Decreased Growth During Therapy With Selective Serotonin Reuptake Inhibitors

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Background: There is no information on the effects of selective serotonin reuptake inhibitors (SSRIs) on growth and puberty in children. We examined growth and growth hormone secretion in 4 children treated with SSRIs for various psychiatric disorders.

Design: Case study.

Participants: Four children (3 boys) aged 11.6 to 13.7 years with obsessive-compulsive disorder or Tourette syndrome.

Main Outcome Measures: Growth, pubertal progression, and hypothalamic pituitary function.

Methods: The patients were treated with SSRIs for 6 months to 5 years (dosage, 20-100 mg/d). All were regularly examined for changes in height and bone age and for pubertal progression. They also underwent evaluation of somatotrophic axis and hypothalamic-pituitary axis function.

Results: All 4 patients had growth attenuation. Three of them exhibited growth retardation at a pubertal stage when a growth spurt was anticipated. Three had a decreased growth hormone response to clonidine hydrochloride stimulation and 2 to both clonidine and glucagon stimulation, and 1 had decreased 24-hour secretion of growth hormone that normalized when therapy was stopped. The rest of the endocrine evaluations were within reference ranges in all patients. At follow-up, 2 patients were being treated with somatropin while continuing SSRI therapy, and the other 2 resumed normal growth after discontinuation of therapy.

Conclusions: A decrease in growth rate, possibly secondary to suppression of growth hormone secretion, may occur during SSRI therapy. As the use of this group of drugs is expected to increase in the young age groups, larger studies are warranted to investigate their effect on growth and growth hormone secretion.

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SELECTIVE SEROTONIN reuptake inhibitors (SSRIs) are a group of antidepressant agents that have been proved effective in the treatment of various psychiatric disorders. They were recently approved for use in children and adolescents with obsessive-compulsive disorder, Tourette syndrome, and other psychiatric disorders.[1] The SSRIs have relatively few adverse effects, the most common being gastrointestinal (abdominal discomfort) and neuropsychiatric (sedation and activation).[1,2] There are several anecdotal reports of increased prolactin levels, galactorrhea, and amenorrhea.[3,4] An increasing number of studies in adults have reported decreased growth hormone (GH) response to pharmacologic stimulation in healthy persons and in patients with psychiatric disorders.[5-9] Studies in children and adolescents have not reported on changes in growth and puberty, either because they were short-term[10,11] or because growth was not addressed, these generally being psychiatric and not endocrinologic investigations.[10-13] The main adverse effects of youth treated with SSRIs were insomnia, fatigue, and abdominal discomfort.[2,13] Fairbanks et al[10] reported sleep problems, decreased appetite, abdominal pain, and excitement, all of them generally transient. However, pooled analysis of weight changes during SSRI therapy showed more weight loss during short-term treatment but more weight gain during long-term treatment.[14]

We describe 4 children who showed growth attenuation and decreased GH secretion, with normal weight gain, during treatment with SSRIs.

REPORT OF CASES

CASE 1

A girl was followed up in our clinic for short stature from age 9 years 8 months. She had been born at 36 weeks after an un-

PATIENTS AND METHODS

Four children (3 boys) aged 11.6 to 13.7 years were treated with SSRIs for obsessive-compulsive disorder or Tourette syndrome. The height of the patients and their parents was measured with a stadiometer (Harpenden; Holtain Ltd, Crymych, Wales), and growth velocity was calculated during 6-month intervals. Auxologic results were expressed in terms of SD score (SDS) for age, based on the standards of Tanner and Whitehouse.[15] Puberty was assessed according to Marshall and Tanner[16,17] and bone age according to Greulich and Pyle.[18] Target height was determined according to midparental height corrected for sex, by means of standard equations.[19] The GH stimulation tests were performed after priming with estrogen (ethynylestradiol, 40 µg/m² per day for 2 days before testing).[20] The clonidine hydrochloride test was performed with a single oral dose of clonidine hydrochloride (Normopresan; Rafa, Jerusalem, Israel), 150 µg/m², and blood samples were drawn at 0, 30, 60, 90, and 120 minutes for GH determination. The glucagon stimulation test was performed with an intramuscular injection of glucagon, 30 µg/kg (maximum, 1 mg) (Novo Nordisk, Bagsvaerd, Denmark), and blood samples were drawn at 0, 120, 180, and 240 minutes. Pass levels were defined as a peak GH level of 10 ng/mL (440 pmol/L) or greater. To determine 24-hour integrated concentration of GH, blood was obtained every 30 minutes with a nonthrombogenic continuous withdrawal pump.[21] The serum GH,

