

Analysis of treatment efficacy in girls with *anorexia nervosa* (III)

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Abstract

OBJECTIVES: So far, no unequivocal answer has been provided to the question of how to treat girls with *anorexia nervosa* (AN). The goal of the study was evaluation of treatment results and search for prognostic factors, regarding the outcome of administered therapy in girls with AN.

PATIENTS AND METHODS: The analysis comprised eighty-seven (87) patients with diagnosis of AN. In the course of treatment, the patients received only a balanced and highly energetic diet. The effects of dietetic procedure were evaluated, comparing clinical data and routine laboratory test results (full blood cell count, serum concentrations of sodium, potassium, glucose, cholesterol, triglycerides, total calcium, phosphates, total protein and the urea) at the onset and on the last day of hospitalisation and also an analysis of clinical data in patients with regained menstrual cycles was performed. Also, on admission to hospital, serum concentrations of TSH, FT₄, FT₃, E₂, T and cortisol were measured (the last hormone – three times – at 8:00, 17:00 and 24:00). Moreover, a stimulation test with GnRH was performed to assess LH and FSH release. A comparison was made between the clinical data, the results of routine laboratory tests and hormone concentrations, obtained at the beginning of the therapy in the group of cured girls (the girls with regained menses) and the group, in which the therapy did not bring complete elimination of the disease. de

RESULTS: After hospitalisation, 75.9% of the patients with AN continued outpatient treatment. In all the patients, who adhered to proposed therapy, menstruation cycles returned within 1 to 12 months. It was found that in the group with positive treatment outcome, the patients were older, demonstrated higher BMI values at the beginning of the therapy, as well as shorter disease duration than those in the group of patients who refused further treatment. In the group of cured patients, estradiol concentrations were significantly higher and cortisol concentrations (at 17:00 and 24:00) were significantly lower, in comparison to the uncured group.

CONCLUSIONS: The findings suggest that body weight increase by proper diet application is the most important element of therapy in AN. Patient's age, disease duration, the degree of body weight loss and serum concentrations of estradiol

and cortisol at 17:00 and 24:00 are the prognostic factors for the outcome of therapy in *anorexia nervosa*.

INTRODUCTION

So far, no unequivocal answer has been provided to the question of how to treat girls with *anorexia nervosa* (AN). Body weight deficit, sometimes very significant, is a dominating symptom in girls with AN. Body weight loss in anorectic patients is accompanied by many metabolic and hormonal disorders, while the scope and degree of these disorders may, from the clinical point of view, influence the efficacy of therapy in girls with AN [9].

Psychotherapists assume that the treatment of nutrition disorders requires, first of all, a certain improvement of the psychic status, while body weight increase and menstruation return are the results of effective, long-term psychotherapy [4, 7].

All the theories, hypotheses and generalised observations, regarding AN, have been oriented towards one common target – the identification of therapy which would be effective against AN.

The goal of the study was evaluation of therapeutic results in girls with AN and a search for factors prognostic for treatment outcomes in anorexia nervosa.

PATIENTS AND METHODS

Retrospective studies involved eighty-seven (87) patients at the age from 13.8 to 21.1 years (the mean age: 16.1 ± 1.5 ; $x \pm SD$) with diagnosed AN, hospitalised during the years 1995–2003 at the Department of Endocrinology and Metabolic Diseases, Medical University of Lodz. *Anorexia nervosa* was diagnosed, following the criteria of the American Psychiatric Society, included in the classification of mental diseases DSM-IV-R [2].

In all the patients, a restrictive type of anorexia was identified; none of them had used any hormonal or psychotropic drugs. In all the patients, secondary amenorrhoea was found, while none of them had been hospitalised before because of AN.

In the course of hospitalisation, anorectic patients were given only a balanced, high calorie diet, first – at the level of 1200–1300 kcal daily, finally – 3000 kcal daily. No psychotropic medications were administered.

Clinical data, namely: height and body weight on admission (BW-A), BW on discharge (BW-D), body mass index on admission (BMI-A), BMI on discharge (BMI-D), BW increase (BW-I), BMI increase (BMI-I), disease duration before hospitalisation, hospitalisation period, outpatient treatment duration, BW and BMI after recovered menstruation cycles (BW-M, BMI-M) were analysed.

