**Obesity Facts** 

**Case Report** 

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# First Account of Psychological Changes Perceived by a Female with Congenital Leptin Deficiency upon Treatment with Metreleptin

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## Keywords

 $\label{eq:leptin} \begin{tabular}{ll} \label{eq:leptin} Leptin \cdot Obesity \cdot Anorexia nervosa \cdot Preoccupation with food \cdot Antidepressant \cdot Executive function \end{tabular}$ 

## Abstract

Two psychiatric interviews of a 39-year old female with congenital leptin deficiency were conducted to define psychological changes 14 and 165 days after initiation of treatment with human recombinant leptin (metreleptin). The most pronounced initial experience related to the reduced preoccupation with food. An improved mood was reported by the patient, which she associated with this reduced preoccupation. Her mood remained elevated upon recontact, whereas she was no longer preoccupied with food. Overall, the interviews provide a vivid account of the subjective experiences upon the initiation of treatment. Some of the findings bear a resemblance to those reported recently in patients with anorexia nervosa who were treated with metreleptin for 1-3 weeks. This case report provides further evidence that metreleptin has strong psychopharmacological effects in patients with absolute or relative leptin deficiency. We strongly recommend profound psychological examinations of pa-

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Introduction

Psychological assessments of patients with congenital leptin deficiency (CLD) have not yet been conducted to any greater extent. Currently, a total of 67 patients have been reported in the literature since 1997 [1]. In the first case study, Montague and coworkers [2] described two children aged 2 and 8 years who were constantly hungry and continuously demanded food; their food intake was substantially higher than that of their siblings. Apart from the extreme obesity with an onset in infancy, most investigators have also focused on the eating behavior in descriptive terms. The term hyperphagia is most common.

J.H. and S.Z., and M.W. and G.G.-D. shared first and last authorships, respectively.

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ly used to illustrate the excessive caloric intake [2–6]. Insatiable appetite [7] or aggressive food seeking behavior [8] represent other terms used to describe the overeating.

Treatment with recombinant human leptin (r-metHu-Leptin; metreleptin) of patients with CLD entails an increased satiety and satiation within 7 days after its initiation; weight loss is pronounced over time [9-11]. A reduced irritability around eating was noted [11]. A 9-year-old female no longer secretly sought food or demanded food between meals [9]. We are aware of two studies on individuals with CLD that report potential psychological effects of metreleptin treatment that extend beyond effects on satiety and satiation; (i) in three adults with CLD, "non-ingestive behavior changed dramatically within 2 weeks" of metreleptin treatment and prior to substantial weight loss [10]. These adults did not have elevated depression or anxiety scores prior to treatment; the authors thus precluded changes in mood or anxiety as an explanation for the observed mental effects, which they describe as a change in behavior and interpersonal attitudes from infantile and docile to assertive and adultlike. (ii) After metreleptin treatment of a 5-year-old boy for a 2-year period, substantial increments in the rates of development in neurocognitive domains were observed.

Due to leptin's role in the adaptation to starvation [12], we postulated that psychological symptoms of starvation, as meticulously delineated in the Minnesota Starvation Study [13], may result from the hypoleptinemia induced by loss of fat mass [14]. Indeed, metreleptin treatment of patients with anorexia nervosa (AN) has recently been shown to entail beneficial and rapid-onset cognitive, emotional, and behavioral effects [15-17]. Thus, preoccupation with food declined within 3-5 days; sleep improved. Mood also improved substantially within 2-4 days and became overly buoyant in 2 patients. Patients became less withdrawn and were able to more readily engage in social interactions. The urge to move and inner tension were reduced; concentration improved. Accordingly, more detailed psychological evaluations of patients with CLD are required to assess if metreleptin induces central effects that extend beyond the well-known effects on eating behavior and body weight. Leptin receptor (both short and long forms: Ob-Ra and Ob-Rb) mRNAs have been detected in hypothalamic nuclei, Purkinje cells, and dentate nuclei of the cerebellum, inferior olivary and cranial nerves nuclei in the medulla, amygdala, and neurons from both neocortex and entorhinal cortex [18, 19].

