Relation of trophic changes in the central nervous system, measured by the width of cortical sulci, to the clinical course of *anorexia nervosa* (II)

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Abstract

OBJECTIVES: In patients with *anorexia nervosa* (AN), computer tomography (CT) scanning and/or magnetic resonance imaging (MR) are usually applied to visualise trophic changes of the brain, resulting from considerable malnutrition or general cachexia of the organism. The goal of the study was an evaluation attempt of the degree of trophic changes in the central nervous system (CNS) of girls with AN, following CT scanning of the brain, together with an analysis of selected clinical and diagnostic parameters, related to the trophic changes in question. **PATIENTS & METHODS:** The study involved fifty-five (55) female patients with AN. Following CT of the brain – scanning of the cortical sulci - four (4) groups of the patients were identified. The following classification of lesions was applied: Group I – width of cortical sulci < 1.5 mm – standard; Group II – the presence of cortical sulci of width < 1.5 mm and 1.5–3 mm; Group III – width of cortical sulci 1.5–3 mm; Group IV – the presence of cortical sulci of width at 1.5–3 mm and > 3 mm. We did not observe any patient with AN in whom the width of all the cortical sulci was bigger than 3 mm (Group V). In all the groups, clinical parameters, as well as routine laboratory tests and selected hormonal tests, were analysed. **RESULTS:** In the performed CT scanning of the head in patients with AN, trophic changes in the CNS (as evaluated by the width of cortical sulci) were revealed in 67.3% of the patients. Among the studied groups, statistically significant differences were found for: body weight loss (BWL), the percent of BWL (BWL%), the BWL to disease duration ratio (BWL/time) and BWL%/time, serum concentrations of potassium, calcium, glucose, total protein and urea, as well as serum concentrations of LH, E_2, cortisol, FT_3 and FT_4. The most pronounced disturbances were observed in Group IV, while the least ones – in Group I. **CONCLUSIONS**: In CT scanning of the head, trophic changes in the CNS were observed in girls with AN, measured by the width of cortical sulci. The higher severity of trophic changes in the CNS was associated with higher BWL/time ratio, higher hypercortisolemia, more enhanced hypogonadotrophic hypogonadism, disorders in the peripheral metabolism of the thyroid hormones and with the obtained values of routine laboratory tests, indicating some tendency towards hypovolemia.

ORIGINAL ARTICLE

INTRODUCTION

In the pathogenesis of *anorexia nervosa* (AN), enhanced disorders of metabolic processes, also intracerebral, resulting from starvation and cachexia, lead to changes in the morphological picture of the brain, observed in computer tomography (CT) scans or magnetic resonance (MR) images [2, 8, 10, 14]. Reductions of total brain volume have been reported, including defects of both grey and white matter, widened sulci and increased fluid spaces.

The trophic changes in the central nervous system (CNS) may, in turn, disturb the control of organism homeostasis, additionally enhancing peripheral disorders [10, 14].

The study aimed at evaluating trophic changes of the CNS, observed in CT scanning in girls with AN, as well as at an analysis of routine laboratory tests and selected hormonal measurements, depending on the degree of trophic changes in the CNS of the examined girls.

PATIENTS AND METHODS

The study involved fifty-five (55) patients, aged from 13.3 to 20.8 years (the mean age: 15.9±1.9) with diagnosis of AN, confirmed vs. the criteria of the American Psychiatric Society, classification of psychic diseases: DSM-IV-R [1].

The following clinical parameters were evaluated in the studied patients: body height, body weight (BW) and body mass index (BMI) at the beginning of the therapy, disease duration, body weight loss (BWL), the percent of body weight loss (BWL%), the body weight loss to disease duration ratio (BWL/time) and the body weight loss percent to disease duration ratio (BWL%/time).

In each patient, routine laboratory tests were ordered on the second (2) day after admission to hospital, including: complete blood cell count, serum concentrations of sodium (Na), potassium (K), glucose (Glu), total cholesterol (Ch), triglycerides (TG), total calcium (Ca), phosphates (P), total protein (Prot) and urea (Ure). Moreover, concentrations of the following hormones were measured: thyrotropin (TSH), estradiol (E_2), testosterone (T), cortisol at 8:00 (Cort8), at 17:00 (Cort17) and at 24:00 (Cort24). A routine stimulation test was also done for the secretion of lutropin (LH) and follitropin (FSH), following an intravenous administration of 100 μg of gonadoliberin GnRH. Blood samples for LH and FSH concentration measurements were collected before and after 30 (LH30; FSH30) and 60 (LH30; FSH60) minutes after the administration of the preparation. Hormonal measurements were performed by the electroluminescence method (ECLIA).