In each patient, laboratory tests were ordered on admission and on discharge of hospitalisation, including: the red blood cell count (RBC), hemoglobin (Hb) concentration, the hematocrit (Ht) index, the mean

percentual concentration of hemoglobin in erythrocyte (MCHC), blood cell count (WBC), the number of thrombocytes (PLT), 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, the following hormonal tests were ordered in each patient: serum concentrations of thyrotropin (TSH), free thyroxine (FT₄), free triiodothyronine (FT₃), estradiol (E₂), testosterone (T), and cortisol concentration at 8:00 (Cort8), 17:00 (Cort17) and at 24:00 (Cort24). A stimulation test for lutropin (LH) and follitropin (FSH) secretion rates was performed, following the administration of 100 µg of gonadoliberein (GnRH). Blood samples for LH and FSH measurements were collected before, after 30 min (LH30, FSH30) and after 60 min (LH60, FSH60) from the injection. All the measurements were performed by the electrochemiluminescence method (ECLIA).

The effects of dietary therapy were assessed, juxtaposing clinical data with routine laboratory tests.

A comparison was made between the clinical data, the results of routine laboratory tests and hormone concentrations, obtained at the beginning of the therapy in the group of cured girls (the girls with regained menstrual cycles) and the group, where the therapy did not bring complete elimination of the disease.

Statistical analysis was performed. Parameters in nominal scales were compared by the typical Chi² test. The ANOVA analysis of variance was used to compare differences between the mean values. The level of significance at $p < 0.05$ was accepted for all the performed comparisons and calculated statistics.

RESULTS

Analysis of data on admission and on discharge from hospital

Table 1 presents a comparison of the clinical data of the anorectic patients, obtained on the admission to hospital and on the last day of their hospitalisation period.

BW-D was statistically significantly higher ($p < 0.001$) than BW-A, as well as BMI-D was statistically significantly higher ($p < 0.001$) than BMI-A. Hospitalisation period lasted from 3 to 70 days (the mean value 28.2 ± 11.6 days).

Table 2 presents the results of routine laboratory tests, performed in the studied patients on the admission and on the last day of their hospitalisation.

Significantly higher WBC and PLT counts were noted, with significantly higher concentrations of K, P, Glu, Ch and Prot on discharge from hospital vs. the same parameters, measured on admission ($p < 0.001$). However, RBC count and the values of Ht and MCHC and the concentrations of Hb, Na, Ca and Ure were significantly lower on the last day of the hospitalisation period ($p < 0.001$).

Table 1. Comparison of the clinical status of patients with AN on admission to hospital (-A) and on the last day of hospitalisation (-D); BW – body weight; BMI – body mass index; -I – increase

	The mean value ± SD	The median value (minimum-maximum)	
BW-A (kg)	38.11 ± 5.27	38.00 (24.70–50.40)	<i>p</i> <0.001
BW-D (kg)	44.79 ± 5.32	45.10 (29.60–57.50)	
BW-I (kg)	6.68 ± 3.21	7.00 (0.40–13.80)	
BMI-A (kg/m ²)	14.40 ± 1.52	14.47 (11.13–17.26)	<i>p</i> <0.001
BMI-D (kg/m ²)	16.94 ± 1.50	17.07 (12.99–20.08)	
BMI-I (kg/m ²)	2.54 ± 1.24	2.66 (0.14–5.90)	
Hospitalisation period (days)	28.2 ± 11.6	28.0 (3.0–70.0)	

▒ Clinical parameters on discharge from hospital.

Table 2. Comparison of routine laboratory test results in AN patients, obtained on the admission (-A) and on the last day of hospitalisation (-D)