While in CLD, leptin deficiency is inborn, a reduced leptin secretion in patients with AN results from an acquired loss of fat mass. In acutely ill patients, serum leptin levels are well below the normal range [20–22] with levels typically ranging between <0.1 and 2.0 ng/mL upon referral for inpatient treatment. As in healthy controls, percent body fat is a better predictor for serum leptin levels than body mass index (BMI; kg/m<sup>2</sup>; [23]). Upon weight gain, leptin secretion increases; however, it can take a number of weeks prior to leptin levels reaching the lower normal range [22]. Attempts have been made to correlate the increased leptin secretion with reductions in physical activity and psychological variables [14, 24].

# **Case History**

The female patient from the Arabian Peninsula developed extreme obesity during infancy as a result of hyperphagia. Congenital leptin deficiency was diagnosed at age 38 by molecular genetic testing using next-generation sequencing of the genes KSR2, LEP, LEPR, MC4R, MRAP2, NTRK2, PCSK1, POMC, and SIM1 (Illumina); her niece with a similar phenotype had initially been diagnosed with this disorder. Genetic sequencing of the leptin gene revealed a novel biallelic homozygous rare variant. The annotation tools MutationTaster and PolyPhen2 classified this variant as probably damaging. Functional characterization has been performed in our laboratory (MW) and is unpublished. Upon initiation of metreleptin treatment by MW at the Division of Pediatric Endocrinology and Diabetes at the University Medical Center in Ulm, height, body weight, and BMI of the index patient were 167.4 cm, 128.8 kg, and 45.9 kg/m<sup>2</sup>. She had hypertension, hypothyroidism, pancreas lipomatosis, steatosis hepatis, lipoedema grade 3, Sjögren syndrome, and spondylolisthesis; she had been medicated with L-thyroxin (125 µg/day), vitamin B12 (1,000 µg/day), and vitamin D3 (50,000 IU/week). The patient was fully informed of the well-known mechanism of action of metreleptin with respect to suppression of hunger and subsequent weight loss. She was also informed at length of potential side effects of metreleptin treatment including the formation of leptin antibodies and the potential risk of development of T-cell lypmphoma; she provided written informed consent.

An hour-long online interview was conducted by JH during the morning of dosing day 14 during the patient's stay at the University of Ulm; at this time the patient had lost 6.95 kg of body weight. The patient was at home for the second online interview five and a half months after initiation of treatment. The first interview was transcribed according to the transcription rules of Dresing and Pehl [25]. The interview pursued two aims: (i) focus on the subjective experience of the patient upon the initiation of metreleptin treatment and (ii) investigation of the extent of overlap of induced changes with those previously observed in AN patients [15-17]. Accordingly, the patient was asked to report all observations she had made within the initial 14 days of metreleptin treatment in a non-directive manner; in the second part of the interview, she was systematically questioned as to potential changes in preoccupation with food, sleep, mood, concentration, and spontaneity. The 20-min long follow-up online interview was not transcribed.

Both the patient and the interviewer are not native speakers of the English language. Several direct citations were included to convey the statements of the patient. To enhance readability, single citations were minimally altered (for instance, the tense of a word was corrected). Words in parentheses within a limited number of direct citations were introduced to better explain the context.

## First Interview

In the *non-directive part of the interview*, the patient repeatedly used the word "magic" to describe what had happened to her. "When I started (treatment), magic." Upon dosing day 3, she started thinking less about food and experienced a greater sense of control. "So I was realizing really starting from my breakfast and my cup of coffee that, oh, things have been changed because before starting with a cup of coffee, I had always been thinking what would be my breakfast?" But during the morning of dosing day 3, the immediate association of coffee with food dissipated. "I was just having the cup of coffee and that's it. After 3, 4 h, I was thinking, oh, I didn't have my breakfast till now."

