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Extremely severe anorexia nervosa: Hospital course of 354 adult patients in a clinical nutrition-eating disorders-unit.

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Abstract:

Background and Aims: The clinical nutrition-eating disorders-unit in Raymond Poincaré Hospital is a reference center for the management of severe malnutrition and its complications in patients with anorexia nervosa (AN). The purpose of this study is to specify socio-demographic, anamnestic and clinical characteristics of AN patients hospitalized for extreme malnutrition, to identify types and prevalence of medical complications presented during their hospitalization for refeeding and the evolution of patients nutritional status.

Methods: Demographic, clinical and paraclinical data of 354 severely malnourished AN patients were collected, during their first hospitalization in the unit, between November 1997 and January 2014, through medical records. The prevalence of medical complications was compared between the 2 AN sub-types (restricting and bingeing-purging).

Results: 339 patients were female and mean age was 28.7 ± 10.7 years old. Duration of AN was 9.5 ± 9 years, 173 (48.9 %) patients had a restricting AN subtype. BMI at admission was 12.2 ± 1.6 kg/m², 280 (79.3%) patients had already been hospitalized for AN in other

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hospitals before. Psychiatric comorbidities were present in 168 (47.5%) patients. Associated somatic comorbidity concerned 70 (19.8%) patients.

Outcomes during hospitalization were marked by 4.1 ± 3.9 kg weight gain on 36.9 ± 30.5 days. Enteral nutrition was provided in 304 (85.9 %) patients. Main medical complications during hospitalization were: anemia (79%), neutropenia (53.9%), hypertransaminasemia (53.7%), osteoporosis (46.3%), hypokalemia (39.5%), hypophosphatemia (26%), hypoglycemia (13.8%), infectious complications (24.3%), cardiac dysfunction (7.1%), and proven gelatinous bone marrow transformation (6.5%). Hypokalemia was more frequent in bingeing-purging sub-type. Lympho-neutropenia and hypertransaminasemia were more frequent in restricting sub-type. During their hospitalization, 35 (10%) patients were referred to medical intensive care unit and 5 patients died.

Conclusions: AN patients hospitalized for severe malnutrition in a specialized clinical nutrition unit have severe and frequent medical complications. Psychiatric comorbidities are also frequent and could complicate medical care. A specialized and multidisciplinary management of these patients is therefore essential.

Keywords: In patient, Anorexia Nervosa, Severe Malnutrition, Medical Complications, Refeeding

1. Introduction

Anorexia nervosa (AN) is a serious eating disorder, defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) as a restriction of energy intake leading to a significantly low body weight, an intense fear of gaining weight or becoming fat and a dysmorphophobia. Two subtypes are described: restricting type (AN-R) characterized by a severe food restriction only and binge-eating/purging type (AN-BP), in which patients calorie restrict but also present purgative behaviors (self-induced vomiting, laxative or diuretic abuse) (1).

The reported prevalence of AN is 1.4% (ranges 0.1–3.6%) for women and 0.2% (0–0.3%) for men (2). There are two main peaks of incidence: one at the ages of 13 and 14 years, the other at 18 and 20 years (3), though later onset cases (after the age of 25 years) have been described also (4,5).

AN can lead to severe malnutrition. Medical complications can be serious and life threatening. Therefore, medical care should be both psychiatric and somatic (6–9). Psychiatric treatments aim to normalize eating behavior and treat psychiatric comorbidities. Somatic care aims to manage emergency situations, ensure medical stabilization, treat somatic complications, and normalize the nutritional status of the patient (6,7,9).

Hospitalization of AN patient is recommended in case of medical complications and/or severe malnutrition with BMI < 14 kg/m² and/or decompensation of psychiatric comorbidity (6,7,9). Admissions of AN patients usually occur through the psychiatric unit. However, initial management should be first provided in a somatic or critical care unit in case of metabolic

disturbance, organ failure (cardiac, renal, liver), neurological impairment, sepsis, refeeding syndrome, or extreme malnutrition with very low BMI (6–9). Ideally, medical management of really sick patients with severe AN should be performed by an expert medical team experienced in the management of severe malnutrition because of a high risk of clinical instability mainly when $BMI < 13 \text{ kg/m}^2$ (6,7). These patients can easily develop complications during the refeeding phase (edema, electrolytes imbalance, fluid overload, organ failure....) (10,11).

Outcomes of in-patient refeeding programs of severe cases of AN patients with extreme malnutrition have been presented in the literature (12–18). However, sizes of these cohorts were limited. Patient socio-demographic characteristics, clinical profile and medical complications were not always comprehensive. Patient characteristics and outcome in these series are presented in table 1 (refer to supplementary material).

The clinical nutrition-eating disorders (ED)-unit in Raymond Poincaré hospital, in Garches, is a twelve-bed unit specialized in the management of extremely severe undernutrition and its complications associated with AN. Thanks to its expertise, the unit is now considered a regional and national “referral center” by the administrative authorities for the treatment of AN patients whose clinical condition is serious and complicated. The unit receives patients on criteria of somatic severity. Both somatic and psychiatric care are provided in the unit thanks to a multidisciplinary therapeutic program where physician nutritionists and psychiatrists coordinate medical care.

