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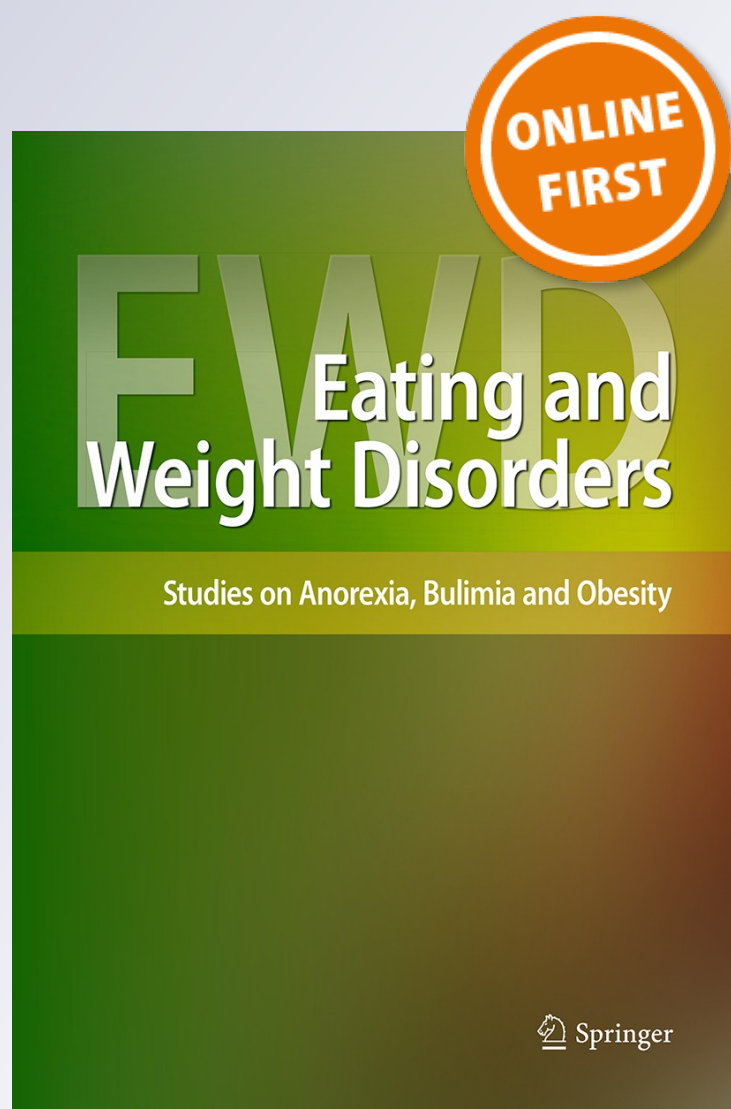
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Impact of somatic severity on long-term mortality in anorexia nervosa

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Abstract

Purpose Anorexia nervosa (AN) is a severe pathology on account of the high levels of associated morbidity and mortality. This study aimed to assess whether time in somatic intensive care unit, justified by a patient's somatic condition in the course of hospital care, has any relationship with patient outcome in terms of mortality in the long term.

Methods 195 patients were hospitalised for AN between April 1996 and May 2002, 97 were re-assessed 9 years later on average.

Results Out of 195 patients hospitalised for AN between April 1996 and May 2002, 29 had required transfer to intensive care. Mortality at 9 years was 20 times higher in the group having been transferred to intensive care, irrespective of the duration of follow-up.

Conclusion The clinical seriousness of the somatic condition during hospitalisation for AN is a risk factor for excess mortality in the medium term.