In all the patients, CT scanning (Picker 2000 PQ) of the head was performed on the 2nd day after the admission to the Department in order to exclude tumour occurrence and to assess the degree of trophic changes in the CNS. Width of cortical sulci was evaluated, following the generally accepted principles, at the level of *centrum semiovale,* in frontal cross-section, on axial scans, on a plane, inclined 25° to the suborbital-auricular line, at the layer thickness of 8 mm [5, 6]. The following classification of lesions was applied:

Group I – width of cortical sulci < 1.5 mm – standard;
Group II – the presence of cortical sulci of width < 1.5 mm and 1.5–3 mm;
Group III – width of cortical sulci 1.5–3 mm;
Group IV – the presence of cortical sulci of width at 1.5–3 mm and > 3 mm;
Group V – width of cortical sulci > 3 mm.

We did not observe any patient with AN in whom the width of all the cortical sulci was bigger than 3 mm (Group V) (Table 1).

Table 1. Number of girls in the particular studies groups, classified according to trophic changes in cranial CT

Group	n	%
I	18	32.7
II	18	32.7
III	15	27.3
IV	4	7.3
V	0	0

Statistical analysis was performed, taking into account the mean values and standard deviations. For the comparison of the differences of means, the ANOVA analysis of variance was used with post hoc RIR-Tukey's test for trials of different numerical force or typical variants of Student's t-test. For all the comparisons and calculated statistics, the level of significance at $p<0.05$ was accepted.

RESULTS

Following CT scanning, the patients were qualified into four (4) groups, depending on the degree of trophic changes (Table 1). Among the studied patients, various degrees of cortical sulci widening were observed in 67.3%, while 32.7% did not present with any changes in CT examination.

Clinical data in the studied groups are presented in Table 2, reflecting the degree of trophic changes in cranial CTs. Statistically significant differences among Groups I, II, III and IV were found, regarding BWL values ($p=0.018$), BWL% ratios ($p<0.001$), BWL/time ratios ($p=0.003$) and BWL%/time ratios ($p=0.001$).

Analysing the obtained results by means of Tukey's test (honestly significant differences), statistically significant differences were found in:

Table 2. Clinical data of girls with AN in the studied groups, depending on the degree of trophic changes in cranial CT. Statistical significance at $p<0.05$

	Group I	Group II	Group III	Group IV	p
	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD	
Age [years]	15.46±1.34	16.18±1.40	15.66±1.09	15.83±0.87	0.400
Height [m]	1.62±0.07	1.66±0.04	1.61±0.07	1.60±0.12	0.105
Body weight [kg]	39.50±3.99	40.04±4.70	37.05±6.97	35.70±6.63	0.402
BMI [kg/m^2]	15.01±1.43	14,46±1,55	14,22±1,86	13.88±0,67	0.402
Disease duration [months]	10.39±4,80	10.17±5.75	8.27±2.91	7.00±2.70	0.363
BWL [kg]	12.68±3.38	16.56±6.64	18.47±8.12	23.00±11.40	0.018
BWL% ratio	24.13±5.33	29.17±7.19	33.06±6.06	37.46±8.98	0.000
BWL/time ratio [kg/months]	1.43±0.60	1.89±0.72	2.53±1.57	3.39±1.68	0.003
BWL%/time ratio	2.77±1.21	3.42±1.43	4.46±1.64	5.87±1.72	0.001

Table 3. The values of routine laboratory tests in girls with AN in the studied Groups (I-IV), depending on the degree of trophic changes in cranial CT. Statistical significance at $p<0.05$.

	Group I	Group II	Group III	Group IV	p
	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD	
RBC [M/µl]	4.48±0.27	4.39±0.34	4.48±0.65	4.01±0.67	0.283
Hb [g/dl]	12.98±0.71	12.74±0.65	12.95±1.53	11.78±1.44	0.200
Ht [%]	40.17±3.05	39.83±2.25	40.83±5.17	38.00±4.16	0.566
MCHC [g/dl]	32.96±1.02	32.93±0.68	32.42±0.90	32.35±0.19	0.189
WBC [K//µl]	4.93±0.98	4.10±0.71	4.48±1.19	3.78±0.52	0.037
PLT [K//µl]	199.11±41.34	182.44±30.94	188.07±48.20	162.75±63.88	0.398
Na [mmol/l]	148.44±3.16	148.72±3.30	149.93±1.79	150.50±1.00	0.319
K [mmol/l]	4.51±0.26	4.38±0.21	4.23±0.26	4.15±0.41	0.013
Ca [mmol/l]	2.27±0.04	2.24±0.04	2.29±0.04	2.27±0.04	0.028
P [mmol/l]	1.25±0.12	1.22±0.04	1.20±0.06	1.19±0,03	0.314
Glu [mg/dl]	73.44±5.28	71.78±7.93	66.67±3.35	60.50±5,80	0.000
Ch [mg/dl]	177.56±36.30	192.56±37.90	197.60±24.15	206.75±18.55	0.230
TG [mg/dl]	75.00±16.88	3.42±22.891	72.67±4.23	77.25±7.50	0.798
Prot [mg/dl]	7.31±0.51	7.06±0.591	6.49±0.42	6.52±0.72	0.000
Ure [mg/dl]	27.11±5.06	33.89±7.561	36.67±7.26	31.75±12.44	0.003

