Successful Treatment with Atomoxetine of an Adolescent Boy with Attention Deficit/Hyperactivity Disorder, Extreme Obesity, and Reduced Melanocortin 4 Receptor Function

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Abstract
Objective: Recent case reports suggest a link between reduced melanocortinergic tone and both obesity and attention deficit / hyperactivity disorder (ADHD). We present the case of a 13-year-old, male, obese MC4R mutation carrier with ADHD. Case Report: The boy carries a heterozygous mutation in the melanocortin 4 receptor gene (MC4R; Met281Val), that leads to a reduced receptor function. Dominant mutations of this type represent major gene effects for obesity. He participated in a lifestyle intervention program for obesity and received treatment with the selective norepinephrine re-uptake inhibitor atomoxetine for 31 months. The boy markedly reduced his BMI from 47.2 to 29.6 kg/m². Conclusion: Atomoxetine proved to efficiently reduce weight in a severely obese MC4R mutation carrier with ADHD. We briefly discuss possible mechanisms for our observation, including evidence for the functional connectivity between melanocortinergic, dopaminergic, and norepinephrinergic brain circuitries.

Introduction
Recent case reports suggest a link between reduced melanocortinergic tone and both obesity and attention deficit / hyperactivity disorder (ADHD). We present the case of an obese 13-year-old male MC4R mutation carrier with ADHD.
Case Report

The 13-year- and 11-month-old male index patient was referred to our hospital by his general practitioner for treatment of his extreme obesity. At time of referral, he had a BMI of 47.4 kg/m² corresponding to a BMI standard deviation score (BMI-SDS) of 3.44 [1] (fig. 1).

Several family members were also overweight/obese (BMI mother 39.42 kg/m²; BMI father 29.22 kg/m²; BMI sister (8 years and 2 months old) 28.1 kg/m², BMI-SDS 2.72). The brother was 11 years and 3 months old and of normal weight (BMI 18.7 kg/m²; BMI-SDS 0.32).

Upon referral to our child and adolescent psychiatric service, he was in a dysphoric state of mood, revealed signs of inattention, and was easily distractible. According to his parents and his teachers he was inattentive, but not hyperactive. His school performance was below average. He experienced frequent bullying at school and reported being physically abused at school, which he claimed made him feel anxious and nervous. His eating pattern had been abnormal since early childhood. Most of his food intake was between mealtimes. He got hungry soon after having finished a meal. He initially became obese as a toddler.

Physical examination revealed acanthosis nigricans in the neck, striae distensae, and Tanner stage 2. Total cholesterol was 241 mg/dl, HDL-cholesterol 46 mg/dl, and LDL-cholesterol 179 mg/dl; the oral glucose tolerance test showed a borderline value at 139 mg/dl after 2 h. The electrocardiogram on admission showed a subtotal right bundle branch block, and 24-hour blood pressure examination revealed an arterial hypertension. 90% of the measurements were above the 95th age-related percentile, pulse frequency varied between 50 and 80 beats/min.

A mutation screen of the MC4R (for details see [2, 3]) revealed heterozygosity for Met281Val of both the index patient and his mother. The same mutation was also detected heterozygously in his 7-year-old sister. She also showed symptoms of inattention but no hyperactivity. The brother carried the wild type.

The Met281Val mutation has been shown to result in a reduced cell surface expression of the receptor and in slightly increased EC50 levels of α-melanocyte-stimulating-hormone (α-MSH) in comparison to the wild-type receptor [4], thus entailing a partial loss-of-function.
Clinical psychiatric assessment by an experienced child and adolescent psychiatrist on the basis of a structured interview with the parents and the child in succession (Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime version (K-SADS-PL), Version 1.0 [5]) and the clinical impression obtained by reports from therapists and teachers of the hospital and school, respectively, revealed that the index patient fulfilled diagnostic criteria for the inattentive subtype of ADHD according to the DSM-IV TR criteria [6]. The diagnosis was further underscored by neuropsychological assessments comprising subtests on inhibitory control (go/no go, incompatibility) of the Test Battery on Attentional Performance (TAP) [7] and the d2 cancellation test [8].