In order to better understand the particularities of patients with a severe form of AN, to get a better knowledge of types and prevalence of medical complications these patients undergo, and to improve patients management, we reported social, demographic and clinical data of 354 different patients severely malnourished admitted for the first time to the clinical nutrition-ED- unit. Every organ concerned by malnutrition and/or refeeding was described.

2. Materials and Methods

2.1. Study design and Aims

We conducted a retrospective observational study in the cohort of AN adult patients admitted in the clinical nutrition-ED- unit in Raymond Poincaré hospital for severe malnutrition and/or medical complications.

The primary objective was to evaluate types and prevalence of medical complications developed by these patients. Secondary objectives were: compare prevalence of medical complications of AN-R subtype and AN-BP subtype, describe the evolution of patient's nutritional status during the refeeding program, specify demographic, anamnesic and clinical characteristics of patients in the cohort.

2.2. Patients

2.2.1. Inclusion criteria

We selected the first hospitalization in the clinical-nutrition-ED unit in Raymond Poincaré hospital between November 1997 and January 2014, of all malnourished patients, aged 15 years or older, diagnosed with AN according to the DSM IV criteria. The patient selection was provided by the department of statistics and medical information of the hospital.

2.2.2. Exclusion criteria

We excluded from the study all patients who did not allow the use of their data for the study and all patients whose BMI was more than 15.9 kg/m².

2.3. Nutritional rehabilitation

In the clinical nutrition-ED- unit, a multidisciplinary team including physicians (clinical nutritionists) specialized in severe malnutrition management, psychiatrists specialized in eating-disorders care, a clinical psychologist, a dietician, a physiotherapist, nurses and nursing assistants, is taking care of patients. In severely malnourished patients, refeeding treatment is performed following NICE guidelines (9) and recommendations of the French National Authority for Health (6).

All patients received an initial intravenous supplementation with vitamins, phosphorus and trace elements. In all patients with BMI below 13 kg/m², enteral nutrition (EN) via a nasogastric feeding tube was started during the first 48 hours of admission with a standard polymeric isocaloric normo-protidic fiber-free enteral nutrition product. The initial enteral caloric intake was 10 kcal per kilogram of body weight per day. EN was administered continuously over 24 hours by means of a pump. Caloric intake was progressively increased according to clinical status and phosphatemia evolution with an objective of 30 kcal/kg/day. Oral nutrition was initiated slowly according to the weight evolution under EN.

2.4. Parameters studied

For each patient, through chart review, we recorded demographic, social, anamnesic data.

Type of AN (restrictive or purging/binging), duration of disease, purging behaviors were detailed. Anthropometric data on admission and on discharge were noted. Patient somatic and psychiatric comorbidities were specified. Referral and length of stay were also notified. Laboratory test results were followed during hospitalization including CBC, platelets count, electrolytes, urea, creatinine, phosphorus, albumin, glycemia, liver enzymes, PT, PTT, and serum micronutrients levels (folate, vitamin B12, vitamin D, zinc, copper, selenium).

A DEXA scan (Dual-energy x-ray absorptiometry) was performed to assess bone mineral density (BMD) of all patients who did not have any BMD evaluation during the 2 years prior to admission. T-score was used to characterize patient's BMD following the international osteoporosis foundation. BMD was considered normal if T-score > -1.0 SD, osteopenia was consistent with -1.0 SD \geq T-score > -2.5 SD, and osteoporosis was considered when T-score ≤ -2.5 SD. All clinical events occurring during hospital stay and documented in physicians notes or nursing assessments were notified.

We reported any acute medical complications occurring during the hospital stay: metabolic such as hypokalemia, hypophosphatemia, hypoglycemia, acute kidney failure; haematological such as neutropenia, lymphopenia, anemia, thrombopenia; liver such as elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT); cardiovascular, digestive, neurological, urological, and infectious complications. Chronic complications of AN highlighted during the hospitalization as low bone mineral density (LBMN) were also recorded.

2.5. Procedures and ethical approval

This study was conducted in accordance with the relevant French guidelines and regulations. It is part of a mortality study for which protocol was approved by the French data protection

authority (CNIL, *Commission Nationale de l'Informatique et des Libertés*) and by two independent review boards (CCTIRS, *Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé* and CPP, *Comité de Protection des Personnes*). An information letter was sent to all patients selected for the study. Patient non-opposition was a prerequisite for the use of their data.

2.6. Statistical analysis

Analyses were performed with R software (version 3.5.3. 2019-03-11, R Foundation for Statistical Computing Platform: x86_64-w64-mingw32/x64 (64-bit)). Univariate statistics were used to describe the sample. Data were expressed as frequencies and percentages for nominal variables, and as means \pm standard deviations (SDs) for continuous variables. Comparison of mean BMI on admission and on discharge was made with paired Student's t test. Differences between length of stay and BMI of AN subgroups (AN-R and AN-BP) were analysed with independent Student's t test. The comparison of the frequencies of occurrence of medical complications between the two AN subgroups was made with the Pearson's Chi square test. A *P*-value < 0.05 was considered statistically significant.

