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Review

Successful methylphenidate treatment of early onset extreme obesity in a child with a melanocortin-4 receptor gene mutation and attention deficit/hyperactivity disorder

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ABSTRACT

We present the case report of a 2 year old boy with early onset extreme obesity (body mass index (BMI) 34.2 kg/m²; body mass index standard deviation score (BMI-SDS) 5.4) who is heterozygous for a non-conservative functionally relevant *melanocortin MC_4 receptor* mutation (Glu308Lys) and who also showed severe symptoms of attention deficit/hyperactivity disorder (ADHD). Treatment with the stimulant methylphenidate led to a sharp decrease of BMI to 21.8 kg/m² (BMI-SDS 2.8) within 24 months. We discuss potential mechanisms for this unusually large weight loss and suggest a potential link between the melanocortinergic and the dopaminergic systems, and the sympathetic nervous system. The potential benefit of methylphenidate in obese *melanocortin MC_4 receptor* mutation carriers with and without co-morbid ADHD warrants further studies.

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Contents

1. Introduction

A 29 month old boy initially presented with early onset severe obesity (BMI 34.2 kg/m^2, BMI-SDS 5.4, Fig. 1) and pronounced symptoms of hyperactivity, inattention and impulsivity fulfilling the DSM-IV TR (Diagnostic and Statistical Manual of Mental Disorders, fourth edition) diagnostic criteria for attention-deficit/hyperactivity disorder (ADHD) (APA, 2000). Throughout the day he was restless

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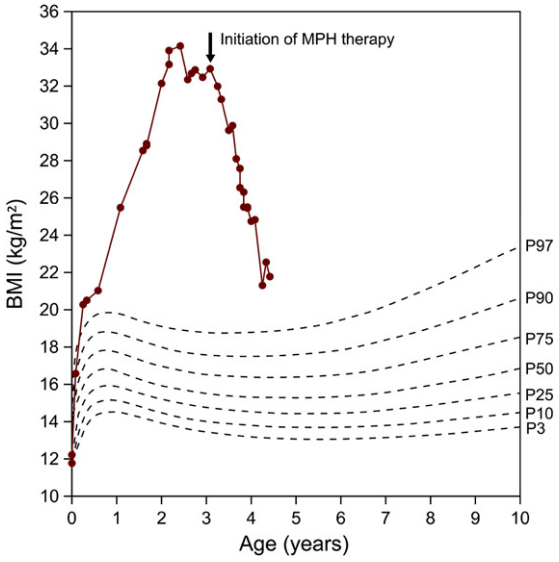

Fig. 1. Development of obesity and MPH induced BMI reduction: maximal weight of 37 kg (height 106 cm) upon initiation of MPH treatment; at age 53 months body weight and height were 28.8 kg and 115 cm. BMIs illustrated at different ages using the German reference BMI percentiles (www.mybmi.de).

and acted impulsively, especially when requests were denied. He was hardly able to perform age-appropriate activities which require attention (e.g. painting or listening to a story). He was heterozygous for a paternally inherited, functionally relevant non-conservative mutation (Glu308Lys; Santini et al., 2004) in the *melanocortin MC_4 receptor* gene; such mutations occur in 2–6% of extremely obese children and adolescents (Hinney et al., 2003; 2010; Hebebrand et al., in press). After birth at 2700 g in gestational week 36 the boy started to gain weight excessively. Upon presentation, the boy was not able to walk more than 15 steps without taking a break; he could not climb stairs without help and complained about painful ankles and knee-joints. He was permanently hungry and hyperphagic; he woke up hungry during the night. Temper tantrums occurred when food was denied. Dietary intervention had not resulted in weight reduction. Blood pressure and heart rate were within the upper normal range. Cognitive development was normal. His father recalled both hyperactive behavior and childhood onset obesity (current BMI 35 kg/m^2 at age 33 years). His hyperactivity remitted during early adulthood.

We prescribed the stimulant methylphenidate off-label at this age in an attempt to ameliorate the severe ADHD symptoms and reduce the voracious appetite, appetite suppression being one of the most common side effects of stimulants. ADHD symptoms strongly decreased (initial methylphenidate dose = 0.41 mg/kg); to continuously control ADHD symptoms the dose was increased to 1.1 mg/kg (methylphenidate extended release) during the first two months of treatment. The appetite suppression was profound and severe weight loss ensued over the whole observation period. Upon the most recent presentation at age 53 months the methylphenidate (current dose: 1.4 mg/kg) effect was reported to wane seven hours after intake, so that excessive appetite and ADHD symptoms re-emerge during the evening. Blood pressure and heart rate were slightly lower than at initial presentation. The boy experiences difficulties falling asleep and wakes up 4–5 times per night complaining of painful knees and feet, caused by genua recurvata. The parents are unable to state whether or not he is hungry, because food after bedtime has long been denied.