prolactin, cortisol, and free thyroxine concentrations were determined with a commercially available solid-phase chemiluminescent enzyme immunoassay; thyrotropin concentration, with an immunometric assay that used an automated analyzer (Immulite; Diagnostic Products Corporation, Los Angeles, Calif); and 24-hour urinary free cortisol excretion with radioimmunoassay (Diagnostic Products Corporation).

The patients' clinical and laboratory evaluations were performed as part of the routine procedure for the diagnosis of abnormal growth.

Reasons for referral were short stature (patients 1 and 2), slow growth rate (patient 3), and short stature and overweight (patient 4). The characteristics of the 4 patients are summarized in **Table 1** and the laboratory results in **Table 2**. The **Figure** shows the individual growth velocity curves and pubertal stage before and during SSRI and GH therapy, where applicable. In all 4 patients, the weight percentile was consistent during SSRI therapy. None of the patients had an underlying chronic disease, as indicated by normal findings for blood chemistry, blood count, erythrocyte sedimentation rate, urinalysis, antigliadin antibodies, thyroid function tests, prolactin levels, 24-hour urinary cortisol levels, or cortisol suppression with 1 mg of dexamethasone. Brain magnetic resonance imaging was also performed to rule out brain tumors or malformations. All 4 patients had supportive families; they functioned well at home and attended regular public school while receiving SSRI treatment.

Table 1. Pertinent Clinical Data in 4 Patients at Initiation of SSRI Therapy*

Patient No./Sex	CA, y	BA, y	Height, SDS	Weight, SDS	Puberty† Pubic Hair Stage	TV, mL/Breast Stage	Type of SSRI	Dose, mg/d	Duration of Therapy, y
1/F	11.6	11.5	−1.8	−2.0	1	2	Fluvoxamine maleate	50	0.5
2/M	13.7	11.5-12.0	−1.6	0.1	2	5	Fluoxetine hydrochloride	80	0.9
	15.9‡	13.3	−2.3	−0.1	4	12	Fluoxetine	20	0.5
3/M	12.6§	12.5	−0.7	0.6	2	5	Fluvoxamine	100	5.0
4/M	12.8	12.5	−0.7	1.6	1-2	2	Fluoxetine	20	1.3

*SSRI indicates selective serotonin reuptake inhibitor; CA, chronological age at referral; BA, bone age; SDS, standard deviation score; and TV, testicular volume.
†Tanner pubertal stage.[16,17]
‡Second therapy period.
§Age at referral after 2.5 years of SSRI therapy.

remarkable pregnancy. Birth length was 46 cm and birth weight, 2280 g (appropriate for gestational age). Growth was consistent along the fifth percentile, compatible with her target height (155 cm). At referral, the girl was prepubertal, with no abnormalities on physical examination. Bone age was 8 years 10 months and karyotype was 46,XX. At age 11 years 7 months, therapy with fluvoxamine maleate (Favoxil; Agis Industries Ltd, Yerucham, Israel), 50 mg/d, was initiated for Tourette syndrome. During the 6 months of fluvoxamine therapy, the patient showed growth arrest despite the concomitant appearance of Tanner stage 2 pubertal signs and consistent weight gain; plasma prolactin and thyroid hormone levels were within the reference range. The GH response to clonidine stimulation after estrogen priming was bor-

derline at 9.4 ng/mL (413.6 pmol/L), and insulinlike growth factor 1 (IGF-1) level was low for pubertal stage. At age 12 years 1 month, the fluvoxamine was discontinued, and normal growth velocity of 6.6 cm/y was resumed. On a second clonidine stimulation test performed 4 months after discontinuation of fluvoxamine treatment, GH level peaked at 18.1 ng/mL (796.4 pmol/L).

