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ORIGINAL ARTICLE

Assessment of adolescents with anorexia nervosa and atypical anorexia nervosa monitored as outpatient

Evaluación de adolescentes con anorexia nerviosa y anorexia nerviosa atípica controlados ambulatoriamente

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What do we know about the subject matter of this study?

Atypical anorexia nervosa shares the same criteria as anorexia nervosa, but individuals present with a weight that is within or above the normal range. The number of patients presenting with this eating disorder, both as outpatients and inpatients, has increased significantly. Recent meta-analyses show that psychopathology and medical complications are the same or worse than in patients with anorexia nervosa.

What does this study contribute to what is already known?

In this study, we demonstrate that atypical anorexia nervosa accounts for twice as many cases of anorexia nervosa in the outpatient clinic and that it has a similar profile of medical complications as anorexia nervosa despite patients having normal weight at admission. It provides new indicators that could be considered as factors related to higher medical risk in anorexia nervosa.

Abstract

Among the restrictive eating and eating disorders, anorexia nervosa (AN) and atypical anorexia nervosa (AAN) are the ones that present the greatest medical complications. **Objective:** Describe the characteristics of patients with AN and AAN and their differences in demographic and clinical parameters. **Patients and Method:** The records of patients <19 years of age with AN admitted to *Clinica Santa María* between 2013 and 2019 were reviewed. The evolution time, amenorrhea, z-BMI, percentage and speed of weight loss, and complications were recorded. Results were expressed as mean and standard deviation or median and range. Comparisons were made using the Mann-Whitney test, the t-student test, and the chi-square test; Pearson's coefficient was used for correlations. **Results:** 76 patients with AN were admitted (64% AAN). The median age was 15.4 years. AN and AAN differed in age at diagnosis ($p < 0.03$), z-BMI ($p < 0.001$), bradycardia ($p < 0.009$), blood pressure ($p < 0.003$),

Keywords:
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and cholesterol ($p < 0.02$), without other differences. The z-BMI correlated with heart rate ($r = 0.39$ $p < 0.002$); systolic pressure ($r = 0.43$ $p<0.000$), and HDL ($r = -0.39$ $p < 0.005$). The percentage of weight loss was correlated with time of amenorrhea ($r = 0.27$ $p < 0.05$); alanine aminotransferase ($r = 0.0.37$ $p < 0.031$), and HDL ($r = 0.47$ $p < 0.001$) and the speed of weight loss with glycemia ($r = -0.46$ $p < 0.001$) and urea nitrogen ($r = -0.39$ $p < 0.005$). **Conclusion:** AAN was the most frequent AN condition in this sample and variables such as the percentage and speed of weight loss were as important as BMI in medical complications.

Introduction

Within the eating disorders (ED), anorexia nervosa (AN) is the one with the highest morbidity and mortality. This pathology is characterized by a disproportionate concern with the body and weight, which is accompanied by food restriction with or without excessive exercise, vomiting, and/or use of laxatives, leading the patient to a weight that is below the normal minimum or, in the case of children and adolescents, below what is minimally expected for their age and height[1]. Without early treatment, the course is prolonged and leads to a high rate of physical, psychological, and social morbidity. Its worldwide mortality is about 5.1%, of which one-third is explained by suicide, followed by metabolic disorders and infections[2].

In the current edition of the DSM-5, atypical anorexia nervosa (AAN) was included in the category of "Other Specified Feeding and Eating Disorders" (OSFED)[1]. It shares the same criteria as AN, but individuals present with weight that is within or above the normal range for height and age despite having experienced significant weight loss. Currently, the prevalence of AN in females ranges from 0.15-0.7% and AAN from 0.39-4.9%[3].

The recognition of AAN challenges the concept that weight is sufficient to assess disease severity. The number of patients with AAN requiring medical hospitalization has increased considerably, comprising approximately one-third of emergency admissions to services managing ED[4]. Sawyer et al.[5] compared disease severity in adolescents diagnosed with AAN versus AN concluding that, despite not being underweight at diagnosis, nearly 1 in 4 adolescents with AAN had bradycardia, 1 in 3 amenorrhea, and > 40% required hospital admission. In addition, they found no differences between physical and psychological morbidity between patients with AAN and AN. Other subsequent studies present similar findings[4,6].

