Hypogonadotropic Hypogonadism in Males with Glycogen Storage Disease Type 1

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Abstract *Background:* Glycogen storage disease type 1 is an autosomal recessive disorder with an incidence of 1 in 100,000. Long-term complications include chronic blood glucose lability, lactic acidemia, short stature, osteoporosis, delayed puberty, gout, progressive renal insufficiency, systemic or pulmonary hypertension, hepatic adenomas at risk for malignant transformation, anemia, vitamin D deficiency, hyperuricemic nephrocalcinosis, inflammatory bowel syndrome (type 1b), hypertriglyceridemia, and irregular menstrual cycles. We describe hypogonadotropic hypogonadism as a novel complication in glycogen storage disease (GSD) type 1.

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Case Studies and Methods: Four unrelated patients with GSD 1a ($N = 1$) and 1b ($N = 3$) were found to have hypogonadotropic hypogonadism diagnosed at different ages. Institutional Research Ethics Board approval was obtained as appropriate. Participant consent was obtained. A retrospective chart review was performed and clinical symptoms and results of investigations summarized as a case series.

Results: All patients were confirmed biochemically to have low luteinizing hormone (LH) and follicular stimulating hormone (FSH), and correspondingly low total testosterone. Clinical symptoms of hypogonadism varied widely. Investigations for other causes of hypogonadotropic hypogonadism were unremarkable. In addition, all patients were found to have disproportionately low bone mineral density at the lumbar spine compared to the hip. Common to all patients was erratic metabolic control, including recurrent hypoglycemia and elevated lactate levels.

Discussion: Recurrent elevations in cortisol in response to hypoglycemia may be the underlying pathology leading to suppression of gonadotropin-releasing hormone (GnRH) release. Incorporating clinical and/or biochemical screening of the hypothalamic–pituitary–gonadal axis may be important in the management of this disease. Testosterone therapy however needs to be carefully considered because of the risk of hepatic adenomas.

Introduction

Glycogen storage disease type 1 (GSD1) is a rare autosomal recessive disorder (Bali et al. 2013) classified into two major subtypes: 1a caused by deficiency in glucose-6-phosphatase

activity and 1b caused by a defect in glucose-6-phosphate (G6P) translocase. These defects result in decreased conversion of G6P to glucose, leading to hypoglycemia, lactic acidemia, organomegaly, and dyslipidemia. Long-term complications include short stature, osteoporosis, delayed puberty, gout, progressive renal insufficiency, systemic or pulmonary hypertension, hepatic adenomas at risk for malignant transformation, anemia, vitamin D deficiency, hyperuricemic nephrocalcinosis, and irregular menstruation (Bali et al. 2013). Patients with GSD1b may develop neutropenia, inflammatory bowel disease, and autoimmune thyroid disease (Bali et al. 2013).

Case 1

A 46-year-old male with a diagnosis of GSD1a prior to age 5 had a history of recurrent hypoglycemia and hyperlactatemia with hypoglycemic unawareness and poor metabolic control which was thought to be related in part to noncompliance with dietary recommendations including duration of fasting.

His clinical course was complicated by biopsy-proven hepatic adenomas, first diagnosed at age 23, measuring 2.5 and 2.8 cm with slow progressive growth. Most recently at age 45, CT imaging showed a 2.3 cm and several sub-centimeter lesions consistent with adenomas which were unchanged for 4–5 years.

His first bone mineral density (BMD) at age 29 showed low BMD at the lumbar spine (LS) (Z-score -3.54 , BMD 0.73 g/cm^2) relative to hip (Z-score -0.97 , BMD 0.89 g/cm^2). With this disproportionate pattern in bone loss, hypogonadism

was considered. Investigations revealed low-normal total testosterone at 12.1 nmol/L ($10\text{--}30$) with normal LH 3 IU/L (<10.0) and FSH 3.4 IU/L (<10.0). The patient denied erectile dysfunction and declined testosterone supplement at this point.

Repeat BMD at age 31 was unchanged but because his bone mass placed him at moderate to high risk of fracture, etidronate was discussed and started at age 32. After 1 year of etidronate, LS BMD increased (0.964 g/cm^2 , Z-score -2.3), and hip BMD was unchanged (0.912 g/cm^2 , Z-score -1.1). He continued etidronate and repeat BMD every 3–4 years was stable. Most recently at age 45, L1–L4 BMD was 0.992 g/cm^2 , Z-score -2.0 , and hip BMD was 0.941 g/cm^2 , Z-score -1.1 . The disproportionate pattern in bone density is still present.