Keywords Anorexia nervosa · Intensive care unit · Follow-up · Mortality

Introduction

Anorexia nervosa (AN) is a severe pathology in both the short and the long term, and is related to high mortality rates [1–6]. Mortality among these subjects seems to be falling as a result of the development of specialised care, but it nevertheless remains high, often more than ten times that of the general population [1, 6–8]. Standardised Mortality Rates (SMR) for long-term mortality among past AN inpatients varies from 3.1 to 17.5 [6, 8]. Interestingly, no significant differences in SMR have been found between patients admitted for compulsory inpatient treatment and those admitted to non-compulsory inpatient treatment in the two decades after admission [6]. However, patients with AN and a psychiatric comorbidity seem to have higher mortality rates than those without comorbidity. In the study by Kask [9], the SMRs for patients with AN and a psychiatric comorbidity were 5.4 (95% confidence interval [CI] = 4.6–6.4) and 18.1 (95% CI 15.2–21.3) for natural and non-natural causes of death, respectively. The SMRs for patients with AN without comorbidity were 2.8 (95% CI 2.3–3.5) and 3.1 (95% CI 2.2–4.1) for natural and non-natural causes of death, respectively.

Morbidity is also an important issue, with an involvement of nearly all organs as a result of the de-nutrition process [10–12]. The improvement of care plans has been obtained by multidisciplinary collaboration [7, 13, 14] including an optimisation of re-feeding techniques. In our team, one of the improvements in the hospital care programme was achieved by closer collaboration with the intensive care team in life-threatening situations, and the development of an indication protocol for transfer to intensive care [13].

As remarked by several authors [8, 15], factors predictive of mortality for patients suffering from severe AN are

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not well documented. Among factors reported as predictive of death, the majority are linked to AN characteristics or psychiatric factors, with the exception of low body mass index (BMI) at admission for AN. Hospitalisation, because of the nature of its indications, selects the thinnest AN patients with the poorest somatic and psychological prognoses [16]. To our knowledge, no study concerning these severely ill patients has considered somatic factors, with the exception of BMI and weight, as possible predictive factors of mortality.

The present study aimed to assess whether severe somatic condition in AN patients in the course of hospital care (on the basis of a transfer to intensive care unit) had any relationship with patient outcome in terms of mortality in the long term, taking into account the duration of follow-up.

Patients and methods

Patients

The sample comprised all consecutively admitted patients (195 patients: 180 girls and 15 boys) with DSM-IV criteria for AN hospitalised in the Psychiatric ward in the Institut Mutualiste Montsouris, Paris, France, between April 1996 and May 2002 (hospitalisation and treatment protocol described in [17–19]).

Method

The moment of inclusion in the study (which is the start of follow-up) was defined as the first admission to the unit during that period. During inpatient treatment, a structured file collecting socio-demographic and clinical data was completed for all patients [20].

In France, recommendations are to transfer patients whose somatic condition is the cause of extreme concern to medical intensive care unit [21]. In our study, severe somatic condition for a patient was defined as follows [13]:

- Weight.
There is no undisputed threshold for weight. A BMI under 13–14 kg/m², or weight loss of more than 25% of normal weight for age and stature, and the rapidity of weight loss were the warning signs retained here. A BMI ≤ 12 kg/m² was systematically a criterion for transfer to intensive care.
- Cardiac and/or haemodynamic signs.
Orthostatic hypotension or systolic blood pressure <80 mmHg.
Sinus bradycardia ≤ 40 /min, or conversely tachycardia.
- Electrocardiographic anomalies, and in particular long QT interval.

- Hypothermia ≤ 35.5 °C, or conversely hyperthermia.
- Ideo-motor slowing, slow speech and difficulty standing.
- Biological parameters—the following motivated application for transfer to intensive care:
 - hypokalaemia <2.5 mmol/l.
 - hyponatraemia <124 mmol/l or hypernatraemia >150 mmol/l.
 - hypophosphoraemia <0.5 mmol/l.
 - repeated episodes of hypoglycaemia or level <2.5 mmol/l.
 - creatinine >100–120 μ mol/l, uraemia >15 mmol/l.
 - leucopenia <1.5 giga/l, thrombopenia <100 giga/l.
 - hepatic cytolysis.

A single sign is not generally sufficient to justify the transfer, and most transfers were motivated by the presence of several signs [13, 20].