Considering the above, the American Academy of Pediatrics, the American Society for Parenteral and Enteral Nutrition, and the Academy of Nutrition and Dietetics propose in 2022 to use a combination of several indices to determine the severity of these patients, possible risks of refeeding syndrome, and medical compromise[7]. They propose to use the percentage of mean BMI and BMI z-score (BMI-z), percentage, and rate of weight loss to stratify patients with AN and AAN into mild, moderate, and severe malnutrition.

Despite the serious complications of this disease and the percentage of patients who become chronic, studies show that only 50% of cases of AN are diagnosed and only 1 in 3 are treated by a specialist. In the case of AAN, the figures are higher because it is less recognized[3,8].

The objectives of this study were to describe the most important clinical characteristics and findings of patients with AN, to determine which AN severity indices are associated with clinical and laboratory variables, to quantify the frequency of AN and AAN, and to compare the characteristics between the two.

Patients and Method

Analytical, retrospective, cross-sectional study. The clinical records of all patients under 19 years of age seen at the nutrition clinic of the Adolescence Unit of *Clínica Santa María* between January 2013 and January 2019 were selected. Patients with neurological, cardiological, and endocrine diseases and renal insufficiency were excluded to avoid that other variables could influence the results (medications in use, weight loss associated with these diseases that could be added to the weight loss due to AN, etc.).

Definitions

AN was defined as anorexia that meets all the criteria in the DSM-5 and AAN as anorexia that meets all criteria except weight involvement.

Age at medical diagnosis, time of evolution of the disease before diagnosis, premorbid weight, weight loss (kg), weight loss percentage, percentage of weight loss per month, psychiatric comorbidity, history of ED in first-degree relatives, laboratory tests (CBC, liver tests, glycemia, plasma phosphate, vitamin D, lipid profile, creatinine, and urea nitrogen), and medical complications (hypotension, cardiological abnormali-

ties, electrolyte alterations) were recorded. In the case of females, age at menarche and amenorrhea time before diagnosis (months) were recorded. In addition, nutritional status were evaluated through body mass index (BMI-z) at admission and the onset of the disease. A BMI-z between -0.99 and +0.99 SD was considered eutrophic; a BMI-z between -1 and -1.99 SD, as at risk of undernutrition; a BMI-z ≤ -2 SD, as undernutrition; a BMI-z between +1 SD and +1.99 SD as overweight; and a BMI-z ≥ +2 SD as obesity, according to the WHO/FAO tables[9].

This study was evaluated and approved by the Ethics Committee of *Clínica Santa María*.

Statistical Analysis

For the analysis, the data were examined for anomalous, miscoded, or duplicated data, and the distribution of quantitative variables was evaluated using Kernel density plots and the Shapiro-Wilks test. Results were expressed as mean and standard deviation (SD) or median and range according to the distribution of each quantitative variable. Comparisons between AN and AAN were performed using the Student's t-test or Mann-Whitney test for quantitative variables and the chi-square test or Fisher test to study associations between categorical variables. Pearson's correlation test was used to evaluate correlations. A p-value < 0.05 was considered significant. Statistical analyses were performed using the STATA 17 SE software.

Results

During the study period, 76 patients with AN (35.5% AN and 64.5% AAN) were admitted to the nutrition clinic. Only 15% of the patients went to the nutritionist for their first consultation, the rest were referred by other professionals: 43% by mental health professionals (psychiatrists and psychologists), 21% by adolescent medicine specialists, and 21% by other physicians (gynecologists, gastroenterologists).

From the medical records, we obtain 100% of the anthropometric data on admission to medical checkups and psychiatric comorbidity and 90% of the history of ED in first-degree relatives and weight before the onset of AN. Regarding cardiovascular parameters (pulse and blood pressure), data were obtained for 92% of the patients, and in laboratory variables, 71% of the lipid profile, urea nitrogen, and glycemia data, and in 60% the values of liver tests and plasma phosphate.

