Bloom Syndrome in Short Children Born Small for Gestational Age: A Challenging Diagnosis

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Background: GH treatment has become a frequently applied growth-promoting therapy in short children born small for gestational age (SGA). In some disorders GH treatment is contraindicated, eg, chromosomal breakage syndromes. Bloom syndrome is a rare chromosomal breakage syndrome characterized by severe pre- and postnatal growth deficiency, a photosensitive facial erythema, immunodeficiency, mental retardation or learning disabilities, endocrinopathies, and a predisposition to develop a wide variety of cancers.

Objective: We report 2 patients with Bloom syndrome illustrating the variety in clinical manifestations. They were initially diagnosed with short stature after SGA birth and Silver Russell syndrome and treated with GH.

Cases: Both patients presented with pre- and postnatal growth failure but no clear other characteristic features associated with Bloom syndrome. Photosensitive skin lesions developed only at a pubertal age and were minimal. Also, both children showed normal immunoglobulin levels, normal development, and no signs of endocrinopathies at start of GH. Dysmorphic features resembling Silver Russell syndrome were observed in both patients. Remarkably, during GH treatment IGF-1 levels increased to values greater than 3.5 SD score, with normal IGF binding protein-3 levels.

Conclusion: Short children born SGA comprise a heterogeneous group. Bloom syndrome should be tested for in children with consanguineous parents, dysmorphic features (particularly resembling Silver Russell syndrome), skin abnormalities, and/or IGF-1 levels greater than 2.5 SD score during standard GH treatment with normal IGF binding protein-3 levels. (*J Clin Endocrinol Metab* **98:** 3932–3938, 2013)

Small for gestational age (SGA) refers to size at birth and is defined as a birth weight and/or a birth length ≤ 2 SD scores (SDS) below the mean for gestational age (1). Children born SGA comprise a heterogeneous group with a broad spectrum of clinical characteristics. Approximately 10% of the children born SGA fail to show sufficient catch-up growth and remain short (2). Since GH treatment was licensed for short children born SGA, it has become a frequently applied growth promoting therapy (3).

The start of GH treatment in short SGA children should be preceded by a thorough diagnostic work-up to identify an underlying cause (1). The causes of pre- and postnatal growth restriction are numerous. Children with genetic disorders are often born SGA. In some specific disorders and syndromes, GH treatment is contraindicated, for example, in DNA repair disorders and the chromosomal breakage syndromes. The latter include Fanconi anemia, ataxia-telangiectasia, ataxia-telangiectasia-like

Abbreviations: IGFBP, IGF binding protein; SDS, SD score; SGA, small for gestational age.

syndrome, Werner syndrome, Nijmegen breakage syndrome, and Bloom syndrome. Because increasing numbers of short SGA children are treated with GH, there is an increasing risk of treating children with such a syndrome.

Bloom syndrome is a rare chromosomal breakage syndrome with fewer than 300 patients known to the Bloom's Syndrome Registry (4). It is characterized by severe pre- and postnatal growth deficiency, an erythematous and photosensitive facial rash, dysmorphic features such as microcephaly and malar hypoplasia, immunodeficiency, and a predisposition to develop a wide variety of malignancies at an early age (5–8). Diagnosing this syndrome is difficult because it is very rare and hallmark features may vary in severity.

We present 2 patients illustrating the variety in clinical manifestations and the difficulty to diagnose this syndrome. Also, we provide a new insight that can lead to diagnosing this syndrome in short SGA children treated with GH.

Patients

Clinical presentation

Patient 1

This girl was born spontaneously after 37 weeks of gestation as the first child of consanguineous Turkish parents. Pregnancy and delivery were uneventful. Her birth weight was 1760 g (−3.0 SDS), her birth length was unknown. During her first year, she exhibited poor appetite, feeding difficulties, and failure to thrive. After extensive investigations, no underlying cause was determined besides mild delayed development of oral and motor skills. She had a somewhat triangular face and patent ears, and Silver Russell syndrome was considered. However, in 1994 genetic testing was not available. Physical therapy was started, and during the next years her intake improved, but growth remained well below the −2.5 SDS (Figure 1).