	The mean value ± SD	The median value (minimum-maximum)	
RBC-A (M/μL)	4.36 ± 0.47	4.41 (2.55–5.32)	<i>p</i> <0.001
RBC-D (M/μL)	4.05 ± 3.56	4.03(3.10–5.16)	
Hb-A (g/dL)	12.81 ± 1.13	12.90 (8.30–16.00)	<i>p</i> <0.001
Hb-D (g/dL)	12.01 ± 0.85	12.00 (10.20–14.20)	
Ht-A (%)	39.63 ± 3.67	40.00 (25.50–50.00)	<i>p</i> <0.001
Ht-D (%)	37.74 ± 2.36	38,00 (31,00–43,00)	
MCHC-A (g/dL)	33.12 ± 1.00	33.10 (30.60–35.30)	<i>p</i> <0.001
MCHC-D (g/dL)	32.70 ± 0.93	32.60 (30.40–35.10)	
WBC-A (K/μL)	4.57 ± 11.11	4.30 (2.26–7.74)	<i>p</i> <0.001
WBC-D (K/μL)	5.12 ± 13.60	4.70 (2.88–8.48)	
PLT-A (K/μL)	193.38 ± 45.20	192.00 (99.00–320.00)	<i>p</i> <0.001
PLT-D (K/μL)	262.71 ± 62.78	259.00 (143.00–391.00)	
Na-A (mmol/L)	147.75 ± 3.76	149.00 (137.00–156.00)	<i>p</i> <0.001
Na-D (mmol/L)	140.49 ± 13.73	142.00 (17.00–151.00)	
K-A (mmol/L)	4.30 ± 0.31	4.30 (3.40–4.90)	<i>p</i> <0.001
K-D (mmol/L)	4.72 ± 0.28	4.80 (3.60–5.20)	
Ca-A (mmol/L)	2.26 ± 0.08	2.27 (2.00–2.51)	<i>p</i> >0.05
Ca-D (mmol/L)	2,21 ± 0.06	2.21 (1.99–2.43)	
P-A (mmol/L)	1.22 ± 0.09	1.20 (0.90–1.43)	<i>p</i> <0.001
P-D (mmol/L)	1,36 ± 0.09	1,37 (1.08–1.52)	
Glu-A (mg/dl)	70.93 ± 6.86	70.00 (51.00–91.00)	<i>p</i> <0.001
Glu-D (mg/dl)	79.70 ± 9.35	80.00 (8.00–96.00)	
Ch-A (mg/dl)	187.69 ± 32.71	187.00 (111.00–268.00)	<i>p</i> <0.001
Ch-D (mg/dl)	202.78 ± 19.54	203.00 (137.00–260.00)	
Prot-A (mg/dl)	6.84 ± 0.64	6.80 (5.30–7.70)	<i>p</i> <0.001
Prot-D (mg/dl)	7.44 ± 0.41	7.50 (6.20–8.30)	
Ure-A (mg/dl)	32.48 ± 7.78	32.00 (17.00–49.00)	<i>p</i> <0.001
Ure-D (mg/dl)	20.48 ± 3.85	20.00 (15.00–31.00)	

▒ Laboratory tests on discharge from hospital

Table 3. Clinical data of AN patients after regained menstruation cycle.

	The mean value \pm SD	The median value (minimum-maximum)
BW-M (kg)	50.46 \pm 4.06	50.00 (42.00–59.00)
BMI-M (kg/m ²)	18.98 \pm 0.72	18.75 (18.14–21.08)
Outpatient treatment duration (months)	3.5 \pm 2.5	3.0 (1.0–12.0)

Table 4. Clinical data, obtained at the beginning of therapy in AN girls, cured after applied therapy (Group I), compared with the clinical data of uncured girls (Group II).

	Group I The mean value \pm SD	Group II The mean value \pm SD	P
The number of patients (n)	66	21	-
The percent of patients	75.86	24.14	-
Age (years)	15.9 \pm 1.2	16.7 \pm 2.0	0.033
Height (m)	1.63 \pm 0.06	1.61 \pm 0.08	0.239
BW (kg)	38.98 \pm 4.94	35.35 \pm 5.49	0.005
BMI (kg/m ²)	14.65 \pm 1.45	13.62 \pm 1.52	0.006
Disease duration before hospital admission (months)	9.9 \pm 4.8	14.9 \pm 7.1	0.000
BWL (kg)	15.80 \pm 6.73	16.45 \pm 4.04	0.673
BWL% (%)	28.49 \pm 7.37	31.70 \pm 5.23	0.067
BWL/time (kg/day)	1.94 \pm 1.17	1.44 \pm 0.84	0.073
BWL%/time (%/day)	3.51 \pm 1.68	2.81 \pm 1.73	0.105

□ Statistical significance at $p < 0.05$

Final treatment results

After discharge from the Department, the anorectic patients could continue their therapy at the Outpatient Clinic. Sixty-six (66) girls (75.9%) with AN enrolled themselves to further therapy. The remaining 21 patients (24.1%) did not accept the treatment method. Menstruation cycles were regained in all the anorectic patients who continued the therapy. The outpatient treatment duration to menstruation cycle recovery ranged from 1 to 12 months (the mean value 3.5 ± 2.5). Clinical data of patients with AN after recovered menstruation cycle are presented in Table 3.