3. Results

3.1. Patients characteristics

395 patients were initially selected but 9 of these were excluded because they did not allow the use of their data for the study and a further 32 patients were excluded because their BMI was ≥ 16 kg/m² (Figure 1). Finally, we included a total number of 354 patients: 339 (95.76%) were female and 15 (4.24%) were male. More than half of them (58%) were transferred from another inpatient unit (Table 2). Mean age at admission was 28.7 (± 10.7)

years old and 48.8% of patients had AN-R subtype while 49.3% had AN-BP subtype. Duration of AN at admission was 9.5 (\pm 9) years. 280 (79.3%) patients had already been admitted in other hospitals for AN before this first admission in the clinical nutrition-ED-unit (Table 3).

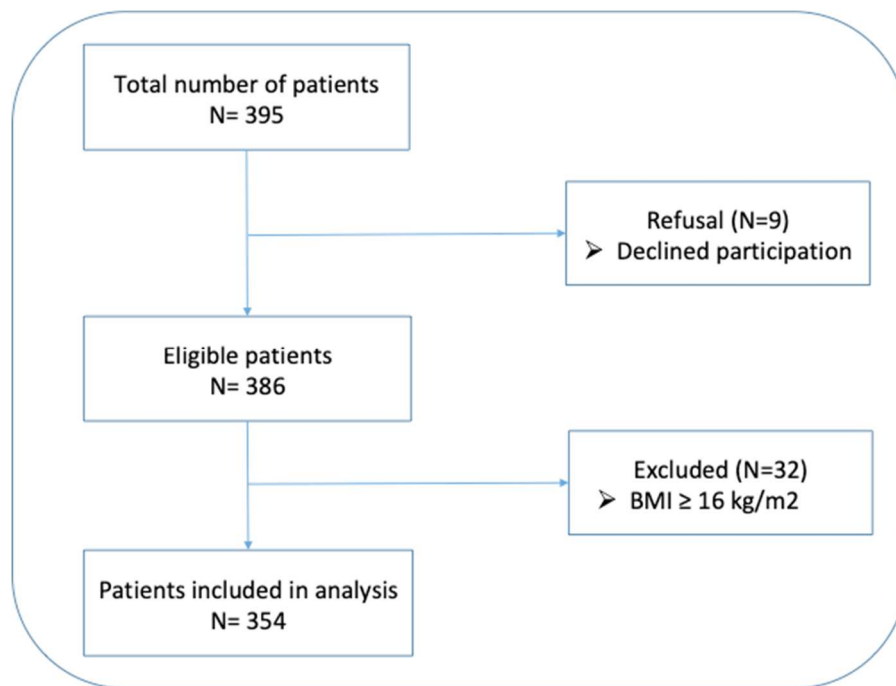


Figure 1: Flow chart of the study.

	Mean \pm SD or n	Range or Percentage
Female	339	95.76%
Age at admission (years)	28.68 (\pm 10.74)	[15-65]
Marital status: couple or married	72	20.34%
Marital status: divorced or separated	25	7.06%
Marital status: single	253	71.47%

Marital status: widow	4	1.13%
Having at least one child	47	13.28%
Qualification level \geq 4 years of higher education	88	26.11%
Student status	121	35.90%
Executive and/or intellectual profession	26	7.56%
Interruption of professional activity \geq 6 months	116	33.33%
Recent interruption of professional activity $<$ 6 months	53	15.23%
Part-time work	7	2.01%
Admitted from		
Outpatient clinic	142	42,01%
Emergency room transfer	25	7,40%
MICU transfer	64	18,93%
Psychiatric inpatient unit	52	15,38%
Medicine inpatient unit	53	15,68%
Surgical ward	1	0,30%
Gynecology ward	1	0,30%

TABLE 2: Socio-demographic characteristics of patients (N=354)

Length of stay was 36.9 (\pm 30.5) days. AN-BP patients had a significantly shorter length of stay compared to AN-R patients (33.4 days vs 39.9 days, p value 0.046, CI 95% [0.111; 12.8472]).

	Mean \pm S.D. or n	Range or Percentage
AN restricting subtype	173	48.87%
AN bingeing/purging subtype	175	49.43%

Atypical anorexia nervosa	6	1.69%
Age at onset (years)	18.73 (\pm 6.92)	[5-56]
Duration of AN at first admission for ED (years)	5.76 (\pm 7.63)	[0-38]
Duration of AN at admission in the unit (years)	9.55 (\pm 9.01)	[0-41]
History of hospitalization for AN in other hospitals before admission in the unit	280	79.32%
Number of hospitalizations for AN	2.93 (\pm 3.49)	[0-28]
Minimum BMI since puberty ((kg/m ²)	11.38 (\pm 1.56)	[7.11- 17.75]
Maximal BMI since puberty (kg/m ²)	20.18 (\pm 4.30)	[11.43-51.27]
Psychiatric or psychological follow up before admission in the unit	284	81.61%
Somatic follow up before admission in the unit	264	78,57%
Patient history of overweight	43	12.15%
Family history of overweight	38	10.73%
Family history of ED	87	24.58%
Family history of psychiatric disorder (other than ED)	107	30.23%
<i>Patients' regular behavior</i>		
Problematic exercise notified in the patient medical file	163	46.05%
Self induced vomiting	141	39.83%
Laxative misuse	75	21.19%
Potomania	48	13.56%
Diuretic use	14	3.95%

Table 3: Characteristics of patients' anorexia nervosa (N=354)

BMI at admission was 12.2 (\pm 1.6) kg/m², range [7.5-15.9] (Figure 2: please refer to Supplementary material). BMI at discharge was 13.8 (\pm 1.5) kg/m². During hospitalization,

304 (85.88%) patients received enteral nutrition and weight gain was 4.1±3.9 kg (0.777 kg per week). 133 (37.57%) patients were still on enteral nutrition when they were leaving the unit (table 4).