At 5 years of age, she was referred to our clinic. Her height was 95.9 cm (−3.7 SDS), weight 11.4 kg (−3.2 SDS weight for height), sitting height to height ratio 0.58 (2.1 SDS), and head circumference 46.3 cm (−2.7 SDS). The height of her father was 169 cm (−0.9 SDS) and of her mother 162 cm (−0.2 SDS, based on Turkish reference data). Neurological, cardiovascular, respiratory, and abdominal examinations were all normal. Psychomotor development was now normal, and she went to a regular primary school. Overall blood examination showed no abnormalities. An arginine stimulation test was performed with a maximum GH response of 13.5 μg/L (35 mU/L). IGF-1 was 223 ng/mL (1.8 SDS) and IGF binding protein (IGFBP)-3 was 2.1 mg/L (0 SDS). Thyroid function was normal. Bone age was not delayed, and skeletal survey was normal. Genetic testing showed a normal karyotype (46, XX) and uniparental disomy 7 was not present. Because no underlying cause was found, she was diagnosed with short stature after SGA birth.

GH treatment was initiated at a dose of 1 mg/m²·day (0.033 mg/kg · d) (Figure 1). During treatment, serum IGF-1 levels in-

creased substantially and after 2 years, IGF-1 was 642 ng/mL (4.0 SDS). Because we suspected IGF-1 insensitivity, we sequenced the *IGF1R* gene, which in the end turned out to be normal. Over the years, IGF-1 fluctuated around 3 SDS, despite treatment with the standard dose of 1 mg/m² · day. IGFBP-3 levels remained well within the normal range. She was 9.2 years at the start of puberty with a height of 128 cm (−1.7 SDS). During treatment, overall blood examination and carbohydrate and lipid parameters were normal. At 10 years of age, she was included in a study to identify genetic variations in children with short stature in relation to their phenotype. Her mild dysmorphic features had become less subtle over the years and showed a long, narrow, and somewhat triangular face, broad nasal bridge, full lips, micrognathia, low-set ears, a low implanted first digit, and mild clinodactyly (Figure 2). However, some of these features were also present in her parents.

At 11 years of age, she developed a mild photosensitive facial rash (Figure 3). After extensive testing by several dermatologists, including skin biopsies, and a rheumatologist, she was diagnosed with cutaneous lupus erythematosus. She was 13-years-old when TSH levels increased to 9.7 mU/L, free T_4 was normal (14.4 pmol/L [112 pg/dL]), antithyroperoxidase antibodies and antithyroglobulin antibodies were negative, and anti-TSH receptor antibodies were normal. She went to a regular secondary school. At 14.8 years of age, she presented with difficulty swallowing, a cough, and weight loss. A chest X-ray film showed a mediastinal mass, a B cell non-Hodgkin lymphoma. Fanconi anemia was considered, and although chromosomal breakage was increased, it was not the type found in Fanconi patients. Subsequent analysis showed an increased sister chromatid exchange, confirming the diagnosis of Bloom syndrome. DNA testing showed a homozygous mutation in the *BLM* gene c.2643G>A (p.Thr881X). GH treatment was discontinued, and because of Bloom syndrome, she was treated with a modified chemotherapy regimen (without cyclophosphamide and adriamycin). She did respond to chemotherapy, but at 16 years of age, she died due to a sepsis.