She began to think more positively. Prior to metreleptin treatment, she had felt punished by having to walk the medically prescribed 10,000 steps. She had not really accepted this physical activity in light of her experiencing it as too strenuous and painful. While still experiencing pain during her walks, she was now enjoying them.

She had been unable to visit a café to just drink a coffee. She would think of a piece of cake or cookies even if she was not hungry; she just liked to eat. She now enjoys drinking her coffee and looking around at other people. She now takes her laptop with her and starts working while drinking coffee. She utilizes her time more efficiently. "Everything has been changed in my mind. So it's like really restarting my lifestyle and it's like ... magic. Like everything in my mind has been changed about thinking of food."

She had telephoned with her mother on the day prior to the interview. "Can you imagine I've been away for more than 2 weeks. I didn't eat chocolate." Her mother had expressed her surprise; the patient, too, was struck by this fact. She had always been the family member, who had brought chocolate home. She now felt proud to be able to stay abstemious, which previously had appeared impossible. She has "changed from inside" and not as a result of external pressure. In accordance with her personal aim she was beginning to actually lose weight. "But there is another goal that started with taking leptin... that I start changing my lifestyle,...start changing my objectives, my goals, how I will think ... " She envisions herself traveling in the future, "not for treatments," just enjoying. "I will be another person, like I will maybe have another kind of clothes, another kind of activities, that I will have not only walking and shopping, sitting in the cafe and looking for more restaurants." She would now be able to pursue novel activities as she sees fitting in light of her goal to become more fit and healthy in the future by losing weight.

In the second half of the interview, the patient was first *queried* as to the previous extent of her preoccupation with food. She had been thinking of food for 70–80% and 60% of her leisure and work time, respectively. Prior to a meeting she had been thinking of the potentially available food/snacks. Whereas she definitely had been able to work, she had experienced the preoccupation with food in the back of her head. She now no longer felt distracted. "I am really completely busy with what I'm doing."

*Did metreleptin affect her sleep*? Before treatment, she woke up briefly every 60–90 min. Now she wakes up every 2 h. "But it's a very slight change." Total sleep duration of 4–5 h had not changed.

Did her mood change in any way? "To be honest, yes...OK, I'm always a funny person, I'm smiling all the time... but I really feel the changes... my mood has been changed a lot." She was experiencing things "more from the positive side." "Before I was like very easy to get angry for anything, for even silly things... But now, no, I'm just like passing it, I'm just taking it more positive, more funny, more like no, I'm not really getting upset too much and I'm not really getting disappointed too much, even if it's like really disappointing. But I'll just put in my mind that that might be the best. That might be something good. I might have the better chance next time, but that's OK. Pass it, go for the next step. So I really feel that... in all the fields of my life." She specifically lists her health, her business, her work, and her relations with family members. "So it's really changing. Even they have noticed that." She rated her mood prior to dosing at three to four and at the time of the interview at seven to eight on a scale from one (extremely depressed mood) to ten (excellent mood).

To what extent did the metreleptin induced reduction of both hunger and preoccupation with food improve her mood? "Oh, I think there's a strong connection." She previously had not concentrated on whether she was hungry or not; she just ate. "Whenever I feel like I'm upset or if I'm free or anything, I'm just trying to find something here or there to grab a snack. But now, no, I'm not eating until I feel hungry... I'm trying to be more healthy... now it's from inside." She is able to better choose between foods, to experience satiation and the satisfaction that goes along with having ingested a meal entailing a greater self-satisfaction.

*Had the quality of her social interactions changed?* She did not perceive any change. "No, I think I was a good listener before. So I don't feel my personality has really changed."