His intelligence level was within the normal range (IQ 95; Culture Fair Test (CFT 20) [9]). The index patient also fulfilled the DSM-IV TR research criteria [6] for binge eating disorder (BED) based on the results of a structured psychiatric interview with the mother and the adolescent (interview version of the Questionnaire on Eating and Weight Pattern (QEWP) by [10]).

**Treatment**

At the age of 11, the boy took part in a 10-week inpatient weight reduction program during which he lost 13 kg. Back at home, he gained 38 kg in the following 6 months. At the current referral for renewed inpatient treatment, his weight was 135.5 kg, his height measured 1.69 m (BMI 47.4 kg/m², BMI-SDS 3.44). He started with a diet of 1,600 kcal/day; physical exercise was promoted. He lost 1–1.5 kg/week; however, during weekend holidays at home he suffered from binge eating episodes, and his weight increased between 1 and 3 kg during each weekend. The patient subjectively attributed his initiation of eating to a high arousal level and feelings of internal agitation associated with a loss of control over eating. He consumed up to 4 l of caffeinated, sugary softdrinks over a day.

In light of our clinical findings and the delineated difficulties of losing weight, we decided to initiate treatment with the selective noradrenergic re-uptake inhibitor atomoxetine during week 3 of inpatient treatment. The dose was increased stepwise to 120 mg/day. Inattention improved; in the attention test (d2 Test of Attention) he scored in the normal range (54th percentile) after treatment for 3 weeks. The incompatibility standard deviation reaction time (T-scores) of the TAP indicated an improvement ranging from 42 at no dose to 54 at a dose of 120 mg/day atomoxetine.

After 8 weeks of inpatient treatment, he was referred to our outpatient lifestyle intervention weight reduction group program for overweight and obese children (FitKds) [11–13]. The BMI at discharge was 42.9 kg/m². He now was able to monitor and control his daily caloric intake, and his school performance improved substantially. During the first 6 months of this outpatient program his weight steadily decreased to a BMI of 36.0 kg/m² (BMI-SDS 2.86).

The boy showed good compliance to the lifestyle intervention and also a significant improvement of attentional and learning problems. Therefore, we reduced atomoxetine dosage for 3 months and then completely discontinued the medication while the boy continued to take part in the lifestyle intervention. Three weeks after having stopped the medication the patient showed a weight gain (3 kg) for the first time in the observed period, although he reported a daily intake of 1,400 calories (fig. 1). Inattention worsened; in the TAP he scored 42 (reaction time). We thus began to treat him with atomoxetine again. Body weight again decreased rapidly (fig. 1). After 12 months, at the end of the program, his BMI was 33.1 kg/m² (BMI-SDS 2.59). Six months after having finished the lifestyle intervention and under continuous medication, his BMI was 30.4 kg/m² (BMI-SDS 2.25). At this time, he showed elevated pulse frequency, whereas blood pressure improved. He received no pharmacological antihypertensive treatment. Consequently, we reduced atomoxetine for a second time, which was followed by a slight increase in body weight (BMI 31.2 kg/m²; BMI-SDS 2.35) and a decrease of pulse frequency. Two months later, the atomoxetine dosage was elevated to 100 mg/day, and consequently his weight decreased again (BMI 29.6 kg/m²; BMI-SDS 2.11), whereas pulse frequency increased.

**Discussion**

This is the second case report on substantial weight reduction upon treatment with ADHD medication in a child with early onset extreme obesity due to reduced MC4R function and comorbid ADHD. In the previous case study [14] the MC4R mutation was at a different position (Glu308Lys; [15]) but also resulted in a reduced receptor function – thus the func-
tional implications of both mutations is similar. In the first patient methylphenidate was used in contrast to the use of atomoxetine in the present study. Although methylphenidate is pharmacodynamically different from atomoxetine, the mechanisms that beneficially resulted in such a massive weight loss and amelioration of ADHD symptoms might be similar to our case and have been extensively discussed [14]. Potentially, the reduced melanocortinergic tone due to reduced melanocortin MC4R activity specifically contributes to symptoms of inattention and to excessive weight gain in thus predisposed individuals, which are both ameliorated by atomoxetine or the stimulant methylphenidate.