Patient 2

Patient 2 is a boy, born as the first child of consanguineous Dutch parents. Intrauterine growth retardation was observed during the third trimester. At 33 weeks, a cesarean section was performed due to fetal stress. His birth weight was 1025 g (−3.6 SDS); the birth length was unknown. Cranial ultrasound showed multiple small hemorrhages, and eye examination showed chorioretinitis caused by a perinatal toxoplasmosis infection. He was treated with antibiotics for 1 year. During his first year, he exhibited poor appetite and gastroesophageal reflux, and his height remained at the −4.0 SDS (Figure 1). The height of his father was 185 cm (0.2 SDS) and of his mother 168 cm (−0.4 SDS). He had frequent mild upper airway infections and a dry eczematous skin; both were attributed to an atopic constitution.

At 4 years of age, he was referred to our clinic. His height was 91.4 cm (−4.5 SDS), weight 10.3 kg (−3.6 SDS weight for height), sitting height to height ratio 0.56 (0.9 SDS), and head circumference 45.9 cm (−3.2 SDS). Neurological, cardiovascular, respiratory, and abdominal examinations were all normal. Psychomotor development was normal, and he went to a regular primary school. Overall blood examination showed no abnormalities. An arginine stimulation test was performed with a maximum GH response of 21.5 μg/L (56 mU/L). His IGF-1 was 65 ng/mL (−0.5 SDS) and IGFBP-3 was 1.3 mg/L (−1.2 SDS). Thy-
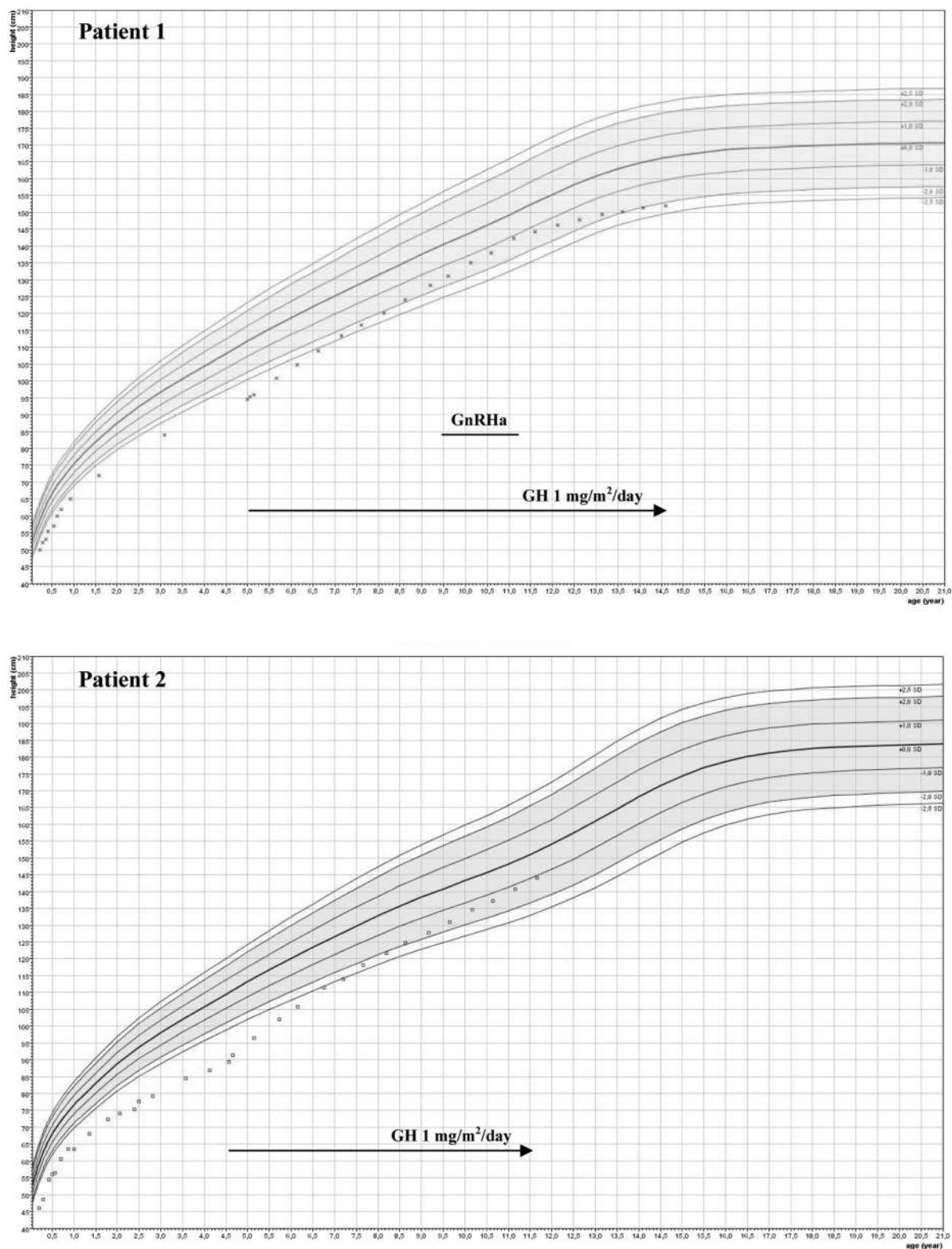
Figure 1. Growth charts of the 2 children with Bloom syndrome. In patient 1, puberty was postponed for 2 years using a GnRHa. GnRHa, gonadotropin releasing hormone analog. Growth chart is according to Growth Analyzer 4.0.