Analysis of data from cured and uncured patients

Clinical data

The subsequent stage of the therapy was provided at outpatient environment. That opportunity was welcome by 66 patients (75.86%), while the remaining 21 patients (24.14%) could not bear the rigorous dietetic regime anymore and refrained from further treatment. In all the patients, who took the chance of continued treatment, menstruation cycles were recovered within 1–12 months of outpatient therapy. The mean BMI value, at which menstruation occurred, was 18.98 kg/m². None of the cured patients turned up at the clinic with any nutrition problems during subsequent 3 years.

Clinical data and the results of routine laboratory and hormonal tests (all the parameters from the beginning of the therapy) were analysed in the anorectic girls, in whom menstruation cycles were recovered after applied treatment (Group I) and in the group of patients, who refused their participation in the proposed therapy (Group II).

Table 4 presents the clinical data of girls from both studied groups.

Disease duration before hospitalisation in the anorectic girls, in whom menstrual cycles were recovered in result of the applied therapy (the mean value: 9.9 ± 4.8 months), was significantly shorter ($p < 0.001$) from disease duration in the patients who refused the offered therapy (the mean value: 14.9 ± 7.1 months).

The mean BW-A was significantly higher ($p = 0.005$) in the patients of Group I (38.98 ± 4.94 kg) than in those of Group II (35.35 ± 5.49 kg).

The patients, in whom menstrual cycles were recovered, revealed significantly higher ($p = 0.006$) BMI values (the mean value: 14.65 ± 1.45 kg/m²), compared to the patients who refused further treatment (the mean value 13.62 ± 1.52 kg/m²).

The patients in Group I were significantly ($p = 0.033$) younger (the mean age: 15.9 ± 1.2 years) from the patients in Group II (the mean age: 16.7 ± 2.0 years).

Table 5. Results of routine laboratory tests, obtained at the beginning of therapy in AN girls, cured after the applied therapy (Group I), compared with the data of uncured girls (Group II)

	Group I The mean value ± SD	Group II The mean value ± SD	P
RBC (M/ μ L)	4.38 ± 4.96	4.28 ± 3.72	0.377
Hb (g/dL)	12.87 ± 1.16	12.62 ± 1.03	0.377
Ht (%)	39.75 ± 3.78	39.24 ± 3.36	0.580
MCHC (g/dL)	33.15 ± 0.97	33.05 ± 1.12	0.694
WBC (K/ μ L)	4.64 ± 12.03	4.370 ± 7.39	0.333
PLT (K/ μ L)	194.92 ± 46.43	188.19 ± 41.81	0.574
Na (mmol/L)	147.91 ± 3.59	147.24 ± 4.31	0.479
K (mmol/L)	4.33 ± 0.31	4.22 ± 0.27	0.147
Ca (mmol/L)	2.27 ± 0.07	2.25 ± 0.11	0.384
P (mmol/L)	1.23 ± 0.09	1.18 ± 0.10	0.075
Glu (mg/dL)	71.14 ± 6.87	70.29 ± 6.98	0.623
Ch (mg/dL)	188.17 ± 34.84	186.19 ± 25.55	0.811
TG (mg/dL)	75.45 ± 16.42	74.57 ± 22.94	0.846
Prot (mg/dL)	6.88 ± 0.65	6.70 ± 0.59	0.237
Ure (mg/dL)	32.29 ± 7.02	33.10 ± 9.99	0.681

Routine laboratory tests

No statistically significant differences were found at the beginning of the therapy between the group of girls with cured and the group of girls with uncured AN, see Table 5.

Hormonal tests

Table 6 presents the values of hormone concentrations, measured at the beginning of the therapy in the cured (Group I) and uncured (Group II) girls.

