

Successful treatment of a morbidly obese and growth-retarded adolescent with Williams-Beuren Syndrome by combining the medication of growth hormone and sibutramine

Bahadori B, Uitz E, Tonninger-Bahadori K, Moghadasian M H

ABSTRACT

A 16-year-old male adolescent diagnosed to have the Williams-Beuren syndrome was referred to our obesity outpatient clinic, due to his morbid obesity (body mass index 39.2 kilogrammes per square metre) and gluttony. After several unsuccessful dietary treatments, we started therapy with sibutramine. As growth hormone (GH) deficiency was diagnosed by an additional GH-stimulation test, we commenced with a GH-treatment. This well-tolerated combination therapy led to a remarkable weight loss of 10 kg and a growth-rate acceleration of 3.7 cm/year. Nine months after stopping the treatment with sibutramine, a partial weight gain was noticed. This case report justifies further research work on a combination therapy with sibutramine and GH for similar cases.

Keywords: growth hormone, growth retardation, Williams-Beuren syndrome, obesity, sibutramine

Singapore Med J 2008; 49(1): e15-e16

INTRODUCTION

We report a 16-year-old Caucasian male adolescent who was referred to our obesity outpatient clinic due to his morbid obesity. The molecular genetical analysis excluded a Prader-Willie syndrome and revealed the Williams-Beuren syndrome (WBS). Fluorescent *in situ* hybridisation [FISH] analysis indicated a deletion of the William-Beuren critical region, with karyotype as follows: 46,XY,ish del(7)(q11.23q11.23)(ELN-,LIMK1-,D7S613-), 7q31(D7S486/D7S522-x2).⁽¹⁾

CASE REPORT

At the time of the first examination the patient was morbidly obese with a body weight of 95 kg and a height of 155.7 cm (body mass index 39.2kg/m²). He had the typical symptoms of WBS, such as elfin face, partial deafness and a moderate valvular aortic stenosis.⁽²⁻⁴⁾ His intelligence quotient (IQ) was not evaluated, but mental retardation was evident. His parents reported of increasing gluttony during the last two years, leading to his obesity. According to his parents, he ate huge amounts of fast food and potato chips particularly in the evenings, and became quite aggressive when they refused to give him his favourite foods. Several dietary interventions had failed so far.

His parents were additionally concerned about his growth retardation. To be small in stature is one of the leading signs of WBS,⁽⁵⁾ but the account of this symptom is not known yet. Growth hormone deficiency (GHD) does not need to be the common reason for being small in stature. However, this does not rule out the possibility of GHD in a subpopulation of WBS.⁽⁶⁾ This treatable disorder of poor growth should be excluded in all cases. Therefore, our first hypothesis was to find out if a possible GHD was evident, and to treat it with growth hormones (GHs) if necessary. Additionally, there was the problem of gluttony, which to our knowledge, has never been described in patients with WBS so far. Interestingly, the extent of gluttony in this patient was quite similar to that of patients with Prader-Willi Syndrome. Sibutramine is an anti-obesity drug, which can significantly decrease the greed for food in adults⁽⁷⁾ and adolescents.⁽⁸⁾ Our second hypothesis was to treat this adolescent patient with sibutramine, since any other behavioural and nutritional modification intervention seemed to be impossible due to his mental retardation.

The patient underwent GH-stimulation test with hypoglycaemia and arginine infusion. GH deficiency was

Department of Internal Medicine,
State Hospital Muerzzuschlag,
Grazerstrasse 63-65,
8680 Muerzzuschlag,
Austria

Bahadori B, MD,
Senior Physician

Uitz E, MD,
Senior Physician

Department of General Surgery,
Division of Paediatric Surgery,
State Hospital Oberwart,
Dornburggasse 80,
7400 Oberwart,
Austria

Tonninger-Bahadori K,
MD,
Senior Physician

Department of Pathology and Human Nutrition,
University of Manitoba,
Winnipeg,
Manitoba R3T 2N2,
Canada

Moghadasian MH, MD,
PhD,
Assistant Professor

Correspondence to:
Dr Elisabeth Uitz
Tel: (11) 43 6642 342 973
Fax: (11) 43 316 948 930
Email: elisabeth.uitz@lkh-muerzzuschlag.at; elisabeth.uitz@chello.at

revealed. Treatment with human GH (Humatrope HGH 0.029 mg/kg daily) was started. Additionally, we commenced a treatment of 10 mg sibutramine daily. After nine months, the patient lost 10 kg and his growth rate accelerated. There was a growth of 2.6 cm in nine months (+0.27 standard deviation score [SDS], 60th percentile) (Table I). There was a significant decrease in fasting leptin level from baseline 144 ng/ml to 49.6 ng/ml (RIA, Linco Research Inc, St Louis, MO, USA). His parents reported a remarkable decrease of his food intake. There were spontaneous signs of puberty with testes volume of 4–5 ml and stage of puberty G3, PH3, according to the Tanner Scale.

After nine months of treatment, the medication with sibutramine was stopped, while HGH treatment was continued. At 12 months, there was a continuous growth, with the patient attaining a height of 159.4 cm. This meant a growth velocity of 3.7 cm/year. Given the growth velocity of this patient was extremely retarded up to the initiation of HGH treatment (Fig. 1), we assumed that the treatment was having an effect on his growth velocity. After completion of treatment with sibutramine, there was a weight gain of 6.5 kg, and we decided to continue to administer sibutramine

Table I: Changes of weight, height and BMI before, during and after treatment with sibutramine.