	Mean ± S.D. or n	Range or Percentage	Missing data
Albumin level at admission (g/l)	35.77 (± 6.60)	[15-55]	
Weight at admission (kg)	32.64 (± 5.29)	[20.2-49.2]	
Weight at discharge (kg)	36.87 (± 5.02)	[23-52]	
BMI at admission (kg/m ²)	12.24 (± 1.62)	[7.54 - 15.89]	
BMI at discharge (kg/m ²)	13.84 (± 1.52)	[8.93 - 18.31]	
Weight gain during hospitalization (kg)	4.14 (± 3.96)	[-5.6 -19.4]	
Enteral nutrition prescription	304	85.88 %	
Discharge on enteral nutrition	133	37,57%	
Length of stay (days)	36.94 (± 30.50)	[1- 202]	
<i>Prevalence of micronutrients deficiencies</i>			
Cutaneous lesions of scurvy	4/354	1.1%	
Zinc deficiency	96/169	56.8%	n=185 (52.3%)
Selenium deficiency	41/192	21.3%	n=162 (45.8%)
Copper deficiency	44/146	30.1%	n=208 (58.8%)
Folate deficiency	31/292	10.6%	n=61 (17.5%)
Vitamin B12 deficiency	12/281	4.3%	n=73 (20.6%)
Vitamin D deficiency	117/186	62.9%	n=168 (47.5%)

Table 4: Nutritional parameters (N=354). Zinc deficiency is defined by zinc plasma level < 12.5

µmol/L, selenium deficiency by selenium plasma level < 0.9 µmol/L, copper deficiency by copper plasma level < 12.7 µmol/L, folate deficiency by folate plasma level <3.90 µg/L, vitamin B12

deficiency by vitamin B12 plasma level < 197 ng/L, vitamin D deficiency by vitamin D plasma level < 30 ng/ml.

Patients with AN-BP had significantly higher BMI on admission compared to AN-R patients (12.45 kg/m² vs 12.04 kg/m², p value 0.018, CI 95% [-0.7495; -0.0708]), and higher BMI on discharge (14 kg/m² vs 13.6 kg/m², p value 0.037, CI 95% [-0.6686 ; -0.0206]). Total weight gain during hospitalization was similar in the 2 subgroups (3.98 kg vs 4.2 kg, p value 0.601, CI 95% [-1.066; 0.6184]).

3.2. Somatic and psychiatric comorbidities

70 (19.77%) patients had one or more somatic comorbidities summarized in table 5.

168 (47.46%) patients had one or more psychiatric comorbidities (excluding personality disorders), presented in table 5.

	n	Percentage
<i>Somatic comorbidities</i>		
Cardiovascular comorbidities	9	2.54%
Dermatological comorbidities	4	1.13%
Digestive comorbidities	23	6.49%
Endocrine comorbidities	11	3.11%
Genetic comorbidities	1	0.28%
Hematologic comorbidities	2	0.56%
HIV infection	4	1.13%

Immunological comorbidities	3	0.85%
Nephrological comorbidities	9	2.54%
Neurological comorbidities	14	3.95%
Otolaryngological comorbidities	1	0.28%
Pulmonary comorbidities	16	4.52%
Rheumatologic comorbidities	9	2.54%
Solid cancers	6	1.69%
Urologic comorbidities	2	0.56%
<i>Psychiatric comorbidities</i>		
Personality disorders	80	22.60%
Obsessive-compulsive disorders	29	8.19%
Mood disorders and/or Anxiety disorders	165	46.61%
History of suicide attempt	74	20.90%
Self-mutilations (non suicidal self-injury disorder)	25	7.06%
ADHD	5	1.41%
Kleptomania	2	0.56%
<i>Addictions</i>		
Alcohol use disorder	31	8.76%
Substance use disorder	23	6.50%
Tobacco use disorder	115	32.49%

Table 5: Patient's comorbidities (N=354)

3.3. Prevalence of micronutrients deficiencies

Vitamin D deficiency was the most frequent micronutrient deficiency (62.9%) followed by zinc (56.8%), copper (30.1%), selenium (21.3%), vitamin B9 (10.6%) and vitamin B12 (4.3%) (Table 4). Cutaneous lesions of scurvy were notified in 4 patients (1.1%) with a low vitamin C blood level.

3.4. Medical complications in the cohort (Table 6)

3.4.1. Low bone mineral density

268 (75.7%) patients had DEXA scans during their hospitalization to assess bone mineral density. For these patients, 80 % had abnormal BMD: 46.27 % had osteoporosis and 40.67 % had osteopenia.

3.4.2. Hematologic abnormalities

Anemia (defined by hemoglobin (Hb) level < 13 g/dl for men and < 12 g/dl for women) was found in 79% of patients and 20 patients required blood transfusion because of severe and poorly tolerated anemia. 54% of patients had neutropenia (neutrophil count < 2000/mm³) and 5 (1.4%) patients presented an extreme neutropenia requiring protective isolation with neutrophil count below 500 /mm³. 59% of patients had lymphopenia (lymphocyte count < 1500 /mm³) and 21% had thrombocytopenia (platelet level < 150 000/mm³). Bone marrow aspiration was performed in 24 patients (6.8%) because of persistent pancytopenia despite improvement of nutritional status; result was normal in 1 patient. A gelatinous bone marrow transformation (GBMT) was present in 23 patients.