roid function was normal. IgA was 0.2 g/L (normal 0.1–1.0 g/L), IgG 6.4 g/L (normal 3.3–11.6 g/L), and IgM 0.5 g/L (normal 0.4–1.7 g/L). His bone age was 1 year behind. After examination by several clinical geneticists, he was diagnosed with Silver Russell syndrome, although DNA testing could not confirm unipa-

rental disomy 7. Genetic testing showed a normal karyotype (46, XY) and Nijmegen breakage syndrome was not present.

At age 4 years, GH treatment was initiated at a dose of 1 mg/m$^2 \cdot$ day (0.033 mg/kg $\cdot$ d) (Figure 1). During treatment, serum IGF-1 levels increased substantially and after 4 years,

Patient 1

Patient 2

Figure 2. Physical characteristics of patient 1 at 10 years of age and patient 2 at 4 years of age.

IGF-1 was 510 ng/mL (3.2 SDS). We suspected IGF-1 insensitivity, but genetic testing of the *IGF1R* gene showed no abnormalities. The GH dose was reduced to 0.7 mg/ m² · day (0.023 mg/kg · d), but IGF-1 levels remained around 3 SDS. IGFBP-3 levels were well within the normal range, and overall blood examination, carbohydrate, and lipid parameters were normal. Over the years, his dysmorphic features became more prominent (Figures 2 and 3). At the age of 7 years, he was reexamined by a clinical geneticist, who reported hypertelorism, mild down slant, a somewhat pointed nose with a wide base, full lips, clinodactyly of the hand and feet, and an eczematous skin.

At 9 years of age, he developed a photosensitive facial rash (Figure 3). He was referred to a dermatologist, who diagnosed him with hemorrhagic polymorphous light eruption. We also referred him to a geneticist for testing of Bloom syndrome. This was confirmed, based on a homozygous mutation in the *BLM* gene (c.1933C>T [p.Gln645X]). GH treatment was discontinued, and he is now screened regularly. Two years after the diagnosis, he is doing well. Despite low immunoglobulin levels, serious infections have not yet occurred.

Discussion

GH treatment has become a frequently applied growth-promoting therapy in short children born SGA (3). These children comprise a heterogeneous group, and before GH treatment is started, an extensive diagnostic work-up should be performed to find an underlying cause (1). GH treatment is contraindicated in several disorders, such as the chromosomal breakage syndromes. However, diagnosing these syndromes can be challenging as illustrated by the 2 patients described here.

