severe and very severe clinical course of AN, may indicate that these subjects may really undergo changes in their myelin sheaths, which results in lowered transmission in the brain-stem area of the auditory pathway. This finding is similar to the results obtained by Swayze *et al.* (2003) reporting anatomic changes in CNS.

A different opinion is held by Pászthy (2007), who claims that prolonged abrosia in anorexia nervosa may affect calcium transport through membrane, which in consequences causes disorders in cell membrane excitability. These disorders cause various symptoms in numerous systems, including CNS.

According to some authors, AN is accompanied by changes determining disorders within the autonomic central system. In the most recent studies with the use of automatic blood pressure monitoring (ABPM), Oświecimska *et al.* observed a decrease in blood pressure (BP) and heart rate (HR) values and disorders in BP alternation in the circadian rhythm of subjects with AN. The changes in the BP circadian rhythm included the lack of physiological decrease in BP at night. Studies conducted by the above-mentioned authors reveal that hormonal disorders may, by influencing the autonomic peripheral system function, disturb the BP and HR regulation in subjects with AN (Oświecimska *et al.* 2006).

CONCLUSION

In children with the very severe course of anorexia nervosa, BAEPs wave I latency was shorter than in the normal subjects.

IPL I–V prolongation was observed in 24.3% of the AN children and reflected a disturbed neural transmission in the brain-stem area of the auditory pathway.

IPL I–V prolongation in patients with AN seems to be directly proportional to the clinical severity of the disease.

In the patients with AN of severe course, decreased transmission within the brain-stem results from changes in the myelin sheath condition.

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