CASE 2

A boy was referred to our clinic at age 13 years 8 months for evaluation of short stature and overweight. He had been born at term after an unremarkable pregnancy, with a birth weight of 2850 g. Growth was consistent along the third percentile, compatible with his target height

Table 2. Endocrine Evaluation During SSRI Treatment*

Patient No.	CA	Puberty†	Prolactin, ng/mL	FT₄, ng/dL‡	TSH, U/mL	24-h Free Urinary Cortisol, nmol · L⁻¹ · 24 h⁻¹	IGF-1, nmol/L	GH Peak, ng/mL§ Clonidine Hydrochloride Test	Glucagon Test
1	11.7	2	3.3	1.2	3.4	NA	17.7	9.4	NA
	12.4‖	2-3						18.1‖	
2	14.6	3	9.9	1.7	1.0	106	18.0	11.4	NA
	14.7‖	3					39.0‖		
3	13.5	3	14.6	1.2	2.6	NA	11.8	5.1	2.6
4	13.8	1-2	6.6	1.7	2.5	93.2	26.0	3.6	2.2
Reference range			5-20	0.8-2.0	0.4-4.0	55-248	T1: 4.8-13.8 T2, T3: 18-50	≥10	≥10

*SSRI indicates selective serotonin reuptake inhibitor; CA, chronological age, FT₄, free thyroxine; TSH, thyrotropin; IGF-1, insulinlike growth factor 1; GH, growth hormone; NA, not available; and T1, T2, and T3, Tanner stages 1, 2, and 3, respectively.
†Tanner pubertal stage.[16,17]
‡To convert to picomoles per liter, multiply by 12.87.
§To convert to picometers per liter, multiply by 44.
‖After SSRI discontinuation.

(162 cm). At referral, the patient's height was at the third percentile and his weight was at the 60th percentile (body mass index [calculated as weight in kilograms divided by the square of height in meters], 24.4). He showed Tanner 2 pubertal signs, and results of physical examination were normal. Bone age was 11.5 to 12.0 years. Immediately after referral, the patient started treatment with fluoxetine hydrochloride (Flutine; Teva Pharmaceuticals Industries Ltd, Netanya, Israel), 80 mg/d, for obsessive-compulsive disorder. Six months later, growth velocity decreased to 1.4 cm/y, followed by complete growth arrest for 4 months (age 14.1-14.5 years) but with consistent weight gain. Laboratory investigation showed normal 24-hour urinary free cortisol level, prolactin level, and thyroid function. Peak GH level in response to clonidine stimulation was normal, but the mean 24-hour integrated concentration of GH during fluoxetine therapy was low at a mean±SD of 1.51±2.19 ng/mL (66.44±96.36 pmol/L) (reference, ≥3 ng/mL [≥132 pmol/L]).[21] The IGF-1 level was low normal at that time. Brain magnetic resonance imaging produced normal results. Therapy with fluoxetine was stopped, and a second GH 24-hour profile was performed 1 month later. Results showed a mean GH integrated concentration (3.18±4.48 ng/mL [139.92±197.12 pmol/L]) and an IGF-1 level within their respective reference ranges, suggesting transient GH neurosecretory dysfunction (probably SSRI induced).[22] After 6 months, growth velocity improved to 5.1 cm/y, and testicular volume increased from 5 mL to 6 to 8 mL. Treatment with fluoxetine was resumed at age 15 years 11 months for 6 months and then was discontinued because of a recurrent decrease in growth velocity to 3 cm/y, concomitant with progression of puberty from Tanner stage 3 to stage 4. After cessation of SSRI therapy, the patient exhibited a normal pubertal spurt of 5 to 6 cm/y, corresponding to his height percentile.[15]