Statistically significant differences ($p=0.020$) were found in E_2 concentrations between Group I and Group II. Statistically significant differences were also found in Cort17 and in Cort24 concentrations between the cured and uncured groups ($p=0.032$ and $p=0.000$).

DISCUSSION

The main goal of therapy in anorexia nervosa is body weight normalisation at the level appropriate for height and age. Taking into account the fact that body weight loss is the key motivation for patients with anorexia, which target is attained by conscious limitation of food intake (causing, in consequence, a number of metabolic and hormonal disorders), it is not possible to define straightforward and unequivocal method of therapy, which would be effective in this disease. Considering the fact that most somatic, metabolic and psychotic disorders result from body weight deficit, it seems, then, fairly logical that body weight increase, obtained in the course of *anorexia* treatment, is – by itself – of a great beneficial significance [1, 5].

In our opinion, the presented results of dietary therapy are, at least, satisfactory – menstrual cycles were recovered in 75.86% of patients.

The majority of authors agree that, in approximately 50% of anorectic patients, body weight normalisation and menstruation cycle recovery are obtained, in 30% – these two aspects are only partially improved, while in the remaining 20%, no improvement is observed at all [3, 7, 10, 12, 13, 15, 18]. Following Beumont et al. [3], patients with AN require hospital treatment, lasting 2–3 months, to improve their general well-being status. McKenzie et al. [4] represented a similar opinion. On the basis of their 15-year observation, Strober and Freeman [14] stated that 75–85% of their anorectic patients were cured, however, the time period of full recovery varied between 56 and 79 months.

Amenorrhoea is one of the diagnostic criteria in AN, while the return of menses is one of the signs of recovery. In our patients with regained body weight the menstrual cycles normalized spontaneously.

Some of authors tried to induce menstruation in anorectic girls, in whom some body weight increase was observed, using a GnRH analogue, pulsatively administered with an electronic pump [17]. However, this way of therapy has not found any broader application interest. The role of hormone replacement therapy is also discussed [6].

Concomitantly to body weight increase and with applied proper nutrition and hydration, sodium and urea concentrations gradually reduced their values. The positive effects of the therapy included also increased mean potassium concentration (most probably associ-

Table 6. Hormonal concentrations, obtained at the beginning of therapy in AN girls, cured after the applied therapy (Group I), compared with the data of uncured girls (Group II)

	Group I The mean value \pm SD	Group II The mean value \pm SD	p
LH (IU/L)	0.47 \pm 0.85	0.25 \pm 0.38	0.249
LH30(IU/L)	2.59 \pm 2.63	2.02 \pm 2.24	0.377
LH60(IU/L)	2.21 \pm 2.35	1.85 \pm 2.17	0.535
FSH(IU/L)	2.42 \pm 2.43	1.55 \pm 1.81	0.134
FSH30(IU/L)	6.47 \pm 4.11	5.15 \pm 4.18	0.207
FSH60(IU/L)	8.19 \pm 4.94	6.97 \pm 5.04	0.330
E ₂ (pg/mL)	16.47 \pm 9.87	11.11 \pm 5.69	0.020
T (ng/mL)	0.33 \pm 0.13	0.34 \pm 0.13	0.704
Cort8 (μ g/dL)	25.33 \pm 6.71	27.28 \pm 6.66	0.249
Cort17 (μ g/dL)	14.73 \pm 4.22	16.99 \pm 3.97	0.032
Cort24 (μ g/dL)	5.53 \pm 2.81	8.61 \pm 5.34	0.000
FT ₃ (pg/mL)	1.66 \pm 0.43	1.56 \pm 0.35	0.368
FT ₄ (ng/mL)	0.90 \pm 0.21	0.89 \pm 0.19	0.855
TSH (mIU/L)	1.44 \pm 0.93	1.14 \pm 0.82	0.183

Statistical significance at $p < 0.05$

ated with secondary hyperaldosteronism regression), as well as higher glucose concentration (Table 2). Higher glycemia reflects increased body weight, obtained in result of enhanced food consumption.

The tendency towards hypocalcemia, observed in the course of applied therapy, indicates a need for supplementation with calcium preparations in anorectic patients [6]. It is possible that the mechanism of standard calcium absorption normalises after much longer time than the observation period in the reported study.