Bloom syndrome is one of the chromosomal breakage syndromes and was first described in 1954 (5). It is caused by a mutation in the *BLM* gene that encodes a protein called BLM and is a member of the RecQ helicase family (9). The function of BLM is to maintain genomic stability during DNA replication and repair, and without this protein the number of chromatid exchanges is greatly increased (9, 10). Bloom syndrome is confirmed by finding excessive numbers of sister chromatid exchanges or pathogenic mutations in the *BLM* gene. This gene is located on chromosome 15 (band 15q26.1) (11). Up until now, approximately 70 mutations in around 300 patients have been described (Mendelian Inheritance in Man 210900) (12, 13).

Hallmark features of Bloom syndrome are pre- and postnatal growth failure, photosensitive erythematous skin lesions, and a predisposition to develop a wide variety of cancers at an early age (5, 7, 8). The skin lesions usually develop on the nose and cheeks during the first 2 years of life (5, 7). Other features frequently described are feeding difficulties, immunodeficiency, mental retardation or learning disabilities, and endocrinopathies such as glucose intolerance and abnormal thyroid function (Table 1) (7, 14–16). However, these features can vary considerably and can be subtle as illustrated in both our patients. In the 2 patients reported here, skin lesions developed only at an older, pubertal age and were minimal, particularly in the girl in whom they resembled cutaneous lupus erythematosus (17). Also, at start of GH treatment, both children showed a normal appetite, normal immunoglobulin levels, normal development, and no signs of endocrinopathies.

Dysmorphological features often described in Bloom syndrome are a small head circumference, a long and somewhat narrow face, malar hypoplasia, nasal prominence, micrognathia, and low-set ears (4, 7). Both our patients had full lips. Although not officially described, this is frequently seen in case reports of patients with

Figure 3. Facial erythema in patient 1 at 13 years of age and patient 2 at 11 years of age. Both patients developed a sun-sensitive facial erythema at an older age.

Bloom syndrome (6, 7, 18–20). In both our patients, dysmorphic features developed with age: from very subtle at a young age to slowly becoming more apparent. Particularly at a young age, there were striking similarities with

Table 1. Overview of Characteristics of Bloom Syndrome in Children

	Bloom Syndrome	**Index Patients at Start of GH**
Clinical parameters	Birth weight << −2 SDS	2/2
	Birth length << −2 SDS	2/2
	Height << −2 SDS	2/2
	Sun sensitive skin lesions	0/2
	Feeding difficulties	2/2
	Gastroesophageal reflux	1/2
	Frequent (upper) airway infections	1/2
Laboratory parameters	Immunodeficiency	0/2
	Hypothyroidism	0/2
	Insulin resistance	0/2
Dysmorphic facial features	Long and narrow face	1/2
	Triangular face	2/2
	Ophthalmological abnormalities	1/2
	Hypertelorism	1/2
	Nasal prominence, broad nasal bridge	2/2
	Micrognathia	1/2
	Malar hypoplasia	0/2
	Protuberant ears	Low-set ears Full lips
Other dysmorphic features	Clinodactyly	2/2
	Short stubby fingers	0/2
	Café au lait spots	0/2
Central nervous system	Microcephaly	2/2
	Mental retardation	0/2
	Learning disabilities	0/2
	Speech delay	0/2

Silver Russell syndrome, and in both patients this syndrome was first suspected. However, because most patients with Silver Russell syndrome have a normal head circumference, this may help to differentiate between these diagnoses.

Since an extensive diagnostic work-up showed no clear abnormalities, one patient was diagnosed with short stature after SGA birth and one with Silver Russell syndrome. Both started GH treatment with a standard dose and responded, increasing their height by 0.7 and 1.1 SDS, respectively, resulting in a height of approximately −1 SDS in the following years. Their first year growth response was comparable with that of other short SGA children ($\sim$ 0.8 SDS) (21). During GH treatment, serum IGF-1 increased to levels well above the normal range in both patients, whereas the IGFBP-3 levels remained within the normal range. We suspected IGF-1 insensitivity and therefore investigated the *IGF1R* gene, but in the end no mutations were found. To our knowledge, high IGF-1 levels during standard or low-dose GH treatment has not been described in children with Bloom syndrome. Our data show that this phenomenon can be an indication for diagnosing Bloom syndrome in short SGA children treated with GH.

