Aggravation of Food-Related Behavior in an Adolescent with Prader-Willi Syndrome Treated with Fluvoxamine and Fluoxetine

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Abstract: *Prader-Willi Syndrome is a congenital multisystem disorder, characterized by a typical dysmorphism, mental retardation, hyperphagia due to insatiable appetite, and resultant morbid obesity. Psychiatric symptoms include obsessions and temper tantrums.* **Method:** *Pharmacotherapy is experimental with a few reports of successful fluoxetine treatment.* **Results:** *We report an aggravation in the food-related symptoms and a consequent weight gain in an adolescent with Prader-Willi syndrome, who was treated with fluvoxamine and fluoxetine. © 2001 by John Wiley & Sons, Inc.* Int J Eat Disord 30: 113–117, 2001.

Key words: *Prader-Willi syndrome; fluvoxamine; fluoxetine.*

INTRODUCTION

Prader-Willi syndrome (PWS), first described in (Prader, Labhart, and Willi, 1956) is a multisystem congenital disorder. It is characterized at birth by hypotonia, feeding difficulties, and failure to thrive. These symptoms are replaced at the age of 3 years by severe hyperphagia due to insatiable appetite, leading to morbid obesity. The typical dysmorphism consists of short stature, narrow bitemporal diameter, almond-shaped eyes, small hands and feet, cryptorchidism in boys, and genital hypoplasia in both sexes. Intelligence is usually subnormal. Behavioral problems are evident from a young age and are mainly related to food. These children will virtually do anything in order to quieten their voracious hunger, including stealing food and eating inedible materials. Frustration often leads to temper tantrums and aggressive outbursts. Other psychiatric symptoms include obsessions and compulsions. Life expectancy is shortened due to complications of morbid

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obesity. Diagnostic criteria based on these features were set by an international consortium (Holm et al., 1993). The etiology of PWS is genetic, with most patients showing a molecular deletion of a critical region on the long arm of the paternal chromosome 15(q11-13). In other patients, the whole paternal chromosome is missing and two copies of the maternal chromosome are present. An intensive search is being conducted in a narrow region of chromosome 15q11-13 for the candidate genes (Kuslich, Kobori, Mohapatra, Gregorio-King, & Donlon, 1999).

Treatment of PWS patients includes active physiotherapy and tube feeding during the early years. Subsequently, prevention of obesity and its sequelae and behavior management become the major goals. Effective measures in preventing obesity remain the close supervision of caregivers, restriction of free access to food, and a low-calorie diet. This regime is usually successful with younger children but becomes difficult to enforce in adolescents. Several pharmacotherapeutic trials and case reports have shown the ability of some medications to suppress appetite and control food-related behavior in PWS patients. Among these medications were naloxone (Kyriakides, Silverstone, Jeffcoate, & Laurance, 1980), fenfluramine (Selikowitz, Sunman, Pendergast, & Wright, 1990), and methylphenidate (Jerome, 1991). Case reports of successful treatment of PWS patients with fluoxetine have also been published (Dech & Budow, 1991; Warnock & Kestenbaum, 1992; Benjamin & Buot-Smith, 1993; Jerome, 1993; Hellings & Warnock, 1994; Warnock, Clayton, Shaw, & O'Donnell, 1995). Although clinicians prescribing fluoxetine and fluvoxamine for PWS patients have noticed adverse behavioral effects, these were not reported in the literature. Martin et al. (1998) mentioned the occurrence of this phenomenon in their patients, but did not elaborate. We report the case of a 14-year-old boy with PWS who suffered an aggravation of his food-related behavior and a resultant weight gain while on therapeutic trials with fluoxetine and fluvoxamine. The reasons for this side effect and the therapeutic implications are discussed.

CASE REPORT

Y., a 14-year-old boy, was brought to our adolescent psychiatric inpatient unit by his parents, who were seeking help for his uncontrollable behavior. There is no history of any psychiatric or genetically transmitted disease in his family. Pregnancy and delivery were normal. Immediately after birth, marked hypotonia and poor sucking were noted. He had bilateral cryptorchidism, which was corrected in a series of operations. His psychomotor development was delayed. At the age of 3 along with an improvement of the hypotonia, severe hyperphagia appeared, which led to accelerated weight gain. At that time, the diagnosis of PWS was made, based on the history, typical dysmorphism, and a chromosomal study. Y. was put on a low-calorie diet and his parents were able to control his food-related behavior, which included stealing from other houses and eating out of garbage cans. At the age of 8, Y. was treated with methylphenidate for restlessness, with good response. The drug had to be stopped after 3 years because of the appearance of tics, which disappeared after its discontinuation. At the age of 10, Y.'s parents were losing control over his behavior. Y. became stronger and smarter and was able to find ways to obtain unlimited amounts of food by stealing and eating inedible materials (such as animal food). At the same time, obsessions and compulsions appeared, such as an insistence on schedules and endless repeating of questions. Any argument over these issues led to aggressive outbursts. Skin-picking of minor sores, especially those secondary to