Most patients were female (91%) with a female:male ratio of 10:1 and a median age at diagnosis of 15.4 years (12-19 years). Table 1 shows the comparison of the characteristics of patients with AN and AAN, showing a significant difference in the median age at diagnosis between AN (16.4 years) and AAN (15.2 years).

In the rest of the comparison variables, no significant differences were found in terms of time of evolution, time of amenorrhea, and history of ED in first-degree relatives. Both groups were also comparable in terms of psychiatric comorbidities, the most frequent being depression in 25% of all patients, anxiety disorders in 7%, and obsessive-compulsive disorder (OCD) in 3%. On admission, 35% of the female patients had amenorrhea and the average number of months without menstruation was 2.5 months, with no differences between AN and AAN.

Regarding nutritional aspects, it was observed that adolescents with AAN presented a higher BMI z before the onset of the disease (0.9 AAN vs -0.4 AN) with 44% of patients with excess weight. In relation to weight loss before diagnosis, both groups lost equal percentages of weight.

Table 2 shows the comparison of clinical and laboratory variables between patients with AN and AAN. Patients with AN presented significantly lower heart rate, systolic and diastolic blood pressure, and higher total cholesterol levels. A vitamin D deficiency of 70% was observed in both groups and in the AN group leukopenia was also found in 24% of the sample, while this was observed in 13% of patients with AAN. No patient presented hypophosphatemia or hypokalemia.

Figure 1 shows the associations between BMI-z, percentage and speed of weight loss with the clinical variables evaluated. It shows that alterations in cardiovascular variables are mostly associated with low BMI-z and metabolic variables more with percentage and speed of weight loss.

Discussion

Adolescents with AAN accounted for more than half of the patients admitted for AN at this health center, with no differences observed with those patients with AN in terms of time of illness before diagnosis, amenorrhea time, psychiatric comorbidities, or percentage and rate of weight loss before diagnosis. In addition, both pathologies showed a similar profile of medical complications.

The increase in the prevalence of AAN over AN is already a constant worldwide[5,10]. In our country, in a previous sample between 2005 to 2015 of patients hospitalized in a Mental Healthcare Center, 53% of patients with AN presented AAN at the time of admission[11]. This could be explained in part, by the increasing prevalence of overweight and obesity which leads to adolescents, despite losing a large percentage of their weight, remaining within normal ranges for their age

and sex. This hypothesis is supported by the fact that 44% of adolescents with AAN were overweight at the onset of their disease, which is very similar to the data on healthy Chilean adolescents in which malnutrition by excess reached 41%[12].

Several studies have shown that excess weight is a risk factor for ED, being 2 times more likely to present them than the population with normal nutritional status and, considering the sustained increase of excess weight in the population, it is partly explained that ED are on the rise[13,14].

Deeping this situation, approximately 40% of patients with AN have associated psychiatric comorbidity. International studies, like ours, show that AAN has the same or greater risk of psychiatric comorbidities than AN, with depression, anxiety disorder, and OCD being the most frequently presented pathologies, which coincides with that seen in other studies such as Sawyer et al and Whitelawet et al.[5,15].

When the AN and AAN groups were compared, significant differences were found only in cardiovascular variables (heart rate and blood pressure), being significantly lower in AN; but there were no differences in other variables such as presence and time of amenorrhea, phosphatemia, glycemia, and other metabolic variables, despite the difference in nutritional status between the groups. It is also observed that when analyzing the entire population (AN plus AAN) the percentage of weight loss was associated with a higher frequency of amenorrhea, HDL and ALT levels, and lower triglyceride levels. These findings support the fact that not only BMI involvement is important in determining the medical and refeeding risk of these patients. The works of Whitelawet et al, Sawyer et al, and Assalone et al (5,15,17) and the recent meta-analysis by Walsh et al.[18] suggest that in addition to BMI involvement (BMI-z), the percentage of weight loss and the rate at which it occurs are the main factors leading to medical instability in both AN and AAN.