In retrospect, we regret that we did not lower the GH dose in patient 1 as was done in patient 2. However, this girl started GH treatment in 1998, when IGF-1 insensitivity was suspected to cause or contribute to the persistent short stature in short SGA children. At that time, treatment with a higher GH dose was advised to stimulate IGF-1 production to overcome IGF-1 resistance in short SGA children (22–24). High IGF-1 levels are not unusual in short SGA children treated with GH (21). Fall et al (25) also showed that children with a low birth weight developed higher IGF-1 levels than expected for their height and weight and that these relatively high IGF-1 concentrations may reflect a degree of IGF resistance. Short SGA subjects with subnormal IGF-1 levels during GH therapy show slower growth, whereas IGF-1 levels close to +2 SDS support catch-up growth (22). When the IGF-1 levels in patient 1 became high despite a standard GH dose of 1 mg/m^2 · day, we suspected severe IGF-1 insensitivity, and for that reason we sequenced the *IGF1R* gene. A decade ago, such genetic analyses took considerable time. At the end, no *IGF1R* mutation or deletion was found. With the present knowledge, we advise to lower the GH dose or even stop
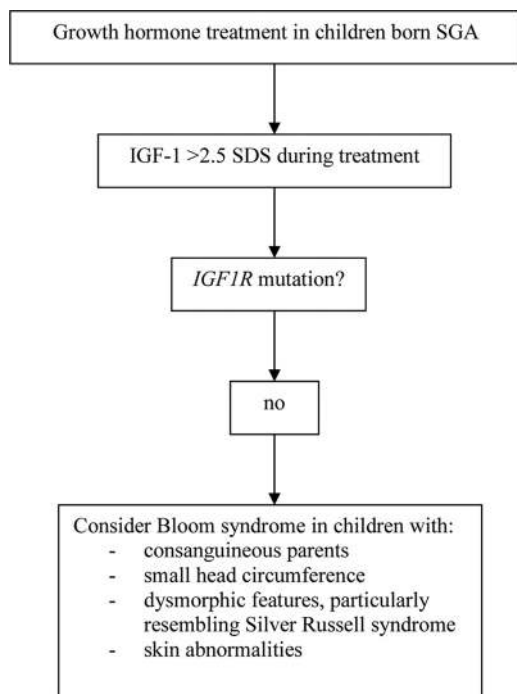
Figure 4. Flow chart increased IGF-1 levels during GH treatment.

GH treatment when a short SGA child has recurrent IGF-1 levels greater than 2.5 SDS and no *IGF1R* mutation or deletion, awaiting the results of testing for Bloom syndrome.

Based on our data, one might consider to exclude Bloom syndrome in very short SGA children with consanguineous parents, microcephaly, and dysmorphic features (particularly resembling Silver Russell syndrome) before starting GH treatment (Table 1). During GH treatment, increased IGF-1 levels might also be suggestive for Bloom syndrome (Figure 4).

IGF-1 has mitogenic and antiapoptotic properties, so in theory GH treatment might affect cancer risk (26). The role of GH in cancer development is not clear. However, epidemiological studies have not demonstrated a significantly increased risk in GH-treated patients, with or without a history of cancer (27, 28). Currently available data do not indicate any increase in cancer risk during or after GH treatment, and at this point, we do not believe that GH is causative in the development of cancer in patient 1. Nonetheless, GH treatment is contraindicated in children with Bloom syndrome because many patients develop cancer at a young age. If cancer is present, GH may stimulate malignant cell growth (29).