Outcome

Information on the living or deceased status of the patients was sought from the French National Institute of Statistics and Economics Studies (Institut National de la Statistique et des Etudes Economiques, INSEE). Identification was based on name, surname, date and place of birth. The date used for the collection of deaths was March 1st 2008. Information on outcome was obtained for all patients, and none were lost to follow-up. Causes of death were obtained from the national registry for causes of death CépiDc (Centre d'Epidémiologie sur les causes médicales de Décès).

Mortality was estimated using both the Crude Mortality Rate (CMR) and the SMR.

Informed consent and ethics

This study was approved by the *Direction Générale de la Santé* (French Health Authority) July 22nd 2007, the *Comité Consultatif des Personnes se prêtant à la Recherche Biomédicale* (biomedical research committee), April 24th 2007, the French Committee for personal freedom (CNIL), October 30th 2007, and an independent review board (CCTIRS, *Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé*).

Statistical analysis

Analyses were performed using SPSS 17.0. Type one error for statistical tests of hypothesis was equal to 0.05.

No adjustments were made for multiple testing, as recommended for this type of study [22]. All tests were two-tailed.

The CMR was calculated as usual by dividing the number of deaths by the total number in the cohort. SMR calculations were performed using indirect methods. The expected number of deaths was obtained by applying age, gender and 10-year specific mortalities for the general French female population (obtained from INSEE) to the corresponding cumulative person-years in the study cohort.

Adjustment on the duration of follow-up was made using logistic regression.

Results

Comparison of subjects transferred to intensive care with the rest of the group at inclusion ($n = 195$)

Among the 195 patients, 29 (14.8%) underwent transfer to intensive care. The mean age of these patients was 17 years ($SD \pm 2.1$) versus 17.1 ($SD \pm 2.2$) for those not transferred (NS). The adolescents hospitalised in intensive care had not been previously hospitalised more frequently than the others, nor was the duration of their illness any longer. The mean duration of hospitalisation was 119 days ($SD \pm 93.91$) for non-transferred patients versus 141 ($SD \pm 84.93$) for those transferred (NS). Mean BMI at admission for the patients transferred to intensive care was 12.55 ± 3.79 , and for those not transferred it was 13.48 ± 1.19 ($p = 0.006$). The mean BMI at discharge was 17.4 kg/m^2 ($SD \pm 1.3$), and this did not differ between the two groups (Table 1).

Death

No death was recorded among the 15 boys.

Of the 180 female patients hospitalised, 4 young women died (CMR 2.2) 6.1 times more (SMR: 6, 1; IC 95% [3, 5, 7, 8]) than in the female population of the same age. For two patients, death was specified as due to cardiac causes (arrhythmia and heart failure, respectively), in both cases linked to AN or under-nutrition, without further

information. The other two committed suicide. All Deaths occurred in the 6 years following the date of inclusion in the study, respectively, at 0.98; 2.51; 3.16 and 5.37 years from inclusion.

Factors predictive of death

Of the four patients who died, one had been transferred to intensive care for bradycardia, and the others for a state of starvation. The transfer to intensive care shows no link with admission BMI (12, 9 versus 13.3 $p = 0.55$), and a trend towards a link with death: 7.7% of the subjects transferred to intensive care (2/26) died versus 1.2% (2/169) of the other subjects ($p = 0.088$). After adjustment on the duration of follow-up, time in intensive care was significantly linked to patient death: the death rate for patients hospitalised in intensive care was 20.1 times greater than for the others (OR = 20 (range 1.8–224) $p = 0.015$).

Discussion

This follow-up study underlines the long-term seriousness of Anorexia Nervosa in adolescents, as in other recent studies [6, 23], despite the fact that specialised units, and in particular medical intensive care units, now provide specifically tailored care for the most severely affected patients, thus enabling the short-term morbidity linked to the state of starvation and to the re-feeding process to be reduced.

