Hebebrand J. Looking back: linking my past experience as a trainee to the pursuit of a hypothesis to improve the treatment of patients with anorexia nervosa. *European Journal of Psychiatric Trainees*. 2023;1(1). doi:10.55922/001c.74136

Cultural, Professional and Experiential Reflections

Looking back: linking my past experience as a trainee to the pursuit of a hypothesis to improve the treatment of patients with anorexia nervosa

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Keywords: anorexia nervosa, eating disorders, reflections

https://doi.org/10.55922/001c.74136

European Journal of Psychiatric Trainees

Vol. 1, Issue 1, 2023

After completion of my five-year-long training in human genetics, I entered child and adolescent psychiatry in 1990 with the vision to make use of my genetic knowledge to improve insight into the etiology of mental disorders. I remember vividly my first year working as a trainee on a unit with 20 patients including a few with anorexia nervosa (AN). I was fascinated by the fact that they were not doing something that I myself deemed trivial, namely eating. I felt overly responsible for their nutritional rehabilitation and had no clue as to the difficulties they were encountering or to the long duration of this eating disorder. I thought my task was to make them healthy again during their several weeks-long stay in the hospital. I was amazed to see that some had to stay in bed for hours and that their physical activity was curtailed substantially by the staff; discussions at the time centered on whether the presence of more than one patient with AN at a time was detrimental in the sense that they would reinforce each other in their aberrant eating behavior.

That fascination stuck to me. So I started reading scientific articles; with a background in human genetics I considered this eating disorder as a biological problem but at the same time realized that I was looking for psychological aspects in the lives of patients that might have triggered AN.

I was confused by the DSM-III-R and DSM-IV weight criterion for AN: "Refusal to maintain body weight at or above a minimally normal weight for age and height (e.g., weight loss or failure to gain weight that leads to a body weight less than 85 percent of that expected for age and height)". I asked my colleagues if they knew what proportion of the population actually has a body weight below this threshold. Nobody was able to provide me with an answer. I became increasingly aware of the fact that for whatever reason specialists in the field of AN were not using the body mass index (BMI; kg/m²), which is otherwise used for assessment of body weight adjusted for height. We resorted to old tables delineating 100% average weight for age, sex and height to come up with BMI-values corresponding to 85% of expected body weight and in parallel came up with the first BMI-centile curves for males and females in Germany.[1] It turned out that the respective BMI-values age-dependently skewed between the fifth and tenth BMI age centile.[2] Fortunately, both ICD-11 and DSM-5 now refer to the absolute BMI threshold of 18.5 kg/m² for adults and the fifth age and sex matched BMI centile for children and adolescents. Both classification systems point out that these cut-offs merely represent guidelines for clinicians.

1994 marks the year that the adipocyte derived hormone leptin was discovered.[3] We seized the opportunity to determine serum levels in patients with AN. We speculated that leptin levels are upregulated in this disorder entailing reduced appetite and hunger. It turned out that this hypothesis was wrong: levels in patients are well below those of healthy age matched controls.[4] However, this result fitted in nicely with the fact that serum leptin levels are correlated with BMI and even more so with fat mass.[5] Because patients with AN do not have an age appropriate fat mass due to weight loss, they show hypoleptinemia.

It takes a long time for leptin levels to reach the lower normal range during inpatient treatment. For a patient who was followed up for a year and who initially had a BMI of 12.7 kg/m² it took a BMI-gain of 2.6 kg/m² over a period of 70 days for her leptin level to bounce back into the low normal range.[4] Further studies linked such increments to the reactivation of the hypothalamus-pituitary-gonadal axis resulting in increments of the gonadotropins follicle stimulating hormone and luteinizing hormone, strongly suggesting that hypoleptinemia underlies amenorrhea as a cardinal somatic symptom of AN.[6]

The major function of leptin is currently a matter of debate. In 1996 Ahima and coworkers showed that leptin acts as the major trigger of the neuroendocrine adaptation to starvation.[7] Hence, application of leptin to food-restricted rodents was able to reverse the starvation-induced up-regulation of the hypothalamus-pituitary-adrenal axis and the down-regulation of the hypothalamus-pituitary-gonadal- and –thyroid axes.

Based on this crucial observation, we resorted to the best-known rodent model for AN. If a rat has access to a running wheel, it will develop hyperactivity upon food restriction. We hypothesized that the food restriction induced drop in leptin levels is responsible for this behavior. Indeed, we were able to both prevent and treat the hyperactivity with exogenous leptin revealing that a complex behavior is under control of endogenous leptin secretion.[8] Unfortunately, rats cannot tell us what cognitions and emotions

they experience during the development of hyperactivity in the respective rodent model. We thus repeatedly tried to link activity levels, mood and anxiety levels in patients with AN to serum leptin concentrations. We found an inverted U-shaped relationship between activity and leptin levels,[9] we came up with suggestive evidence that leptin level is also important for mood regulation.[10] Indeed, all clinicians are aware of the fact that the mental condition of patients with AN improves during nutritional rehabilitation. For instance, depression scores drop, patients become less preoccupied with food and concentration and memory functions improve.