Did her ability to concentrate or focus on work or a specific task change? "Yeah, a little bit. I really feel that I can concentrate more on what I'm doing, what I'm thinking and coming up with a good plan. Before... I had so much on my mind..." She had sometimes compiled a to-do list in an attempt to structure her tasks. She now feels more concentrated as to what she would like to do and what she would want to accomplish during the day. She comes up with goals for the day and is more satisfied upon their completion. She relishes a greater perception of self-efficacy.

The patient confirms that she is now better organized and focussed. The patient was again asked to rate her current ability to focus on a scale from one to ten. She had noticed that she was not well organized and had been trying to find and use skills to become more focused. "I'm really satisfied that I've reached (a score of) eight, even before I started leptin." She confirms having searched for self-management strategies and that she had been quite successful prior to metreleptin treatment. "But now, I feel it's more organized from my mind, like, OK, once I wake up in the morning, it's easier. I know the steps that I'm going to follow for the day and that's it. But before I had to still write it down and follow some skills that I had learned." Self-organization had now become a more automatic process and she no longer had to invest as much.

Are the improved self-management skills helpful for her work? She points out that this is really helping in the context of defining her own responsibility and that of others. "I'm trying to give more responsibility to others, authorizing other people, delegating... Despite being on leave from home I'm really more concentrating on what are the other things that I have to do for my work." Her improved ability to concentrate is related to the fact that she is not thinking about food or losing weight as much. "So I have a chance to think about other things more than before... I feel my mind is like more clean, it's like I have a better chance of categorizing things in my mind and being more focused because I have enough space in my mind."

*The patient is queried as to inattention* and *proneness to anxiety*. She does not have the perception that she had problems with inattention. Anxiety does not in any way play a greater role in her life.

The next set of questions focus on perfectionism, obsessiveness, and compulsivity. She has been perfectionistic and somewhat obsessive in some situations. After initially negating a change upon initiation of metreleptin treatment, she points to a greater flexibility: "sometimes I used to have my own thinking and I will stick to that this is the right way and I know that this is the right way. I'm not going to listen to anyone else. Maybe it's (metreleptin) changing my way of thinking like with the nutrition." Prior to treatment, a nutritionist had cautioned her that she should adjust her diet to control her hypertension and her hypothyroidism. Nevertheless, she had thought to herself: "I would love to eat nice food and I would like to have the chance to eat something nice or to enjoy my life with eating and with going to a cafe and enjoy all these things. I was really having that in my mind that I'm right. As a person I have the right and I'm right." But now, this perspective has shifted. "I've changed that. This is a big change from my thinking before."

Would you say that you're more spontaneous now? "Oh, yeah. Not sure, but I think yes." She then asks for more explanations to better grasp what the interviewer is aiming at. The interviewer specifically mentions her getting a phone call from somebody to see if she will come along to a movie theater. Is she now more readily able to deal with such a decision? She affirms that in some situations this is the case. Her sister, who had accompanied her to Ulm, had persisted that they visit a particular place. The patient to her own surprise had readily consented. Prior to treatment, she would have had to go into more details to reach a decision. She now perceives herself as being able to reach a decision much more quickly. "It's like a lesser level of hesitation. Before I was hesitating much and taking time to reach some decisions... whether it's serious or not serious. But now I feel I'm better at taking decisions and not hesitating too much or thinking too much. If it's easier to take and it will not harm me, then I will just go and try it." She affirms having perceived herself as more contemplative prior to metreleptin treatment; the speed with which she is able to reach a decision has increased.

She does not view this change as being related to the reduced hunger and preoccupation with food. "I don't think so. Maybe it's the medication itself, but not with the food. Again, maybe I will go back to the main issues that my overweight, my pain, my kind of food, I'm eating or like thinking of food was taking the full part of my mind. And I was always thinking about it and looking for a solution... Now, as I said, maybe I'm free or I'm more open for other things to think and to enjoy my life more rather than thinking about that part of my life that was taking up the whole way of my thinking, my searching. I was upset all the time that no one understands me. No one knows what I'm feeling. No one knows my pain. Now, I feel that they (team of Prof. Wabitsch) really know what I'm feeling and they give me the right things to do and the right plan."