CASE 3

A boy was referred to our clinic at age 12 years 7 months for short stature and slow growth rate. He had been born small for gestational age at 31 weeks because of maternal preeclampsia, with a birth weight of 900 g. The patient had received methylphenidate hydrochloride (Ritalin; Novartis International AG, Basel, Switzerland) from age 5 to 10 years and then switched to combined risperidone (Risperdal; Janssen Pharmaceutica, Inc, Beerse, Belgium), 1.0 to 1.5 mg/d, and fluvoxamine maleate, 100 mg/d, for treatment of Tourette syndrome and attention-deficit/hyperactivity disorder. From age 6 to 11 years, he grew along the 25th to 50th height percentile (midparental height, 174.5 cm). At that time, growth attenuation was first noted. At referral, he was at the 20th percentile for height and 75th percentile for weight (body mass index, 22.4). Results of physical examination were normal, with Tanner stage 2 pubertal signs, and bone age was appropriate for chronologic age. There were no signs of Cushing syndrome. During 1 year of follow-up, growth velocity decreased from 4.5 to 2.4 cm/y, with consistent weight gain, while puberty advanced to stage 4, with an increase in testicular volume from 5 mL to 12 to 15 mL and in testosterone level from 58 to 202 ng/dL (2 to 7 nmol/L) (normal ranges for Tanner stages 2 and 4, 17-167 ng/dL [0.6-5.8 nmol/L] and 112-476 ng/dL [3.9-16.5 nmol/L], respectively). Laboratory investigation showed normal suppression of cortisol in response to 1 mg of dexamethasone, and normal prolactin level and thyroid function. The postpriming peak GH levels in response to clonidine and glucagon stimulation were subnormal (Table 2). The IGF-1 levels were low for pubertal stage. Brain magnetic resonance imaging results were normal. As treatment with fluvoxamine could not be stopped, therapy with somatropin was initiated at age 14.5 years, resulting in a marked improvement in growth rate to 12 cm/y.