In the present study, 14.9% of the patients required transfer to medical intensive care. It is well known that AN patients admitted to intensive care have a poor prognosis, first as a result of mortality during hospitalisation. In their study, Vignaud et al. [24] reported 7/68 (10.3%) deaths during inpatient treatment in a population of severely ill adults with AN. Similarly, in the Japanese study by Nakamura [15], 5 out of 669 (0.7%) AN patients died during their hospitalisation. All were extremely severely ill; with a BMI under 11 kg/m^2 and 4/5 were adults at the time of in-patient treatment. Second, the prognosis of

Table 1 Characteristics of patients transferred or not into intensive care

All patients $N = 195$	Transferred to intensive care $N = 29$	Patients not transferred to intensive care $N = 166$	
Mean age (years)	17 ($SD \pm 2.1$)	17.1 ($SD \pm 2.2$)	NS
Length of hospitalisation (days)	141 ($SD \pm 84.93$)	119 ($SD \pm 93.91$)	NS
Number of previous hospitalisations	1.17 ($SD \pm 1.26$)	1.16 ($SD \pm 1.54$)	NS ($p = 0.590$)
Illness duration (months)	17.95 ($SD \pm 11.03$)	20.40 ($SD \pm 19.43$)	NS ($p = 0.444$)
Mean BMI at admission (kg/m^2)	12.55 ($SD \pm 3.79$)	13.48 ($SD \pm 1.19$)	$p = 0.006$
Mean BMI at discharge (kg/m^2)	17.4 ($SD \pm 1.3$)	17.4 ($SD \pm 1.3$)	NS

extremely ill patients remains critical even after several years, as reported by Vignaud et al. [24], who showed a crude mortality rate for these adult patients of around 10% (7/68), and by Ramsay et al. [25] with 7.6% mortality after 5 years. In the present study, there was, however, no AN death in intensive care, nor during hospitalisation, which is probably attributable to a combination of factors. It is true that the patients in our study were adolescents for whom the duration of the illness was considerably shorter than the subjects in the adult studies, but it should also be underlined that the intensive care team in our facility is trained in the care of these particular patients, that they have 30 years' experience behind them. No inappropriate re-feeding syndrome was observed and no complications were observed in the re-feeding process.

The CMR observed in our study is 2.2%, comparable to the 4.4 and 1.3% reported by Lindblad in two Swedish cohorts [7]. However, the present study showed that mortality was higher among patients whose clinical condition warranted transfer to medical intensive care, irrespective of the duration of follow-up. This is an important element, since it underlines the fact that the severity of clinical condition in adolescence in the course of care is a risk factor for subsequent mortality. Hebebrand [26] concluded that the outcome of patients with a low BMI (under 13) was less favourable than that of patients who did not fall below a BMI of 13. But in a recent meta-analysis, Arcelus did not evidence a significant correlation between mortality and BMI at admission [5]. The difference observed in our study is probably because the transfer to intensive care was not motivated solely by BMI but also by the intensity of the physical impact of denutrition, even with a BMI still within the norms. This nevertheless raises the question of the mechanisms involved: is the psychological profile of these patients who put themselves in life-threatening situations different from that of other patients, or do the sequelae of a state of starvation play a part? Further study on these issues is required.

Strengths and limitations

The mortality data is exhaustive and therefore includes all patients. It would have been interesting to study the different factors that could influence mortality separately, such as BMI, bradycardia, psychiatric factors, etc., but the small number of patients who died did not enable this option.

Otherwise, the variable that discriminates the two groups is simple, not disputable and repeatable for future patients.

Conclusion

In summary, transfer to intensive care for acute condition during hospitalisation of AN patients seems to be a risk factor for excess mortality. Further studies evaluating the different risk factors involved in mortality should be performed. Particular attention is needed in the follow-up of patients with severe acute somatic status during inpatient treatment for AN during adolescence.

Compliance with ethical standards

Source of funding Fondation de France; Fondation PFIZER.

Conflict of interest All authors declare that they have no conflict of interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the *Direction Générale de la Santé* (French health authority) July 22nd 2007, the *Comité Consultatif des Personnes se prêtant à la Recherche Biomédicale* (biomedical research committee), April 24th 2007, the French Committee for personal freedoms (CNIL), October 30th 2007, and an independent review board (CCTIRS, *Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé*).

Informed consent Informed consent was obtained from all individual participants included in the study.

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