Therefore, a patient with AAN may be normal weight, but have life-threatening complications, especially after rapid weight loss. This highlights the need to standardize terminology and methodology around the assessment of malnutrition and severity for clinical and research purposes, which is why organizations such as the American Academy of Pediatrics, the American Society for Parenteral and Enteral Nutrition, and the Academy of Nutrition and Dietetics in 2022 propose using a combination of several scores for this purpose.

Another factor to consider is that adolescence is a period of rapid growth, so nutritional demands are greater, and when malnutrition occurs, phenomena that affect growth and development, such as amenorrhea, frequently occur. In our patients, we observed that the participants with AAN had the same frequency of amenorrhea as the patients with AN (67% and 68%, respectively). In the literature, its frequency is up to 84% in AN and is related to complex physiological aspects such as hormonal changes, including a drop in serum

Tabla 1. Comparación de las características de los pacientes con AN y ANA

	AN (n = 27)	ANA (n = 49)	Valor p
Female, n (%)	24 (89)	45 (91.8)	0.67§
Diagnostic age (years), median (range)	16.4 (12.5-19)	15.2 (12.2-18.1)	**0.03†**
Evolution time (month), median (range)	1 (0.2-4)	0.7 (0.1-6.5)	0.16†
Age menarche (years), median (range)	11 (9-14)	12 (12-14)	0.24†
Amenorrhea time (month), median (range)	2.5 (0-24)	2.5 (0-15)	0.87†
BMI-z premorbid, mean (SD)	-0.44 (0.44)	0.92 (0.61)	**< 0.001‡**
BMI-z admission, mean (SD)	-1.77 (0.64)	-0.14 (0.65)	**< 0.001‡**
Weight loss (kg), median (range)	7 (0-12)	8 (0-25)	0.14†
Weight loss (%), median (range)	14.6 (0-23.6)	14.6 (0-31.1)	0.6†
Monthly weight loss (%), median (range)	2.4 (0.4-10)	2.3 (0.03-9.9)	0.57†
First grade relatives ED history, n (%)	3 (12.0)	14 (33.3)	0.05§
Psychiatric comorbidity, n (%)	11 (40.7)	19 (38.8)	0.86§
Amenorrhea rate, n (%)	18 (68)	32 (67)	0.86§

BMI: Body mass index; AN: anorexia nervosa; AAN: atypical anorexia nervosa; ED: eating disorder, †Test Mann-Whitney; ‡Test Student; §Test chi-cuadrado. Variables with significant difference appear highlighted in bold.

Table 2. Comparison of clinical and de laboratory variables among AN y AAN

	AN (n = 27)	ANA (n = 49)	Valor p
Bradiycardia, n (%)	12 (46.2)	8 (21)	**0.01§**
Hearth rate	60 (44-80)	65 (45-95)	**0.04†**
Systolic blood pressure (mmHg)	100 (90-120)	110 (80-130)	**0.00†**
Diastolic blood pressure (mmHg)	60 (50-75)	60 (50-87)	**0.03†**
Hematocrit (%)	40.4 (34.2-45.4)	40.3 (32.4-49)	0.67†
Hemoglobin (g/L)	13.4 (11.9-15.2)	13.1 (9.8-16)	0.84†
Leukocytes (mg/dl)	5.500 (3.300-7.600)	5.800 (3.200-10.000)	0.16†
AST (UI/L)	20 (8-43)	18 (12-38)	0.13†
ALT (UI/L)	16 (9-42)	16 (6-49)	0.83†
Glycemia (mg/dl)	82 (64-94)	80 (58-99.5)	0.55†
Phosphatemia (mg/dl)	4.1 (3.5-4.9)	4.3 (2-4.8)	0.93†
Vitamin D (ng/dl)	25.3 (12.6-39)	23.7 (10.2-47.6)	0.86†
Total cholesterol (mg/dl)	173 (115-260)	151 (112-242)	**0.03†**
Triglycerides (mg/dl)	64 (43-158)	63.5 (35-262)	0.74†
HDL (mg/dl)	63.8 (45-93)	57.4 (33-97)	0.18†
LDL (mg/dl)	92 (42.8-157)	76.5 (40.7-140)	0.09†

Results are expressed as median and range. AN: anorexia nervosa; AAN: atypical anorexia nerviosa; AST: aspartate aminotransferase; ALT: alanin aminotransferase; HDL: high density lipoprotein; LDL: low density lipoprotein; †Test Mann-Whitney ᵟTest chi-cuadrado. Variables with significant difference appear highlighted in bold.