CASE 4

A boy was referred for evaluation of overweight at age 12 years 9 months. Perinatal history was unremarkable, and birth weight was 3200 g. The mother had a history of delayed puberty. Previous medical history disclosed
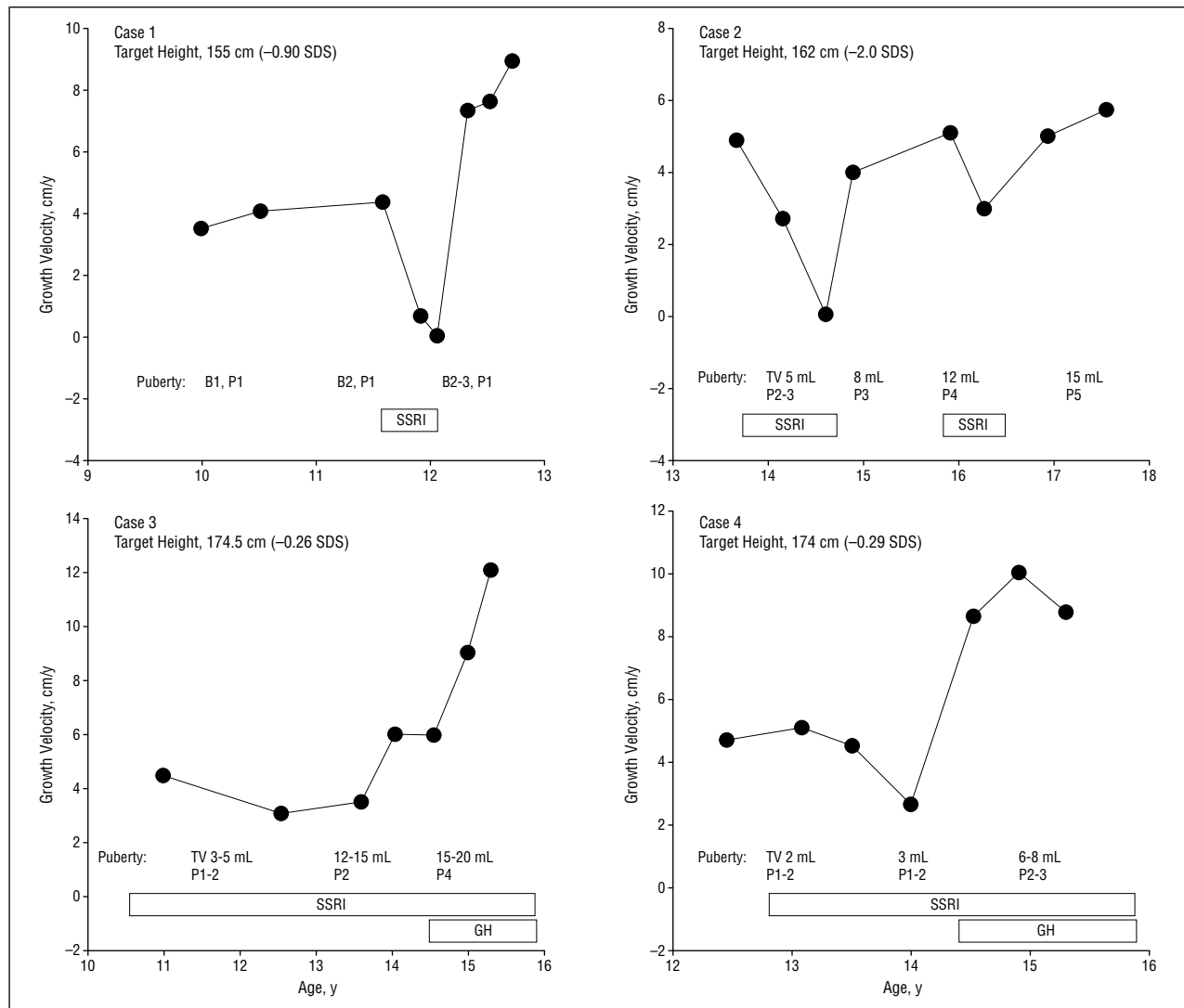
Growth velocity curves of 4 patients during periodic treatment with selective serotonin reuptake inhibitors (SSRIs) with or without the addition of growth hormone (GH). SDS indicates standard deviation score; B, breast; P, pubic hair; and TV, testicular volume. Breast and pubic hair were staged according to Marshall and Tanner.[16,17]

therapy with methylphenidate hydrochloride, 10 mg/d, for attention-deficit/hyperactivity disorder since the age of 7 years. Growth was consistent along the 50th percentile for height (compatible with the midparental height of 174 cm) and 90th percentile for weight. On physical examination, he appeared mildly obese and pre-pubertal. At the age of 12 years 9 months, obsessive-compulsive disorder was diagnosed and therapy with flu-voxamine maleate, 150 mg/d, was added. It was later changed to fluoxetine hydrochloride, 20 mg/d. Thereafter, the patient's growth rate slowed from 5.1 to 2.6 cm/y, decreasing from the 50th to the 15th height percentile within 1 year, with consistent weight gain. Laboratory data showed normal thyroid, prolactin, and 24-hour uri-nary free cortisol levels. Postpriming GH response to cloni-dine and glucagon stimulation was subnormal (Table 2). As fluoxetine treatment could not be stopped, therapy with somatropin was initiated at the age of 14 years 4 months. Thereafter, growth rate increased to 10 cm/y. Tanner 2 pubertal signs appeared at age 14.6 years, with progression to Tanner 4 during the next year while the

patient was receiving combined treatment with SSRIs and somatropin.