3.4.3. Infections

86 (24.29%) patients developed one or several **infectious complications** during their hospital stay. Details are presented in Table 7 (please refer to supplementary material section).

3.4.4. Hypertransaminasemia

Hypertransaminasemia defined by elevated Liver Function Tests (LFTs) with AST (aspartate transaminase) > 31 IU/L and/or ALT (alanine transaminase) > 65 IU/L, as per our laboratory's normal parameters, was found in 190 (53.7%) patients.

Mild increase in serum transaminase level (greater than the normal range but lower than 10 times the normal upper limit) **was reported in 156 (44.07%) patients and marked increase in serum transaminase level with LFT \geq 10 times the normal upper limit in 34 (9.6%) patients.** Among these last patients, a transjugular liver biopsy was done for 3 patients because of worsening hypertransaminasemia despite cautious refeeding, showing hepatocyte autophagy in two of them. Autoimmune and viral workup were negative. Hypertransaminasemia was not drug induced.

3.4.5. Metabolic complications

During hospitalization, dysnatremia was present in 86 (24.3%) patients, hypophosphatemia in 92 (26%) patients, hypokalemia in 140 (39.5%) patients and acute kidney failure defined by creatinine clearance below 60 ml/minute was recorded in 166 (49%) patients.

Hypoglycemia was reported in 49 (13.8%) patients.

3.4.6. Other medical complications

Other medical complications were cardiovascular (abnormal heart rhythm, pericardial effusion, cardiac failure) reported in 25 (7.1%) patients, neurological (cerebellar syndrome, central pontine myelinolysis, peripheral neuropathy, axial hypotonia) in 56 (15.8%) patients, urological (urinary incontinence, urinary retention) in 18 (5.1%) patients.

Two patients presented a spontaneous and non-traumatic **pneumomediastinum associated with a retro pneumoperitoneum and a subcutaneous emphysema** over the neck and upper chest walls. Complementary investigations were negative, no causative pulmonary or digestive disease was found.

	Frequency	Percentage
Bone Mineral density (DEXA) (a)		
Normal (T score > -1)	35	13.06 %
Osteopenia (T score -1 à -2,5)	109	40,67%
Non-fracture osteoporosis (T score < -2,5)	102	38,06%
Fracture osteoporosis	22	8,21%
Hematologic complications (b)		
Neutropenia	191	53,95%
Frank neutropenia	51	14,41%
Lymphopenia	210	59,32%
Frank lymphopenia	132	37,29%
Anemia	281	79,38%
Frank anemia	78	22,03%
Thrombocytopenia	74	20,90%

Frank thrombocytopenia	23	6,50%
Gelatinous bone marrow transformation	23	6.5%
Infections during hospitalization	86	24,29%
Hypertransaminasemia (c)	190	53,67%
Mild hypertransaminasemia (< 10 X normal)	156	44.07%
Marked hypertransaminasemia (≥ 10 X normal)	34	9.6%
Digestive complications		
Biological pancreatitis	18	5.08%
Constipation	141	39,83%
Gastroesophageal reflux and / or esophagitis	29	8,19%
Spontaneous pneumomediastinum	2	0.6%
Metabolic complications		
Dysnatremia	86	24,29%
Hypernatremia > 145 mmol/l	4	1.1%
Hyponatremia < 135 mmol/l	79	22.3%
Hypophosphatemia < 0,8 mmol/l	92	26%
Hypokalemia < 3,6 mmol/l	140	39.5%
Hypokalemia with ECG changes	27	7.6%
Kidney failure (creatinine clearance < 60 ml/min)	166	49%
Hypoglycemia	49	13,84%
Hypoglycemic coma	1	0,28%
Edema	93	26.3%
Cardiovascular complications (d)	25	7,1%
Cardiac rhythm disorders (bradycardia < 40/min, tachycardia, cardiac repolarization abnormalities)	6	1.7%

Cardiac failure (acute pulmonary edema and/or LFEVG \leq 50%)	18	5.1%
Angina (with elevated troponin)	1	0.3%
Pericardial effusion	5	1.4%
Neurological complications	56	15,82%
Axial hypotonia	52	14,69%
Lower limb hypoesthesia	17	4,80%
Cerebellar syndrome	2	0.6%
Central pontine myelinolysis	1	0.3%
Urological complications		
Bladder-sphincter dysfunctions (urinary incontinence, urinary retention)	18	5,08%

Table 6: Medical complications in the cohort during hospitalization (N=354). (a) 268 patients with DEXA scans during this admission. (b) neutropenia is defined by neutrophil count $< 2000/\text{mm}^3$, frank neutropenia by neutrophil count $< 1000/\text{mm}^3$, lymphopenia is defined by lymphocyte count $< 1500/\text{mm}^3$, frank lymphopenia by lymphocyte count $< 1000/\text{mm}^3$, anemia is defined by hemoglobin (hb) level $< 13 \text{ g/dl}$ for men and $< 12 \text{ g/dl}$ for women, frank anemia by $\text{hb} \leq 9\text{g/dl}$, thrombocytopenia is defined by platelet level $< 150\ 000/\text{mm}^3$, frank thrombocytopenia by platelet level $< 80\ 000/\text{mm}^3$. (c) hypertransaminasemia is defined by AST (aspartate transaminase) $> 31 \text{ IU/L}$ and/or ALT (alanine transaminase) $> 65 \text{ IU/L}$. (d) LFEVG=left ventricular ejection fraction.