Management of patients with Bloom syndrome consists of surveillance and treatment of complications. One complication in patients with Bloom syndrome is diabetes mellitus type 2 (19). There is a high frequency of impaired glucose tolerance and insulin resistance in children, and approximately 15% of patients develop diabetes mellitus

(4, 14). In the 2 patients described here, there were no signs of an altered carbohydrate or lipid metabolism before or during GH treatment. The most frequent long-term complication is cancer, with a mean age at diagnosis of 26 years (range < 1 to 49 years) (8). There is a wide variation in sites and types of malignancies, but patients younger than 20 years are prone to develop leukemia or lymphomas and patients older than 20 years are more prone to develop carcinomas, particularly gastrointestinal and skin carcinomas (8). Patients with Bloom syndrome often develop more than one primary malignancy (8).

There is very little evidence regarding an appropriate screening regimen in children. Yearly evaluation of glucose metabolism, thyroid function, and immunoglobulins has been suggested in addition to a regular hematological examination (14, 19). However, whether early diagnosis of, for example, leukemia improves prognosis is unknown, and frequent examination might also increase the risk of psychological morbidity (8, 19).

In conclusion, we present 2 patients with Bloom syndrome who were initially diagnosed with short stature after SGA birth and Silver Russell syndrome and started on GH treatment. Based on our data, we suggest that very short SGA children with consanguineous parents, a small head circumference, dysmorphological features (particularly resembling Silver Russell syndrome), skin abnormalities, and/or IGF-1 levels greater than 2.5 SDS during standard GH treatment with normal IGFBP-3 levels are tested for Bloom syndrome.

Acknowledgments

References

1. Clayton PE, Cianfarani S, Czernichow P, Johannsson G, Rapaport R, Rogol A. Management of the child born small for gestational age through to adulthood: a consensus statement of the International Societies of Pediatric Endocrinology and the Growth Hormone Research Society. *J Clin Endocrinol Metab*. 2007;92:804–810.
2. Hokken-Koelega AC, De Ridder MA, Lemmen RJ, Den Hartog H, De Muinck Keizer-Schrama SM, Drop SL. Children born small for gestational age: do they catch up? *Pediatr Res*. 1995;38:267–271.
3. Van Pareren Y, Mulder P, Houdijk M, Jansen M, Reeser M, Hokken-Koelega A. Adult height after long-term, continuous growth hormone (GH) treatment in short children born small for gestational age: results of a randomized, double-blind, dose-response GH trial. *J Clin Endocrinol Metab*. 2003;88:3584–3590.

4. **Registry BS.** Bloom Syndrome Registry. New York: Weill Cornell Medical College.

5. **Bloom D.** Congenital telangiectatic erythema resembling lupus erythematosus in dwarfs; probably a syndrome entity. *AMA Am J Dis Child*. 1954;88:754–758.

6. **Bloom D.** The syndrome of congenital telangiectatic erythema and stunted growth. *J Pediatr*. 1966;68:103–113.

7. **German J.** Bloom's syndrome. I. Genetical and clinical observations in the first twenty-seven patients. *Am J Hum Genet*. 1969;21:196–227.

8. **German J.** Bloom's syndrome. XX. The first 100 cancers. *Cancer Genet Cytogenet*. 1997;93:100–106.

9. **Ellis NA, Groden J, Ye TZ, et al.** The Bloom's syndrome gene product is homologous to RecQ helicases. *Cell*. 1995;83:655–666.

10. **Monnat RJ Jr.** Human RECQ helicases: roles in DNA metabolism, mutagenesis and cancer biology. *Semin Cancer Biol*. 2010;20:329–339.

11. **German J, Roe AM, Leppert MF, Ellis NA.** Bloom syndrome: an analysis of consanguineous families assigns the locus mutated to chromosome band 15q26.1. *Proc Natl Acad Sci USA*. 1994;91:6669–6673.