The interviewer wraps up the exploration by repeating the changes the patient had reported including an improved mood; an improved ability to concentrate, focus, and self-organize; a more spontaneous attitude; the capability to more readily reach a decision; and an altered attitude towards life. At the meta-level, me-

treleptin has apparently led to liberation from her total absorption with everything related to food, weight and other issues that come along with eating so much. The patient responded, "I don't have anything in mind except like, as I said from the beginning, it's like really working like a magic to my life. It's switching off and on like I was sometimes and I'm starting something else. Again going to the main point, everything around my mind was like thinking or concentrating more about my weight, my pain, my kind of food. I'm already like 39 years old and I have not been living like normal human beings before... And I was searching maybe more than 5 years for the right medication and for the right treatment plan... I'm (now) starting correctly with everything, with the right plan. So here comes the magic. I'm turning, I'm just putting all my old life behind, and I'm just looking forward to everything."

## Psychiatric Assessment

The patient wearing a tightly fitting headscarf established a rapid contact with the interviewer; she seemingly relished being able to speak of the psychological dimension of her treatment. Her mood appeared buoyant, she smiled repeatedly and at times gesticulated with her arms to underscore her statements. Despite her not being able to speak in her native language she spoke without hesitation and provided detailed answers to those questions, which seemed to relate to her situation. In contrast, answers to questions that she could not relate to were short (see paragraph on anxiety). Cognitive abilities and memory performance appeared normal. A mental disorder was not detectable. Recurrently, the patient spoke of her preoccupation with food. During the interview the interviewer spoke 1,616 words; the patient's elaborate initial report and the answers to the specific questions encompassed 4,161 words.

#### Follow-Up Interview

The patient now described herself as being a "normal person" with respect to thoughts of food, appetite and hunger; she has consistently been able to make healthier food choices; these thoughts and her behavior were ego-syntonic "coming from inside," she was not "forcing" them on herself. Food was no longer a recurring topic during the interview; preoccupation with food was no longer evident.

She reported a loss of 32 kg since initiation of metreleptin treatment. She found it easier to exercise and visited the gym regularly. Her style of clothing had changed as a result of greater self-confidence. She experienced the sagging skin folds associated with her weight loss as bothersome.

She experienced her mood as continuously improved; within this context she observed an increment in self-confidence and a substantially reduced irritability; she had become more "accepting." She perceived herself as being more stress tolerant. Wakenings during the night occurred to a lesser extent; she estimated that in total this accounted for her being able to sleep an hour longer per night. Some of her acquaintances had remarked that her personality had changed describing her as "more flexible, humorous and relaxed." She described her way of thinking as "wiser" and "more mature." Whereas she had previously made fast decisions, she now had "calmed down." Problems no longer appeared to represent such a heavy load. She recently had begun to experience openness for a relationship. She still was a rather forgetful person, but now more organized and able to better prioritize. Her former procrastination had given way to a more efficient completion of tasks.

# Discussion

This is the first detailed report of the psychological changes experienced by a patient with CLD upon initiation of metreleptin treatment. The initial interview was conducted during dosing day 14; the accounts of the 39year old female are vivid and readily convey why she has experienced these changes as "magic." Content wise, the amazement as to the reduced preoccupation with food and the ensuing mental liberation were readily perceptible. Throughout the interview, she repeatedly spoke of the seemingly all-encompassing extent to which she had been engaged with her preoccupation with food. Whereas she viewed her improved mood as a consequence of this reduced preoccupation, other changes were deemed as not being directly related (see paragraph on self-organization). According to the patient's recollection the initial psychological effects of metreleptin were experienced within 3 days. The second interview in essence confirmed the improved mood with reduced irritability, greater stress tolerance and self-confidence and fewer awakenings at night. The reduced preoccupation with food was no longer a dominant topic. Due to the metreleptin induced weight loss of 32 kg indirect effects resulting from this weight loss cannot be excluded. However, overall the initial improvement was confirmed in the second interview suggesting direct central complex effects of metreleptin, which mainly pertain to mood and aspects of executive functioning.