A growing number of clinical and epidemiological studies suggest a link between ADHD and obesity in children, adolescents, and adults [16–20]. Vice versa, obesity is associated with ADHD in subjects of all ages [21–36] in both clinical and epidemiological samples. However, the evidence for the association of ADHD and obesity is not completely consistent [37–39]. It has been hypothesized, that, at least in part, disturbances in eating behavior, such as impulsive binge eating and eating in response to external rewarding cues caused by reward deficiency and/or low inhibitory control capacity, mediate the association between ADHD and obesity [12, 16, 40].

About 2% of extremely obese German children heterozygously harbor \( MC4R \) [2]. Single reports have linked \( MC4R \) deficiency with ADHD ([14, 41], current study). Based on these case reports the co-occurrence of ADHD and obesity might be related to the reduced melanocortinergic tone of \( MC4R \) mutation carriers. Further studies are warranted to assess the strength of the association to ADHD; we identify ADHD in a subgroup of mutation carriers only (personal observation). The beneficial effect of atomoxetine or methylphenidate [14] on both ADHD and obesity could be related to the improvement of attention deficit and impulse control, which in turn may have helped to improve BED symptoms, thus resulting in substantial weight loss. Indeed, a reduced impulse control may constitute a neuropsychological link between obesity and BED [11, 12]. In obese individuals, lack of impulse control entails a reduced ability to resist palatable foods [42, 43]. In overweight youths, the amount of overweight is negatively correlated with neuropsychological impulse control performance [11]. It has been shown that the presentation of high-calorie food pictures to obese individuals leads to striatal and frontal activation [44, 45]. Other studies also showed reduced activity in prefrontal regions, which are involved in the development of adynamia [46]. Probably, the neurophysiological basis is a deviation of the frontostriatal dopamine-modulated network [43, 47]. While MC4R-null mice are hyperphagic and obese, they exhibit impairments in acquisition of operant responding for a high fat reinforcement. Restoration of MC4R signaling in D1R neurons normalizes procedural learning without affecting motivation to obtain high-fat diet [48].

Atomoxetine, which is a second line pharmacological treatment option in ADHD, selectively inhibits noradrenergic re-uptake [49, 50]. Adults with reduced MC4R function show a lowered adrenergic level, a decreased pulse rate [51], and a reduced systolic and diastolic blood pressure and catecholamine elimination in the urine [52]. The extensive consumption of caffeine reported by the index patient prior to beginning the medication might be interpreted as a kind of self-stimulation of his central sympathetic system. Indeed, our patient reduced caffeine intake significantly during the course of stimulant treatment. Norepinephrine can stimulate the sympathetic nervous system, resulting in an elevated modified basic metabolic rate; in our patient pulse frequency was intermittently well above average, leading to intermittent cessation of treatment. Single studies of obese adults with comorbid ADHD have shown a significant weight reduction during medical treatment with atomoxetine [53, 54]. These changes were not as dramatic as in our patient. We therefore hypothesize that the main reason for this strong weight loss is related to the reduced MC4R function. Elevation of noradrenergic levels due to atomoxetine might therefore be beneficial in conditions associated with a low noradrenergic/sympathetic tone.
To conclude, our case report underlines the assumption that a reduced melanocortinergic tone and ADHD symptomatology might result from possible common mechanisms, involving the dopaminergic, noradrenergic, and sympathetic nervous system. A psychopharmacological intervention that affects these systems might have therefore a beneficial effect for this subgroup of obese individuals. However, before generalizing this treatment, it should be taken into account that atomoxetine may provoke cardiovascular side effects, as seen in our patient. Because of these side effects, treatment with atomoxetine has to be carefully monitored. Future research is warranted to determine if the weight-reducing effect of atomoxetine and stimulants result from the beneficial effects on ADHD symptoms which in turn lead to an improved eating behavior or if, alternatively, the weight loss is due to an increased sympathetic tone. Both mechanisms may prove to be relevant in one and the same individual.

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Disclosure Statement

The authors declare that they have no conflict of interest.

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