Following the comparison of clinical data at the beginning of the therapy between the uncured patients with AN and those girls, whose body weights normalised and menstruation cycles regained, we found that the cured patients demonstrated statistically significantly shorter disease duration before admission to hospital, bigger body weight at the beginning of the therapy, higher BMIs and were younger than the patients, who were not treated (Table 4). The obtained data demonstrate that the parameters, such as the age, body weight, BMI and disease duration, may be regarded to be prognostic factors in the therapy of anorexia.

The results of the analysis comply with the observations by Steinhäuser [13], who claims that shorter disease duration gives more chances for effective treatment than long-term disease process. The degree of cachexy is also prognostically significant for the author. Steinhäuser [13] is also convinced that terminal cachexy of the organism (approximately, 60% body weight deficit) provides much worse prognosis. In such patients, any undertaken attempts of treatment either fail or are but little effective. In their retrospective study, Zipfel et al. [18] draw our attention to poor prognosis of treat-

ment in girls with long-term anorexia, recommending, in these cases, early and intensive hospital treatment. Rubin et al. [11] claim that positive prognosis may be expected in anorexia before the 16th year of life, providing that early diagnosis is obtained and disease duration before diagnosis is not long. According to the authors, the prognostically unfavourable factors include: anorexia preceding obesity, disease onset after the 18th year of life, long duration of the disease and prior hospitalisation periods because of malnutrition.

Comparing the results of routine laboratory tests in the group of cured and uncured patients, no significant differences were observed between the studied groups, what indicates that any deviations of these parameters are not prognostic factors for the therapy in AN. It should strongly be stressed that the above discussed laboratory tests are necessary elements of the diagnostic and therapeutic protocols in anorexia.

Comparing the groups of cured and uncured patients, we found out that the patients, who declared their intent to further treatment, demonstrated statistically significantly higher E₂ values in blood serum (16.47 \pm 9.87 pg/mL) at therapy onset than those in whom the applied treatment was not successfully completed (11.11 \pm 5.69 pg/mL). Therefore, E₂ concentration in girls with AN may be regarded a prognostic factor in the therapy of this disease. Hypoestrogenism in AN, even if it is a symptom, secondary to hypothalamo-pituitary insufficiency, still enhances functional disorders of this system, especially with disappearance of the positive feedback mechanism and reduced sensitivity of certain neurocontrollers of the hypothalamo-pituitary system. Among others, the role of estrogens in sensitisation of

the opioid receptor is perceived by many as fairly significant [6, 8].

Hypocortisolemia, observed in patients with *anorexia*, may additionally inhibit the hypothalamic release of GnRH in malnutrition status, enhancing hypogonadism [14].

Comparing the groups of cured and uncured patients, we found out that Cort17 and Cort24 concentrations at the onset of the therapy were significantly higher in the girls who did not comply with treatment protocol than in those who adhered to proposed therapy and menstruated again. Therefore, it may be assumed that, similarly as in hypoestrogenism, the degree of hypocortisolemia in blood serum, measured at 17:00 and 24:00, may be a useful information for the prognosis of therapy outcome in anorectic girls.

Our observations are in compliance with the opinions of many authors, who claim that hormonal disorders in AN result from cachexy and from adaptation of the organism to caloric deficit, while body weight increase and normalisation lead to hormonal compensation and stabilisation [5, 11, 9, 16].

It should be underlined that the prevailing majority of the authors, describing AN treatment, are psychotherapists. Their approach to patients with this disease is – sometimes – different from that presented by endocrinologists – a therapy in AN is first of all psychotherapy, resulting in body weight gain [4, 7, 15]. In this study, we tried to find some evidence for the assumption that body weight increase is the key condition for effective therapy in *anorexia nervosa*. Zerbe [16] admits that, after several weeks, when a patient is brought back from cachexy and her malnutrition is improved, the patient becomes more susceptible to psychological stimuli.

Our studies confirm that body weight increase, resulting from proper diet implementation, is the basic element of therapy in AN, while also allowing us to identify the factors of prognostic significance for therapeutic outcome in *anorexia*. The age, disease duration, the degree of body weight loss and serum estradiol and cortisol concentrations, measured at 17:00 and 24:00, are prognostic factors for therapy in AN.

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