Limitations of this first report are numerous and include the online conductance of both interviews 14 days and 165 days into dosing with metreleptin precluding a pre-post comparison, the lack of any use of standardized psychological self or clinician ratings or of tests for the assessment of executive functioning and potential bias of the interviewer. As such, this case report can merely serve to point out the potential gain in knowledge to be obtained by future systematic psychological assessments of patients with CLD prior to and after initiation of treatment with metreleptin. Such assessments should ideally include a longer follow-up to judge the (perceived) effects over time.

The interview also allows a rudimentary comparison with the subjective experiences of patients with AN who were treated with metreleptin for 6–24 days [15, 16]. In these patients, the pronounced preoccupation with food also decreased within a matter of days. It is unclear if the strong antidepressant effect experienced within the same time period is as directly related to the reduced preoccupation with food as this case report of a patient with CLD suggests. In contrast to the patients with AN, there was no indication that the patient with CLD had been depressed in a clinical sense prior to initiation of metreleptin treatment. A direct assessment of mood upon use of the Hamilton Depression Rating Scale in three adult patients with CLD did not reveal scores qualifying for the diagnosis of a depressed mood [10]. The improved ability to concentrate and focus may also represent a finding common to both AN and CLD upon metreleptin treatment.

We assume that metreleptin induced mental and behavioral changes reflect central effects. The rapidity of the onset of an improved mood begs the question as to the involved brain region(s) and the cellular mechanisms. In light of the wide distribution of leptin receptors and different post-receptor pathways we can only speculate. The long form of the leptin receptor has recently been found to colocalize with brain-derived neurotrophic factor, a key factor in depression, in the dentate gyrus of the hippocampus [26].

In conclusion, this case report substantiates profound psychological effects of treatment with human recombinant leptin; in contrast to patients with AN who develop hypoleptinemia as a result of loss of fat mass, patients with CLD have inborn leptin deficiency. Systematic research is definitely warranted to uncover the metreleptin induced overlap in psychological changes and the underlying mechanisms via which metreleptin entails these changes in both acquired and inborn leptin deficiency.

## Acknowledgment

We thank the patient for sharing her experience.

## **Statement of Ethics**

The patient provided written informed consent to the publication of the case report. Due to German law ethics approval is not applicable for an off-label application of an otherwise approved drug in an individual patient.

## **Conflict of Interest Statement**

Johannes Hebebrand, Gertraud Gradl-Dietsch, and Jochen Antel declare that they will be named as inventors in a patent application that the University of Duisburg-Essen prepares to file on the use of leptin analogs for the treatment of depression. Johannes Hebebrand and Jochen Antel declare that they were named as inventors in a patent application that the University of Duisburg-Essen had filed on the use of leptin analogues for treating anorexia nervosa and related conditions. Julia von Schnurbein and Martin Wabitsch received speaker's honoraria from Amryt. Stefanie Zorn has no conflicts of interest to declare. No funding was received for this study.

#### **Author Contributions**

Johannes Hebebrand, Stefanie Zorn, Julia von Schnurbein, and Martin Wabitsch made substantial contribution to data acquisition. Johannes Hebebrand, Jochen Antel, Martin Wabitsch, and Gertraud Gradl-Dietsch made substantial contribution to analysis and interpretation of data. Johannes Hebebrand, Stefanie Zorn, Jochen Antel, Julia von Schnurbein, Martin Wabitsch, and Gertraud Gradl-Dietsch made substantial contribution to the conception of the work, manuscript preparation, critical revision, and final approval.

#### **Data Availability Statement**

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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