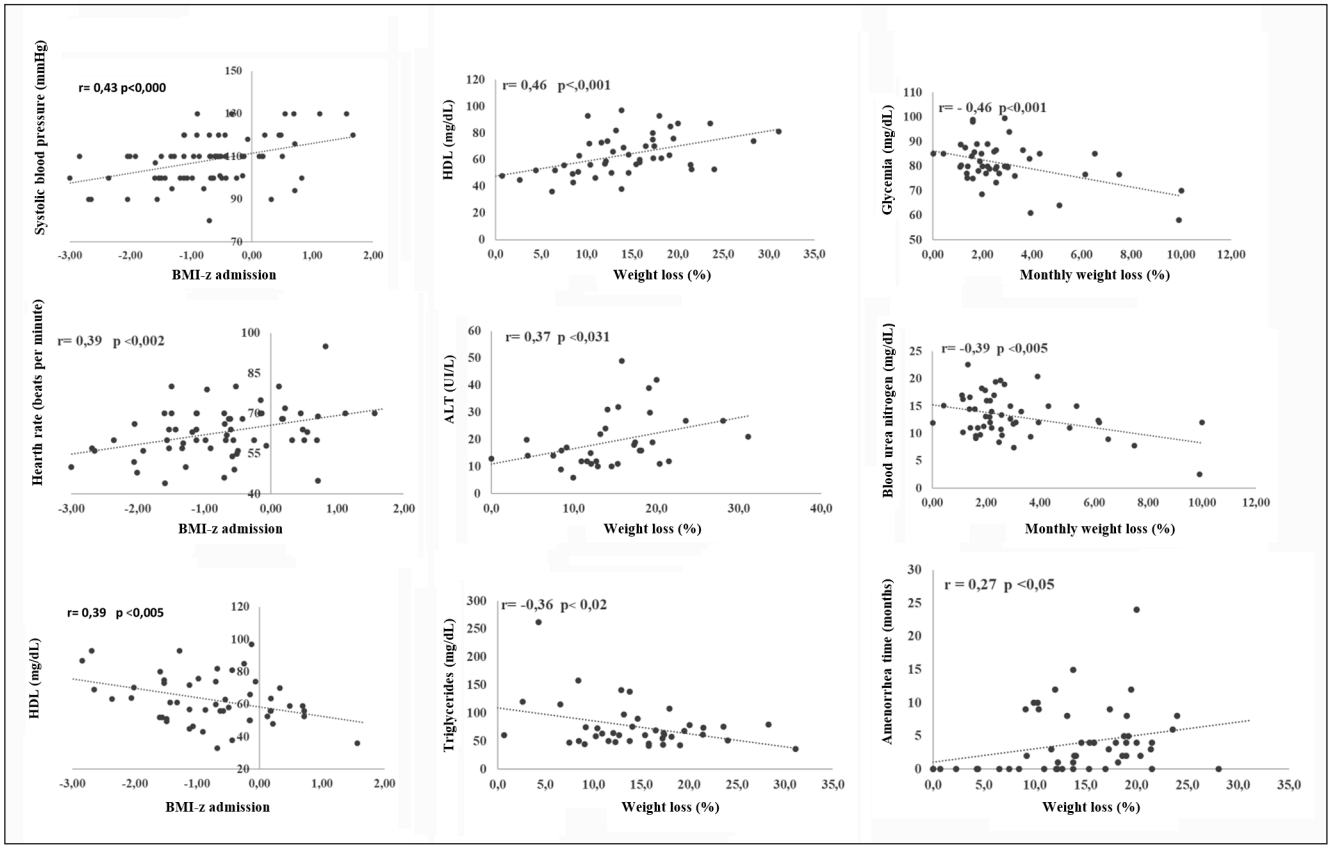

Figure 1. Associations between zBMI, percentage and speed of weight loss with the clinical variables evaluated.