12. **German J, Sanz MM, Ciocci S, Ye TZ, Ellis NA.** Syndrome-causing mutations of the BLM gene in persons in the Bloom's Syndrome Registry. *Hum Mutat*. 2007;28:743–753.

13. **Amor-Gueret M, Dubois-d'Enghien C, Lauge A, et al.** Three new BLM gene mutations associated with Bloom syndrome. *Genet Test*. 2008;12:257–261.

14. **Diaz A, Vogiatzi MG, Sanz MM, German J.** Evaluation of short stature, carbohydrate metabolism and other endocrinopathies in Bloom's syndrome. *Horm Res*. 2006;66:111–117.

15. **Ahmad U, Fisher ER, Danowski TS, Nolan S, Stephan T.** Endocrine abnormalities and myopathy in Bloom's syndrome. *J Med Genet*. 1977;14:418–421.

16. **Van Kerckhove CW, Ceuppens JL, Vanderschueren-Lodeweyckx M, Eggermont E, Vertessen S, Stevens EA.** Bloom's syndrome. Clinical features and immunologic abnormalities of four patients. *Am J Dis Child*. 1988;142:1089–1093.

17. **McGowan J, Maize J, Cook J.** Lupus-like histopathology in bloom syndrome: reexamining the clinical and histologic implications of photosensitivity. *Am J Dermatopathol*. 2009;31:786–791.

18. **Bhisitkul RB, Rizen M.** Bloom syndrome: multiple retinopathies in a chromosome breakage disorder. *Br J Ophthalmol*. 2004;88:354–357.

19. **Thomas ER, Shanley S, Walker L, Eeles R.** Surveillance and treatment of malignancy in Bloom syndrome. *Clin Oncol (R Coll Radiol)*. 2008;20:375–379.

20. **Vanderschueren-Lodeweyckx M, Fryns JP, Van den Berghe H, Eggermont E, Eeckels R.** Bloom's syndrome. Possible pitfalls in clinical diagnosis. *Am J Dis Child*. 1984;138:812–816.

21. **Sas T, de Waal W, Mulder P, et al.** Growth hormone treatment in children with short stature born small for gestational age: 5-year results of a randomized, double-blind, dose-response trial. *J Clin Endocrinol Metab*. 1999;84:3064–3070.

22. **Ali O, Cohen P.** Insulin-like growth factors and their binding proteins in children born small for gestational age: implication for growth hormone therapy. *Horm Res*. 2003;60(suppl 3):115–123.

23. **de Zegher F, Francois I, van Helvoirt M, Beckers D, Ibanez L, Chatelain P.** Growth hormone treatment of short children born small for gestational age. *Trends Endocrinol Metab*. 1998;9:233–237.

24. **de Zegher F, Maes M, Gargosky SE, et al.** High-dose growth hormone treatment of short children born small for gestational age. *J Clin Endocrinol Metab*. 1996;81:1887–1892.

25. **Fall CH, Pandit AN, Law CM, et al.** Size at birth and plasma insulin-like growth factor-1 concentrations. *Arch Dis Child*. 1995;73:287–293.

26. **Grimberg A, Cohen P.** Role of insulin-like growth factors and their binding proteins in growth control and carcinogenesis. *J Cell Physiol*. 2000;183:1–9.

27. **Bogarin R, Steinbok P.** Growth hormone treatment and risk of recurrence or progression of brain tumors in children: a review. *Childs Nerv Syst*. 2009;25:273–279.

28. **Ergun-Longmire B, Mertens AC, Mitby P, et al.** Growth hormone treatment and risk of second neoplasms in the childhood cancer survivor. *J Clin Endocrinol Metab*. 2006;91:3494–3498.

29. **Brock PR, de Zegher F, Casteels-Van Daele M, Vanderschueren-Lodeweyckx M.** Malignant disease in Bloom's syndrome children treated with growth hormone. *Lancet*. 1991;337:1345–1346.