2. Discussion

Although weight loss is a common side-effect of methylphenidate treatment (Poulton and Cowell, 2003; Barkley et al., 1990), to our clinical experience the steep and long-lasting BMI decline (see Fig. 1) in this obese *melanocortin MC_4 receptor* mutation carrier with comorbid ADHD appears rather unusual. The effect is stronger than the anorexic effect of methylphenidate normally observed in ADHD patients (with and without obesity). Hence, our observation raises the question, as to whether the altered melanocortinergic signalling due to reduced *melanocortin MC_4 receptor* activity specifically contributes to the marked effect of methylphenidate. Alternatively, our observation merely depicts the upper edge of the variability of weight loss following stimulant treatment.

2.1. Obesity and ADHD as comorbid conditions

During the last decade, compelling evidence substantiated the link between ADHD and obesity/overweight (for review see Davis, 2010). There is a growing number of clinical studies on adults (Altfas, 2002) and children (Holtkamp, 2004), as well as epidemiological studies comprising large population based samples (Pagoto et al., 2009; Waring et al., 2008). For example, Altfas et al. (2002) described a clinical sample of 215 adult bariatric patients (mean age 43.4 years, mean BMI before treatment 36.2 kg/m^2). The prevalence of ADHD was 27.4% in the whole sample. Most of these comorbid patients (42.6%) were found among the most obese individuals (BMI > 40 kg/m^2). Those with ADHD reduced their weight during treatment to a lesser extent than those without ADHD. In children a significantly higher BMI-SDS was reported in a clinical sample of 97 boys with ADHD (mean age 10 ± 2 years, mean BMI-percentile 57 ± 30; Holtkamp et al. 2004). In a clinical sample of 177 children and adolescents aged 8 to 15 years (mean BMI = 29.2 ± 4.33) high body weight was associated with high impulsivity, especially at younger ages (Pauli-Pott et al., 2010). This is in line with the observation of Tsukayama et al. (2010), who were able to show that low impulsivity predicted prospective decrease of BMI percentile rank during transition from childhood into adolescence. Population-based data based on 6,735 adult persons yielded a 1.6 odds ratio (95% confidence interval = 1.1, 2.4) for patients with ADHD to be overweight and a 1.8 odds ratio (95% confidence interval = 1.1, 2.6) to be obese (Pagoto et al., 2009).

ADHD medication might actually weaken the relationship between ADHD and obesity (Poulton and Cowell, 2003; Barkley et al., 1990). In this respect the findings of Waring et al. (2008) are of special relevance. In a population-based survey comprising 62,884 children and adolescents aged 5–17 years (5,680 with ADHD) children and adolescents with ADHD who did not take any medication at the time of assessment showed a higher rate of overweight. In contrast, those who were on medication for ADHD were more likely to be underweight than the children and adolescents without ADHD.

2.2. Link between reduced melanocortinergic tone and ADHD

Melanocortin MC_4 receptor mutation carriers could represent a subgroup of obese patients with comorbid ADHD. *Melanocortin MC_4 receptor* mutations that lead to a reduced receptor function have consistently been found to be associated with obesity (Hinney et al., 2006; Farooqi and O'Rahilly, 2006; Lubrano-Berthelier et al., 2003). Within a Palestinean consanguineous family homo- and heterozygous carriers of a functionally relevant *melanocortin MC_4 receptor* mutation (Cys271Arg; Agranat-Meged et al., 2008) presented with both obesity and ADHD. 29 subjects from 5 related nuclear families underwent thorough physical and psychiatric examination. ADHD was significantly more prevalent in the homozygous (80%) as well as in the heterozygous mutation carriers (21%) compared to the expected prevalence rates in the general population. Further, among the pedigree members the ADHD prevalence increased with the number of *melanocortin MC_4 receptor* obesity risk alleles. An impaired self-regulation and higher levels of impulsivity might indicate a common patho-mechanism both for ADHD and obesity due to a *melanocortin*

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