Treatment	Before	At	At
with sibutramine	treatment	9 months	12 months
weight (kg)	95.0	85.0	91.5
height (cm)	155.7	158.4	159.4
BMI (kg/m ²)	39.2	33.9	36.0

DISCUSSION

The very significant weight loss during the first nine months was probably due to a synergy between the GH treatment and sibutramine. It is known that patients receiving sibutramine lose weight and regain it partly after discontinuing their medication.⁽⁹⁾ So far, there has been little documented evidence of using sibutramine in adolescents and no evidence in patients with WBS. In this special case, the rapid initial weight loss was life saving, since according to paediatricians, the patient could have faced a life-threatening situation if he had not lost weight so fast. As far as growth retardation is concerned, the acceleration of growth rate was most probably due to the treatment with HGH, but it is also likely that the onset of puberty had an impact on his growth rate. This case report also indicates the necessity of GH measurements in every single case of a child with a congenital defect and growth retardation, even if the GHD is not common in this type of disease. Following this success, further research

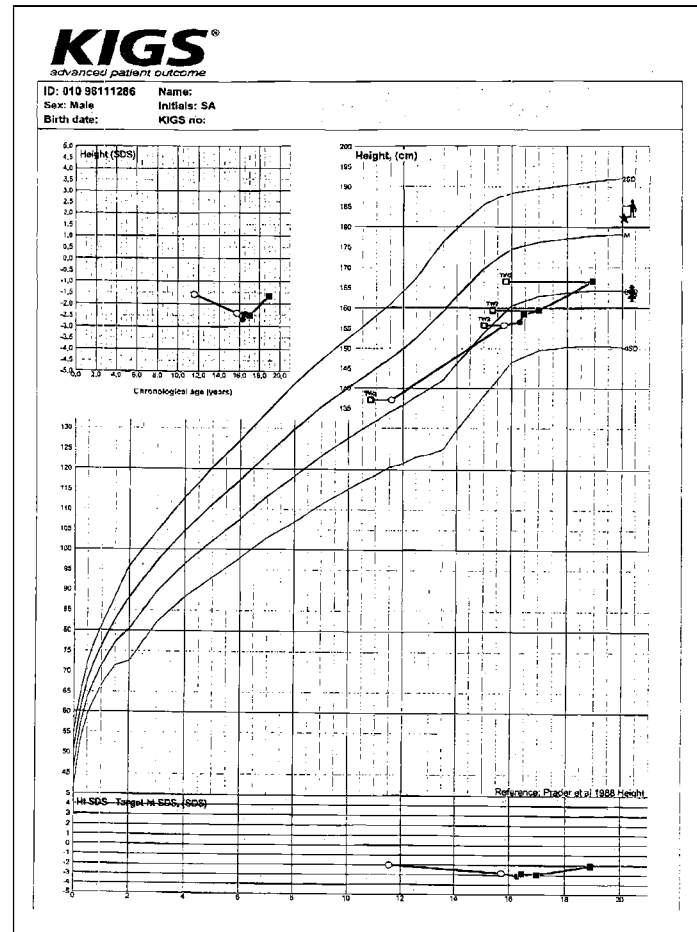


Fig. 1 Growth chart shows the effect of HGH treatment on the patient's height.

work (and eventually a case-controlled study) on a combination therapy with sibutramine and HGH for similar cases should be performed.

REFERENCES

- Hirota H, Matsuoka R, Kimura M, et al. Molecular cytogenetic diagnosis of Williams syndrome. *Am J Med Genet* 1996; 64:473-7.
- Williams JCP, Barratt-Boyes BG, Lowe JB. Supravalvular aortic stenosis. *Circulation* 1961; 24:1311-8.
- Beuren AJ, Apitz J, Harmanjanz D. Supravalvular aortic stenosis in association with mental retardation and certain facial appearance. *Circulation* 1962; 26:1235-40.
- Beuren AJ, Schulze C, Eberle P, Harmanjanz D, Apitz J. The syndrome of supravalvular aortic stenosis, peripheral pulmonary stenosis, mental retardation and similar facial appearance. *Am J Cardiol* 1964; 13:471-83.
- Kotzot D, Bernasconi F, Brecevic L, et al. Phenotype of the Williams-Beuren syndrome associated with hemizyosity at the elastin locus. *Eur J Pediatr* 1995; 154:477-82.
- Kuijpers GMC, De Vroede M, Knol HE, Jansen M. Growth hormone treatment in a child with Williams-Beuren syndrome: a case report. *Eur J Pediatr* 1999; 158:451-4.
- Bray GA, Blackburn GL, Ferguson JM, et al. Sibutramine produces dose-related weight loss. *Obes Res* 1999; 7:189-98.
- Godoy-Matos A, Carraro L, Vieira A, et al. Treatment of obese adolescents with sibutramine: A randomized, double-blind, controlled study. *J Clin Endocrinol Metab* 2005; 90:1460-5.
- James WP, Astrup A, Finer N, et al. Effect of sibutramine on weight maintenance after weight loss: a randomised trial. STORM Study Group. Sibutramine Trial of Obesity Reduction and Maintenance. *Lancet* 2000;356:2119-25.