3.5. Comparison of medical complications by AN subtypes (AN-R and AN-BP):

Patients with AN-BP had a significantly higher frequency of **hypokalemia** during hospitalization compared to AN-R patients (51.4% vs 27.7%, p value 6.313×10^{-6}). They also presented a higher frequency of **constipation** (48% vs 32.4%, p value 0.003).

Patients with AN-R presented a higher frequency of **lymphopenia** compared to AN-BP (67.6% vs 50.3%, p value 0.001), and **neutropenia** (59.5% vs 48%, p value 0.03).

Hypertransaminasemia was also more frequent in AN-R patients than in AN-BP patients (60.7% vs 48.6%, p value 0.023).

There were no significant differences between the AN subtypes for the prevalence of LBMN, osteoporosis (49.63% vs 42.06%, p value =0.25), infection (p value=0.19), thrombocytopenia (p value = 0.17), anemia (p value = 0.99), edema, hypoglycaemia and other medical complications (table 8).

	AN-R (N=173) n(%)	AN-BP (N=175) n(%)	p value*
Bone Mineral density (DEXA) (a)			
Low bone mineral density (T score < -1)	84 (61.3)	70 (35.6)	ns
Osteoporosis (T score < -2,5)	68 (49.6)	53 (42.1)	ns
Hematologic complications			
Neutropenia	103 (59.5)	84 (48)	0.031*
Frank neutropenia	34 (19.6)	17 (9.7)	0.009*
Lymphopenia	117 (67.6)	88 (50.3)	0.001*
Frank lymphopenia	75 (43.3)	54 (30.9)	0.016*
Anemia	138 (79.8)	138 (78.9)	Ns

Frank anemia	37 (21.4)	40 (22.9)	ns
Thrombocytopenia	40 (23.1)	32 (18.3)	ns
Frank thrombocytopenia	11 (6.4)	11 (6.3)	ns
Infections during hospitalization	38 (22)	44 (25.1)	ns
Hypertransaminasemia	105 (60.7)	85 (48.6%)	0.023*
Mild hypertransaminasemia (< 10 X normal)	88 (50.9)	68 (38.9)	0.024*
Marked hypertransaminasemia (≥ 10 X normal)	17 (9.8%)	17 (9.7)	ns
Digestive complications			
Biological pancreatitis	7 (4)	11 (6.3)	ns
Constipation	56 (32.4)	84 (48)	0.003*
Gastroesophageal reflux and / or esophagitis	11 (6.4)	18 (10.3)	ns
Metabolic complications			
Dysnatremia	36 (20.8)	50 (28.6)	0.093*
Hypophosphatemia < 0,8 mmol/l	39 (22.5)	51 (29.1)	ns
Hypokalemia < 3,6 mmol/l	48 (27.7)	90 (51.4)	6.313 x 10 ⁻⁶ *
Kidney failure (creatinine clearance < 60 ml/min)	78 (45.1)	87 (49.7)	ns
Hypoglycemia	26 (15)	22 (12.6)	ns
Edema	46 (26.6)	45 (25.7)	ns
Cardiovascular complications	10(5.8)	13 (7.4)	ns
Neurological complications	26 (15)	30 (17.1)	ns
Urological complications	8 (4.6)	9 (5.1)	ns

Table 8: Prevalence of medical complications in AN subtypes during hospitalization (N=354).

Abbreviations: AN-R anorexia nervosa restrictive subtype, AN-BP anorexia nervosa bingeing/purging

subtype, ns: not significant. * chi square test. (a) 137 AN-R patients and 136 AN-BP patients with DEXA scans during this admission.

3.6. Transfer to medical intensive care unit

35 patients (10%) were transiently transferred to MICU during their hospitalization in the clinical nutrition unit. The main reasons for MICU referral were: major metabolic abnormalities (n=23), cardiovascular complications (n=14), hepatic problems (n=6), sepsis (n=6). Details of MICU referrals are presented in table 9 (please refer to supplementary material section).

3.7. Deaths during the hospitalization:

Five (1.4%) patients died because of septic shock of pulmonary origin (n=1), septic shock of urinary origin (n=1) and suicide (n=3).

3.8. Discharge against medical advice and care refusal:

During hospitalization, 45 (12.71%) patients were discharged against medical advice (DAMA). A compulsory admission was required with 24 (6.78%) patients because of association between medical instability and care refusal. In their past medical history, 113 (31.92%) patients had a history of DAMA and 57 (16.10%) patients had a history of compulsory admission in different hospitals.

4. Discussion

This article presents the socio-demographic characteristics as well as the main medical complications and the clinical course of a large cohort of 354 severely malnourished adult patients with severe forms of AN, hospitalized in the clinical - nutrition-ED-unit in Raymond Poincaré hospital. To our knowledge, this is the largest cohort of AN severely malnourished adult patients with a description of somatic complications.