leptin levels and a decrease in gonadotropin-releasing hormone, leading to a decrease in LH, FSH, and anovulation. This also results in a decrease in bone mineral density with an increased risk of fractures[19] and a decrease in fertility, however, in adolescents with AN, there is an almost twofold increase in unplanned pregnancy, which is probably due to the belief on the part of health workers and the family that by presenting amenorrhea patients are not at risk of pregnancy[20]. Although menstruation returns when weight is regained in AN, in AAN it is not well known what weight is the goal. Studies have reported that in patients with AAN, this would occur with weights significantly lower than the maximum premorbid weight; however, it is not yet known what percentage of weight should be regained[21].

We observed that both plasma ALT and HDL levels increased as nutritional compromise increased. Elevation of liver enzymes is often seen in AN and this increase fluctuates between 12 to 25%. ALT is most frequently altered and correlates primarily with decreased fat mass[10,22,23]. After a period of nutritional replacement, most patients present enzymes normalization. The causes of this alteration are not well known; however, a multifactorial etiology has been hypothesized, involving phenomena such as acute hepatic hypoperfusion, hepatic steatosis with increased oxidative stress, and alterations in hormonal regulation that increase the risk of nonalcoholic fatty liver disease and starvation-induced hepatocyte autophagy[22,23]. Furthermore, this enzyme could be a marker of recovery speed, as elevated ALT during the refeeding period is significantly associated with a delay in the onset of weight gain[23] which could be an indicator of slower recovery. With respect to HDL levels, Duncan et al.[24] found a significant genetic correlation between AN and "favorable" metabolic phenotypes (high HDL and low triglycerides) and negative correlations with "unfavorable" metabolic phenotypes (high insulin and high fasting glucose). This could be explained in part by lipid-hormone interactions. Lipid concentrations are tightly regulated by hormones and very low fat intake associated with a low-calorie diet, which is common in AN, can induce hypoinsulinemia and increase insulin sensitivity. All this background demonstrates that AN has, in part, a complex inherited phenotype with significant genetic correlations not only with psychiatric disorders but also with multiple metabolic traits.

The literature describes that the relative risk of having AN is four times higher in family members of patients with AN and, in the case of female relatives, up to 11 times higher[25,26]. This inheritability is higher in AN than in subsyndromal AN conditions such as AAN. In this sample, a quarter of the patients had a history of ED in first-degree relatives and there was no significant difference in these 2 types of AN[26].

Our findings should be considered under several limitations. One of the main ones is the relatively small size of both groups (AN and AAN), which may have affected the ability to explore the differences between these groups. On the other hand, being a retrospective study, some data could not be obtained or were based on the recollection of the patients or parents, such as premorbid weight, family history of ED, and the time in which they lost weight. Likewise, in the absence of premorbid height, the height obtained at admission was used, this may lead to overestimation of premorbid BMI in some adolescents. However, the overall effect on the results is expected to be small and would affect both groups equally. Being conducted in a single center, the generalizability of our findings may be affected by the lack of diversity in the sample. Despite these limitations, this is one of the first studies in our country to evaluate the characteristics and frequency of AAN and possible similarities and differences with AN.

Conclusions

Early recognition and diagnosis of this pathology are relevant since early intervention is one of the best predictors of success in long-term treatment (27). Currently, considering a low BMI as the main indicator of severity in AN is a mistake because as we have seen, the percentage of weight loss, probably associated with the time in which it occurred and the duration of the disease, plays an important role in most medical complications.

There are still many questions about AAN, such as how it evolves, which therapy is the most effective, how it responds to treatment, and the risk of relapse; from the nutritional point of view, a great unknown is what body weight is adequate to achieve medical recovery and emotional well-being of patients.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This docu-

ment is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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