Based on these neuroendocrine but also genetic studies indicating a rather high heritability estimate for AN, we had a second look at the DSM-IV criteria.[11,12] Our major concern was related to the words refusal and denial. How can we conclude that patients are refusing to maintain a minimal normal body weight? The word refusal suggests a patient is actively striving to reduce their weight. What if instead patients via biological and in particular neuroendocrine mechanisms just cannot maintain a healthy body weight? Obviously, the term refusal is not used in the context of any other mental disorder: a depressed patient does not refuse to be happy nor does an adolescent with a conduct disorder refuse to behave. Fortunately, both DSM-5[13] and ICD-11[14] have omitted refusal and denial in the diagnostic criteria for AN, the latter word being inappropriate in light of diagnosticians having to infer denial. We should note that the perception of AN as being the result of refusal may indirectly have led to isolation therapy for patients with AN.[15]

The European Medicines Agency (EMA) marketing approval of metreleptin (r-metHuLeptin; recombinant human leptin) for lipodystrophy[16] enabled us to pursue our long-standing medical hypothesis,[4,17–20] that the alleviation of leptin deficiency improves starvation-related cognitive, emotional and behavioural manifestations of AN. We have currently treated or been involved in the off-label treatment of fourteen patients (two males) with metreleptin in five hospitals (five published or submitted case studies[21–23]), thus marking the first time that metreleptin was applied to patients with AN. The dosing periods varied between six days and four months (comorbidity of partial lipodystrophy and AN). Four patients were aged ⩾ 18 years; the age span of the remaining patients was 15 to 18 years. All patients had severe AN albeit for different reasons including long-standing AN, extreme hyperactivity or severe depression.

The results were striking: the majority of patients experienced a rapid onset of profound improvements of sleep, mood, sociability, eating disorder specific cognitions, inner tension, urge to move, hyperactivity, and motivation to overcome their eating disorder. The mood improvement was mostly discernible as of dosing day 3 as determined with visual analogue scales and clinician and/or self-rating depression scales. The observation of improvements in self-rated depression (Beck Depression Inventory-II) is astonishing in light of the fact that in meta-analyses for childhood, adolescent or adult depressive disorders, self-rated depression scores did not or only minimally differed between verum and placebo arms.[24,25]

Surprisingly patients, who had been entrenched in their eating disorder for an extended time, were able to experience a 'holiday from AN', or 'look over the rim of the plate' (wordings used by patients). Another patient realized that she for the first time wished to leave an imaginary room into which she had locked herself. A re-emergence of libido was reported in a male patient in whom gonadotropins and testosterone increased upon initiation of metreleptin treatment.[22] Psychoeducation and psychotherapy are required to prepare a patient for this treatment and to make maximal use of the induced boost in motivation; the patient directly experiences that a hormone deficiency causes many of his/her symptoms.

Interestingly, our case studies revealed either no or a moderate increase in hunger and in three patients an increase in appetite; one patient was able to gain 20 kg in the ten-week period after cessation of dosing.[21,26] These findings are clearly in contrast to the assumed anorexigenic effects of leptin. We speculate that the rapid restoration of leptin levels might retrigger appetite, which was lost during prolonged starvation.[23]

In addition to leptin's central effects in AN, hypoleptinemia may also underlie somatic symptoms of AN.[27] Apart from the successful treatment of hypothalamic amenorrhea with metreleptin,[28] other findings deserve mentioning. Consistent with known functions of leptin, blood cell counts increased in patients upon metreleptin treatment, general appearance (skin turgor) and wound healing improved.[21] The implications for metreleptin's gastrointestinal effects in starvation and AN in particular are clear; hypoleptinemia is likely to slow gastric emptying, decrease absorption, and increase the vulnerability of the stomach/intestine to damage.[27] This pattern of leptin effects may explain the persistent gastrointestinal symptoms reported by patients in response to conventional treatment.[29] It is noteworthy to point out that constipation of single patients resolved rapidly with administration of metreleptin.[21]

The limited case number and the lack of solid evidence preclude an assessment of the medium and longer-term weight changes induced by metreleptin. However, the case reports appear promising because out of the six published case reports all patients achieved a BMI in the normal range within a few months to two years.[21–23] Obviously, RCTs are definitely required to prove that indeed metreleptin underlies the beneficial changes observed in the case studies.

In a recent review, we have delineated potential mechanisms (including interactions between leptin and the dopaminergic system) that could underlie the mental and somatic changes observed in these off-label treatments.[27] We also stressed the overlap of the observed improvements with the symptoms of "starvation neurosis", which is a term Keys and coworkers used to describe the profound mental symptoms of starvation in the volunteers of the Minnesota Starvation Study conducted in 1944/1945.[30] Our hypothesis is that hypoleptinemia underlies not only the mental changes of starvation neurosis, but also a proportion of the

symptoms observed in AN. We argue that AN is in part a hormone deficiency disorder.[21,27]

In conclusion, we need to be aware of the fact that mental disorders have a biological substrate. The current psychotherapeutic and pharmacological armamentarium definitely requires improvement. It is crucial that we come up with testable treatment related hypotheses so that patients may in the medium and longer-term profit from the insight we gain from them and by studying mental disorders overall. I encourage psychiatric trainees to never stop asking questions. I have learnt so much from patients and their parents; in this respect, empathy is crucial. We should listen carefully to what patients and their parents are telling us about the respective disorder. This holds true for whatever field of psychiatry trainees are personally attracted to – it is important to allow such an attraction to evolve over time. Looking back, I started-off with very simple questions. It is amazing to see how complex these have become.

CONFLICT OF INTEREST AND ACKNOWLEDGEMENTS

We thank numerous patients who provided their insights into the symptomatology of anorexia nervosa; we particularly thank those patients (additionally in case of minors their parents) who agreed to off-label metreleptin treatment. Johannes Hebebrand declares that he is named as an inventor in two patent applications that the University of Duisburg-Essen has filed on the use of leptin analogues for the treatment of anorexia nervosa and depression. Johannes Hebebrand received speaker's honoraria from Amryt Pharmaceuticals and from Novo-Nordisk. The Christina Barz Stiftung and the University Hospital Essen, University of Duisburg-Essen funded the metreleptin case studies.

Submitted: December 17, 2022 CEST, Accepted: February 28, 2023 CEST

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