Considered as a referral center for the management of severe malnutrition secondary to AN, the clinical nutrition-ED-unit in Raymond Poincaré hospital manages the care of a particular patient profile, who has already had a complex care pathway with a chronicized illness evolving for about ten years on average. Thus, the majority of patients have already had previous psychiatric and/or somatic follow-up and 79% have been hospitalized at least once before in other medical units for AN. AN has strongly negative effect on the social life of patients; 33% of them were on medical leave for over six months at the time of hospitalization. To our knowledge there is no literature data on medical leave prevalence in AN patients. However literature data show that patients with EDs have poor quality of life and impairment increases with illness severity (19,20).

Patient's nutritional status in the cohort is severely impaired, which is illustrated by extremely low BMI at admission: almost 70% of patients have a BMI <13 kg / m² and 7.12% a BMI < 10 kg/m². The type of malnutrition is mainly marasmic, with a subnormal plasma albumin of 36 g/l (± 6.6) at admission despite very low BMI. Indeed, AN patients present an adaptive chronic malnutrition with a prolonged semi-fasting undernutrition (21). This malnutrition is accompanied by frequent and multiple micronutrients deficiencies. Despite missing data, prevalences of micronutrients deficiencies are similar to prevalences identified in a recent specific study performed in the unit (22). Zinc and vitamin D have the highest

deficiency prevalences (56.8% and 62.9% respectively), followed by copper and selenium. Vitamins B9 and B12 have the lowest deficiency prevalences. In comparison with a large cohort of healthy young Australian female students (n=308, mean age 22.6 years, mean BMI 21.5 kg/m²), the main difference in micronutrient status was the status of zinc. In this last cohort, zinc deficiency was observed only in 2% of participants (23). This low prevalence of zinc deficiency was also found in a French epidemiological study where only 5% of the general population had a zinc deficiency and 14% of men under 50 years of age had a copper deficiency (24). In the SU.VI.M.AX study, only 2% of the French general adult population had a selenium deficiency (25).

In our cohort, psychiatric comorbidities were frequent: mood and anxiety disorders were present in 46.6% of patients, personality disorders in 22.6%, a history of suicide attempts in 21%, alcohol use disorder in almost 9%, OCD in 8% and substance use disorder in 6.5% of patients. A high prevalence of psychiatric comorbidities in ED patients has been reported in the literature (26–28). EDs are associated with elevated rates of mood, anxiety, substance use and impulsive control disorders (29). Psychiatric comorbidities increase with the symptoms severity of the ED (29). It can therefore be assumed that patients with severe psychiatric comorbidities are likely to be most at risk of developing severe malnutrition. These psychiatric comorbidities make care more complex. Keeping the patient in hospital was also sometimes made difficult by a patient's refusal of care and non-compliance. Thus, specialized multidisciplinary care that is both psychiatric, somatic and nutritional appears essential.

Regarding somatic complications, low bone mineral density was the most frequent complication. It involved 86.9% of the cohort with an osteoporosis rate of 46.3%, which

seems to be higher than that observed in most series in the literature (33% in a serie of 25 patients (14), 38% in a serie of 130 patients with mean BMI 17.1 kg/m² (30), 21% in a serie of 113 patients with mean BMI 15.5 kg/m² (31)). In the meta-analysis by Solmi et al. (32) the prevalence of osteoporosis in AN patients was 21.6%, and the prevalence of osteopenia 45.5%. This higher prevalence of osteoporosis in our cohort could probably be explained by the severity of the malnutrition (mean BMI 12.2 kg/m², mean weight 32.6 kg at admission), the long duration of illness (10 years on average) and the patient's age (28.7 years on average)-slightly older than in other series. Indeed, predictive factors of LBMD reported in the literature are a low BMI (30,31), a longer illness duration and amenorrhea (31,32). In the cohort of Legroux et al. (31), patients with osteoporosis were significantly older.

Frequency of hematologic abnormalities (anemia 79%, lymphopenia 59%, neutropenia 54%, thrombopenia 20.9%) was much higher than in most series of the literature. These abnormalities could be severe as illustrated by the 23 cases of GBMT, which is an association of marrow hypoplasia and interstitial infiltration of a ground gelatinous substance, diagnosed on bone marrow aspiration, usually described as an uncommon complication of AN (33). GBMT cases were probably underestimated in our cohort because a myelogram was performed only in case of persistent pancytopenia despite refeeding, this diagnostic procedure being invasive in fragile patients. In the literature, mild anemia and/or mild neutropenia are reported in one-third of all AN patients and the incidence of thrombocytopenia is usually ranging between 5 and 11% (34). Our results are closer to those of the study published by Sabel et al.(35): of 53 AN severely malnourished adult patients (mean BMI 12.4 kg/m²), 83% were anemic, 79% leukopenic, 29% neutropenic, 25% thrombocytopenic. The high frequency and severity of hematologic abnormalities in our

cohort are likely related to the severity of malnutrition and the long average duration of illness in patients. Indeed, a correlation has been shown between duration of illness and severity of WBC cytopenia or presence of thrombocytopenia (34). The extent of bone marrow damage is related to the amount of weight loss (36), and to the reduced total fat mass index (34).