- BWL – between Group I and Group IV (p=0.035);
- BWL% – between Group I and Group III (p=0.001) and between Group I and Group IV (p=0.002);
- BWL/time ratio – between Group I and Group III (p=0.025) and between Group I and Group IV (p=0.009);
- BWL%/time ratio – between Group I and Group III (p=0.008), between Group I and Group IV (p=0.003) and between Group II and Group IV (p=0.034) (see: Table 2).

In all the groups (I–IV), the results of routine laboratory tests (ordered at the beginning of the therapy in all the girls with *anorexia*) were analysed. These data are presented in Table 3.

The following statistically significant differences were observed in the concentrations of: K (p=0.013), Ca (p=0.028) Glu ($p<0.001$), Prot ($p<0.001$), Ure (p=0.03) and WBC (p=0.037) among the studied groups.

Having analysed the obtained results by Turkey's test, the following statistically significant differences were identified:

- WBC – between Group I and Group IV (p=0.034);
- K concentration – between Group I and Group III (p=0.030);
- Ca concentration – between Group II and Group III (p=0.029);
- Glu concentration – between Group I and Group III (p=0.015), between Group I and Group IV (p=0.016)

Table 4. Hormonal concentrations in patients with AN in the studied Groups (I-IV), depending on the degree of trophic changes in cranial CT. ☐ Statistical significance at $p<0.05$

	Group I	Group II	Group III	Group IV	p
	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD	
LH	0.93±1.40	0.37±0.45	0.11±0.02	0.10±0.00	0.037
LH30	3.64±3.39	2.15±1.89	0.64±0.91	0.10±0.00	0.001
LH60	2.88±2.87	1.93±2.01	0.51±0.66	0.10±0.00	0.006
FSH	2.28±2.47	2.08±2.49	1.51±1.42	0.23±0.12	0.323
FSH30	6.21±4.16	5.46±3.75	5.12±3.03	0.98±0.51	0.086
FSH60	7.85±5.15	6.91±4.27	6.90±4.10	2.73±0.79	0.236
E_2	20.50±11.40	14.78±7.64	9.07±4.02	9.75±4.03	0.001
T	0.34±0.10	0.39±0.12	0.30±0.11	0.30±0.08	0.176
Cort8	22.10±3.61	24.82±5.30	31.57±4.53	37.27±3.97	0.000
Cort17	12.33±1.74	14.73±3.11	18.30±2.95	23.36±4.08	0.000
Cort24	3.91±1.78	5.52±2.85	7.90±1.94	10.86±2.95	0.000
FT_3	1.83±0.34	1.58±0.23	1.25±0.29	1.33±0.28	0.000
FT_4	0.97±0.16	0.82±0.13	0.75±0.24	0.75±0.05	0.004
TSH	1.57±1.07	1.45±1.01	1.03±0.77	0.92±0.98	0.341

and between Group II and Group IV (p=0.046);
- Prot concentration – between Group I and Group III (p<0.001) and between Group II and Group III (p=0.03);
- Ure concentration – between Group I and Group II (p=0.031) and between Group I and Group III (p=0.034) (see: Table 3).

Concentrations of selected hormones in the studied girls, taking into account particular groups with various degrees of trophic changes, are presented in Table 4, together with statistical evaluation of the differences (p).

Among the groups, statistically significant results were found for: LH (p=0.037), LH30 (p=0.001), LH60 (p=0.006), E_2 (p=0.001), Cort8 (p<0.001), Cort17 (p<0.001), Cort24 (p<0.001), FT_3 (p<0.001) and FT_4 (p=0.004).

Having analysed the obtained hormonal results by Turkey's test, the following statistically significant differences were identified:

- LH concentration – between Group I and Group III (p=0.049);
- LH30 concentration – between Group I and Group III (p=0.004);
- LH60 concentration – between Group I and Group III (p=0.014);
- E_2 concentration – between Group I and Group III (p=0.002);
- Cort8 concentration between Group I and Group III (p<0.001), between Group I and Group IV (p<0.001), between Group II and Group III (p<0.001) and between Group II and Group IV (p=0.001);
- Cort17 concentration – between Group I and Group III (p<0.001), between Group I and Group IV (p=0.001), between Group II and Group III (p=0.004) and between Group II and Group IV (p<0.001);
- Cort24 concentration – between Group I and Group III (p<0.001), between Group I and Group IV (p=0.001), between Group II and Group III (p=0.033) and between Group II and Group IV (p=0.010);
- FT_3 concentration – between Group I and Group III (p<0.001) and between Group II and Group III (p=0.016);
- FT_4 concentration – between Group I and Group III (p=0.007) (see: Table 4).