compulsive fingernail cutting, was also evident. Y. was moved to a special education school where a strict behavioral approach was tried with some success, but only while Y. was watched. At the age of 12, fenfluramine (with doses up to 60 mg a day) was started. There was an initial improvement in his behavior, but a relapse occurred (the skin-picking did not recur). The only way to restrain Y. was to add propericiazine at the cost of oversedation. Y. gained 50 kg in the last 4 years and his weight increased from average to over the 97th percentile for his age. His height remained under the 3rd percentile. His parents, in their despair, were willing to admit him for a long-term psychiatric hospitalization. On examination, Y. appearded as a short (144 cm) and morbidly obese (91 kg) young boy. He has the typical facies of PWS with a narrow bitemporal diameter, small hands and feet, and hypogenitalism. Symmetrical deep tendon hyporeflexia and a bilateral positive Babinski sign were noted. With these exceptions, his physical and neurological examination was normal. A comprehensive laboratory workup was normal, apart from minimally reduced total lung volume and low luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone levels. On mental examination, perserverations and obsessions were noted. There was no evidence of any affective or psychotic disorder. Intelligence testing (WISC-R) resulted in an overall IQ of 67.

With Y.'s admission, we constructed a treatment program based on stopping his former medications, a low-calorie diet, a behavioral plan, and pharmacotherapy with Selective Serotonin Reuptake Inhibitor (SSRI). First, propericiazine was discontinued and Y. was observed for a week. There were a few attempts to steal food from other patients and to eat out of garbage cans. These attempts disappeared very quickly and were interpreted as "testing of limits." Apart from that, his behavior was tolerable. After a week, Y. was put on a low-calorie diet (1,200 kcal per day). He managed to adhere to it, with the exception of eating candy which he persuaded other patients to give him. Y. succeeded in losing 4 kg during the first 2 weeks on this diet. A behavioral program, based on the token system, was developed for Y., but he did not cooperate. Fenfluramine was stopped gradually when no change was noted in Y.'s food-related and aggressive behavior, although there was an increase in obsessive-compulsive symptoms such as nagging questions, rituals, and skin-picking (which was absent for several years). After discontinuation of fenfluramine for 1 week, we observed Y. for another week without medication. There was no change in his situation. We started treatment with fluvoxamine, an SSRI. The dose was gradually increased from 50 to 200 mg a day. Immediately after beginning treatment, there was a marked improvement in Y.'s obsessive-compulsive symptoms, but this was accompanied by aggravation of his food-related behavior. Y. was practically uncontrollable. He seemed to be motivated only by his hunger, reported by him to be markedly increased. He disregarded the consequences of his actions. He would steal food from any patient in the ward, including the most violent. He ate out of garbage cans constantly. He ate his own feces. He disregarded threats of punishment by the staff for misbehavior. He was aggressive, both physically and verbally, when attempts to set limits for him were tried. Y. gained 3 kg during this period. The staff and other patients could not tolerate his behavior. Fluvoxamine was stopped after 2 weeks without completion of the intended 6-week trial. With its discontinuation, his food-related and aggressive behavior disappeared. However, obsessive-compulsive symptoms reemerged. With regard to the possibility that these reactions were unique to fluvoxamine, we started Y. on a trial of fluoxetine. Unfortunately, the same pattern of improvement in obsessive-compulsive symptoms and aggravation of food-related and aggressive problems was noted. An attempt to control the side effects of fluoxetine with a low-potency phenothiazine (levomepromazine) proved ineffective because hunger increased and cognitive performance

was severely impaired. Thus, fluoxetine was stopped after 2 weeks. Again, the same reversal of symptoms was noted.

DISCUSSION

There are some reasons for using SSRIs in the treatment of PWS patients. First, SSRIs are indicated for the treatment of obsessive-compulsive disorder. They might be useful in treating the obsessive-compulsive–like symptoms of these patients, as is exemplified by the rapid response of our patient. Second, they have been shown to be effective in reducing food comsumption in bulimic and obese patients, unrelated to their antidepressant effect or adverse reaction of nausea (Ferguson & Feighner, 1987; Freeman & Hampson, 1987; Marcus et al., 1990). Thus, it was very surprising to find increased appetite and aggravation of food-related and aggressive behavior in our patient while being treated with fluoxetine and fluvoxamine. It could be argued that these changes resulted from the initial pharmacological effect of SSRIs, which increase serotonin levels in synapses before down-regulation of postsynaptic serotonin receptors ensues (Blier & de Montigny, 1994). This effect is believed to be the basis of an increase in anxiety and agitation, which are noted in some patients when SSRI treatment begins. It may also explain the increased hunger reported by our patient, although serotonin is believed to suppress hunger. The rapid improvement in the obsessive-compulsive–like symptoms is puzzling. It is expected to occur only after 2–4 weeks of treatment, when down-regulation of serotoninergic receptors begins. It could be argued that the aggravation of Y.'s symptoms while on SSRIs was idiosyncratic. Nevertheless, from personal communication with other clinicians, we have learned that fluoxetine was used in the treatment of their PWS patients with no or limited success. In others, the drug was useful but led to the same kind of undesirable side effects that we describe. In the face of the small number of reports in the literature on SSRI treatment in PWS patients, we urge clinicians to share their experiences with others. Double-blind placebo-controlled studies are needed. Until further research is done, SSRIs should be used with caution in PWS patients. Lowering and titrating the dose slowly might prevent this adverse reaction.

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