Leukopenia and anemia in AN can promote a functional immune suppression with an alteration of the humoral and cellular immune response. The response to pathogens is then lowered with an extended response time and a high infectious complication rate (37). Apart from classical pyogenic infections, cases of serious and complicated infections that can cause death even in the hospital sector have been identified. These could be "opportunistic" infections, as evidenced by the occurrence of atypical mycobacterial lung infections and clostridium difficile colitis, infections usually restricted to true immunosuppression situations. If malnutrition is an important and common risk factor for tuberculosis, some authors hypothesized that it could also be risk factor for non-tuberculous mycobacterial lung disease (38). Special attention should therefore be paid to the possibility of opportunistic infection in AN, particularly in case of lymphopenia (39).

Hypertransaminasemia is highly prevalent in our cohort: it concerns 57.6 % of all patients. This result is higher than the average prevalence reported in most series in the literature (40,41) but comparable to those reported in series of severely malnourished inpatients (42,43). Lower BMI was associated with hypertransaminasemia in these series (41–43). The pathophysiologic mechanism seems multifactorial. A report of 12 liver biopsies in severely malnourished AN patients found that liver autophagy could be involved (44). Hepatic hypoxia secondary to myocardial dysfunction has been mentioned also (44).

Regarding metabolic complications, few cases of hypophosphatemia (26%) and hypoglycemia (13.8%) were observed in comparison to other series, particularly the series of 25 patients by Gaudiani et al. (14) in which 45% of patients had hypophosphatemia and 44% had hypoglycemia. Our hypothesis is that this difference in outcome could be explained by a systematic initial phosphorus IV supplementation of all patients in our cohort and a large continuous low flow EN prescription (85.88%), unlike the 25 patients in the cohort by Gaudiani et al. (14).

Indeed, continuous low flow EN over 24 hours has the advantage of providing a low calorie intake per hour, without interruption. It avoids a nocturnal fasting state which can promote early morning hypoglycemia, in a context of severe malnutrition where the liver glycogen stock is already released. It also decreases the postprandial insulin response that can lead to secondary hypoglycemia. Thus, the most severe hypoglycemia cases have been observed early morning and in the postprandial period in the cohort by Gaudiani et al. (14). EN also facilitates the gradual increase in calorie intake which aims to reduce the risk of refeeding syndrome (45,46).

Difference in medical complication prevalences were found between the 2 AN subtypes. Not surprisingly, hypokalemia was more frequent in AN-BP patients, as also shown in a series of 232 severely malnourished AN patients (47), which can be explained by purging behaviors (vomiting and laxative abuse). In our cohort, constipation was also more frequent in AN-BP patients as it is likely associated with laxative abuse (48). Lymphopenia, neutropenia and hypertransaminasemia were more frequent in AN-R patients, as also reported by Rylander et al. (47). However, unlike Rylander et al. (47), we did not find any difference in the prevalence of anemia, thrombocytopenia, edemas, dysnatremia and hypoglycemia between the 2 AN

subtypes. In the literature, the comparison of prevalence of medical complications in 142 AN severely malnourished inpatients did not show any significant difference across the different age span (49). These differences between the subtypes are also illustrated through a higher BMI at admission and at discharge and a shorter length of stay for AN-BP patients compared with AN-R patients. These last results were also found in the serie by Rylander et al (47).

Despite severe malnutrition and frequent somatic complications, only 10% of patients were transferred to the medical intensive care unit during their stay. This could be explained by a specific, intensive and adapted patient management by a multidisciplinary expert team. In a serie of 195 patients admitted for AN, 15% had required transfer to intensive care (50). Main reasons for MICU referral (metabolic abnormalities, cardiovascular monitoring, sepsis) were similar to those mentioned in the literature (13).

After one month of hospitalization, weight gain was significant. Clinically stabilized, patients could continue the process of refeeding, while initiating a therapeutic program in a specialized psychiatric unit. More than a third of patients (37.6%) were still on EN at discharge. Indeed, weaning of EN must be progressive in parallel with the increase in oral calorie intake (6).

The limitations of the study are: the monocentric study design and the retrospective data collection which explains the presence of some missing data, in particular blood test results were not always found in the patient file because until 2008, plasma micronutrients levels were not systematically determined and blood samples for these analyses were sent to another hospital.

5. Conclusion

AN patients hospitalized in the clinical nutrition-ED-unit because of extreme malnutrition present frequent medical complications that can be serious and life threatening. Frequent psychiatric co-morbidities complicate the management and probably aggravate the prognosis. Continuous low flow EN seems an effective refeeding method. At the crossroads of somatic and psychiatric medicine, the care of these patients remains a challenge because of the morbidity and possible chronicization of the disorder. Thus, multidisciplinary management of these patients by an expert team is essential. Further studies are needed to determine: profiles of patients at risk of somatic complications and death and the mortality rate in this specific patient population with extremely severe AN.

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- M.G.: performed the study design, collected the patient's data and carried out the statistical analyses. She contributed to the data analysis and wrote the manuscript.
- J.-C.M.: contributed significantly to the study design and to the data analysis, reviewed the manuscript.
- N.G.: Contributed to the study design and the data analysis. She also reviewed the manuscript.
- M.H.: Contributed to the study design and the data analysis. She also reviewed the manuscript.

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