DISCUSSION

Morphological brain changes in patients with *anorexia nervosa* are reported in medical literature [4, 7, 9, 12, 13, 14]. These changes are not specific for AN [5]. When it comes to causes of trophic changes in cerebral cortex, then, first of all, scarce supplementation of carbohydrates, protein and water in diet is mentioned [2, 3, 4, 7, 11]. The reversibility of cortical atrophies depends on body weight normalisation [2, 4, 16].

Among the studied patients, various widening degrees of cortical sulci were observed in 67.3%, while 32.7% did not present with any changes in CT examination. These results are comparable with the report of Artmann et al. [2]. The authors found out that, in 60% of anorectic patients, trophic changes occurred, affecting, first of all, cortical sulci and fissures and, in lesser degree, the cerebral ventricles, while most rarely they were found in the cerebellum. They also observed a certain correlation between the described changes and body weight loss and the reversibility of cortical atro-

phies, dependent on body weight normalisation [2]; a similar opinion presented Golden et al. [4].

Having analysed the results, we found that more enhanced trophic changes, visualised in CT examinations of the head, are associated with bigger BWL and higher the BWL% ratio, as well as higher values of the BWL/time ratio and higher proportion of the BWL%/time ratio. Out of the above presented parameters, particularly the BWL%/time proportion turned out to have been significantly lower in the group of patients with normal CT results than in the groups of patients with more advanced trophic changes; body weight and BMI values did not significantly differ among themselves in the studied groups (Table 2). It can then be stated that the rate of body weight loss is an important parameter in prognosing the presence of trophic changes in the CNS of girls with AN.

Attempting to explain the effects of body weight loss and, especially, the effects of the rate of this process on the degree of trophic changes in the CNS of anorectic girls, it should be taken into account that quick body weight loss may sooner lead to disturbances of appropriate adaptation mechanisms of patients with *anorexia*, resulting in changes of brain morphology in these patients, observed in radiological examinations.

Analysing the results of routine laboratory tests with regards to the degree of trophic changes in the CNS, we found that – in consecutive groups – together with the intensification of trophic changes, the concentrations of glucose, total protein and potassium decreased, while increased were the concentrations of urea and sodium.

Insufficient water supplementation in diet is regarded to be one of the causes of trophic changes in the brain. Higher concentrations of urea and sodium with lower concentrations of potassium in groups with more advanced trophic changes in the brain, may be explained by various degrees of brain hydration in particular groups of patients [11]. Chronic deficit of extracellular water volumes, oedemas and secondary hyperaldosteronism may enhance trophic changes of the CNS [11]. It is worth mentioning that no statistically significant differences in sodium concentration were found in particular groups of the patients, although it was elevated in all of them.

The causes of trophic changes in the cerebral cortex include also, beside insufficient water supplementation, too small levels of carbohydrates and protein in diet [2, 3, 4, 7], what was indirectly confirmed by our studies (Table 3). The excessively low intake of carbohydrates, including monosaccharides, brings about a tendency towards hypoglycaemia, which cannot be, in anyway, compensated, despite the elevated concentrations of cortisol and growth hormone, characteristic for this disease [3].

Extending the fluid space in the brain in the course of *anorexia nervosa* may influence the activity of neuropeptides in the CNS, among others, the secretion of corticoliberin (CRH) and of antidiuretic hormone (ADH), the concentrations of which in the cerebrospinal fluid are increased [14, 15]. Our own observation – statistically significant differences of cortisol concentrations, depending on the degree of trophic changes in the CNS of girls with *anorexia nervosa* – seems to confirm the hypothesis.

Summing up, we conclude that in CT examination of the head, performed in girls with *anorexia nervosa*, trophic changes are observed in the central nervous system, measured by the width of cortical sulci. The degree of the observed changes is significant for the clinical evaluation of such patients. In girls with AN, a higher severity of trophic changes in the CNS is associated with greater body weight loss, calculated per time unit, higher hypercortisolemia, more enhanced hypogonadotropic hypogonadism and more distinct decrease of gonadotropin reactivity to GnRH, disorders of the peripheral metabolism of thyroid hormones and characteristic values of routine laboratory tests, indicating a tendency towards hypovolemia.

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