COMMENT

The 4 patients described in this report showed growth at-tenuation or arrest with normal weight gain during SSRI therapy, possibly secondary to decreased GH secretion, with normal progression of puberty in 3 of them and no evi-dence of chronic disease or abnormalities in other hypo-thalamic-pituitary functions. These findings suggest a se-lective impairment of the somatotrophic axis by SSRIs. Our observation is in line with the studies of Coplan et al[6] and O'Flynn et al[5] showing blunted GH secretion during fluox-etine treatment in adults, either in response to clonidine stimulation in patients with remitted panic disorder or me-diated by desipramine hydrochloride (used as a GH stimu-lation test) in patients with major depression. The cen-tral α_2-noradrenergic pathways serve as major stimulants of growth hormone–releasing hormone secretion,[23] and the central α_2-noradrenergic receptors mediate clonidine-

What This Study Adds

Selective serotonin reuptake inhibitors have been associated with endocrinologic adverse effects in several reports in adults, but there is no information on their effect on growth and puberty in children. Our study of 4 patients aged 11.6 to 13.7 years receiving selective serotonin reuptake inhibitors for 6 months to 5 years suggests an isolated effect of therapy on growth and possibly growth hormone secretion. These data, although limited to only 4 patients, might have important clinical implications in view of the increasing use of these agents in the management of psychiatric disorders in younger age groups. The findings are reported to increase the awareness of psychiatrists and physicians in other fields who treat and follow up these patients.

induced release of GH.[24] Therefore, as desipramine is a known noradrenergic reuptake inhibitor,[25] these studies suggest that SSRIs affect GH secretion via reduction of central α_2-adrenoreceptor–mediated GH release.

The new 2-site chemiluminescent assays used currently in most endocrine laboratories for GH determination show lower GH levels, by about 30%.[26] However, using this method, our group[27] and others[20] reported mean GH levels of 16 to 20 ng/mL (704-880 pmol/L) in prepubertal and early-pubertal children with short stature. Therefore, we believe the low levels found on 2 primed tests in patients 3 and 4 were true lows. An impairment of the somatotrophic axis is further supported by the low IGF-1 levels with normal weight gain and normal hypothalamic-pituitary imaging in the absence of evidence of any chronic disease. Excess cortisol secretion as a cause of the growth attenuation was also ruled out. In patients 1 and 2, the normal growth before institution of SSRI therapy and its resumption after the drug's discontinuation, with concomitant rise in their IGF-1 levels, suggest a causal relationship.

In contrast to the impaired somatotrophic axis in our patients, prolactin levels and other anterior pituitary functions were normal. Indeed, elevations in prolactin levels have been found in only a small percentage of SSRI users[4] and are apparently dose dependent.[3] Of note is the growth attenuation or arrest in 3 of our patients (cases 1-3) despite the normal progression of puberty and at a point when the growth spurt was expected. This finding is consistent with the study of Urban and Veldhuis[28] showing the normal pulsatile release of luteinizing hormone during 1 week of fluoxetine administration.

Delayed puberty might cause growth deceleration[15] and transient GH deficiency.[29] Among our 4 patients, only patient 4 had delayed puberty, with subnormal GH responses on 2 postpriming stimulation tests. According to our experience and that of others,[20,27] the probability of a false-positive response on 2 postpriming stimulation tests is very low.

We are not aware of any studies conducted to date on the incidence of growth attenuation in children treated with SSRIs. Our study, in 4 adolescents, suggests an isolated effect of SSRI therapy on growth and possibly GH secretion. Owing to their high efficacy and low adverse-effect profile, SSRI drugs have become increasingly popular in the treatment of various psychiatric disorders, and their use during childhood and adolescence is expected to increase.[11] Therefore, knowledge of their effect on growth and puberty is extremely important. As the large studies conducted in children and adolescents treated with SSRIs have not addressed growth, and our study includes only 4 patients, an individual variation in the effect of SSRIs on the somatotrophic axis cannot be ruled out. Larger studies are needed to investigate the effect of SSRIs on growth and GH secretion and the prevalence of disordered growth in treated children and adolescents. These findings may also raise awareness among psychiatrists and physicians in other fields who treat and follow up this patient subgroup.

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