Around age 43, he developed erectile dysfunction but declined testosterone therapy. Repeat investigations showed gradual testosterone decrease: at age 43, 44 and 45, total testosterone was 7.6 , 5.3 and 5.1 nmol/L , respectively, with inappropriately normal FSH and LH (Table 1). Pituitary MRI at age 44 was normal and evaluation of his other pituitary hormones revealed no other deficiencies (Table 1). Ferritin and iron saturation were normal. Hemoglobin was low at 123 g/L ($131\text{--}169$) with an mean corpuscular volume (MCV) of 88 fL ($80\text{--}95$).

Case 2

An 18-year-old male was diagnosed with GSD1b at 3 weeks of age. He had erratic metabolic control, with recurrent

Table 1 Laboratory results

Test	Case 1	Case 2		Case 3	Case 4	Normal
		Age 12	Age 18			
Total testosterone	3.4	1.6	4.4	5.0	2.1	$8.4\text{--}28.8 \text{ nmol/L}$
FSH	4.0	2.7	6.6	4.4	2.4	$<10.0 \text{ IU/L}$
LH	7.0	0.3	7.8	6.1	0.7	$<10.0 \text{ IU/L}$
AM cortisol	700	527	636	–	252	$>500 \text{ nmol/L}$
Cortisol post-ACTH stimulation	–	–	–	–	637	$>500\text{--}550 \text{ nmol/L}$
Prolactin	17.0	10.3	10.3	6.1	–	$4.0\text{--}15.0 \text{ } \mu\text{g/L}$
TSH	2.0	1.74	1.72	2.1	–	$0.30\text{--}5.50 \text{ mU/L}$
Free T4	12.0	9.6	12.0	11.9	12.0	$11\text{--}22 \text{ pmol/L}$
Ferritin	134	171	171	134	58	$15\text{--}300 \text{ } \mu\text{g/L}$
IGF-1	–	4.3 nmol/L (N $24\text{--}68$)	–	–	$14 \text{ } \mu\text{g/L}$ (N $82\text{--}807$)	–
GH post-stimulation	–	$6.6 \text{ } \mu\text{g/L}$ (N >5.6)	–	–	$13.0 \text{ } \mu\text{g/L}$ (N >8)	–
Iron saturation	0.29	–	–	0.29	–	$0.20\text{--}0.55$

N normal; AM morning; ACTH Adrenocorticotrophic hormone

hypoglycemic symptoms, including a hypoglycemic seizure. He is currently managed with Glycosade[®] at night but compliance with other recommended aspects of dietary therapy and home blood glucose monitoring is incomplete and he has symptoms suggestive of hypoglycemia, which respond to eating, and persistent hyperlactatemia.

At age 12 years, growth hormone (GH) stimulation test with arginine and clonidine was normal although his IGF-1 was low for his age. LH, FSH, and testosterone were consistent with his pre-pubertal clinical status (Table 1). Other pituitary hormones were normal. At age 12 years 11 months, growth velocity was 4.2 cm/year but by 13 years and 6 months, fell to 1.7 cm/year. He did undergo spontaneous puberty and by age 13 years 11 months was noted to be Tanner stage 3 pubic hair and stage 2 genitalia, with a growth velocity of 7.0 cm/year. However, at age 14 years and 6 months, growth velocity decreased to 0.6 cm/year and pubertal progression was stalled so GH therapy was initiated given his low IGF-1 with improvement in linear growth (9.5 cm/year) and pubertal progression to Tanner stage 5 by age 17. Of note, he did have a longstanding history of low bone mass. At age 9, L1–L4 BMD was 0.475 g/cm² (Z-score −1.7) and total body less head (TBLH) BMD 0.745 g/cm² (Z-score −1.0). He suffered a T8 compression fracture at age 7 and had received IV pamidronate between age 9 and 14. At age 11, BMD at all sites was >−2.0. At the conclusion of his linear growth, L1–L4 BMD was 0.844 g/cm² (Z-score −1.5), TBLH BMD 1.130 g/cm² (Z-score −0.9), and TH BMD was 1.130 g/cm² (Z-score +0.2). GH was discontinued at age 18 years, as his growth rate had plateaued for 3 years. Most recently at age 17 LS BMD was 0.844 g/cm² (Z-score −1.5) and TH BMD 1.130 g/cm² (Z-score 0.2).

At age 18, biochemical testing confirmed hypogonadotropic hypogonadism; other pituitary hormones and ferritin were normal (Table 1). Hemoglobin was low at 87 g/(MCV of 81 fL). MRI revealed a normal pituitary gland. At age 19, testosterone cypionate was started at 50 mg IM every 2 weeks IM with improvement in energy. A hepatic lesion was first seen at age 15 on CT, measuring 1.4 × 1.5 × 1.7 cm but not seen on follow-up MRI at age 18.

Case 3

A 24-year-old male diagnosed with GSD1b in infancy had a history of recurrent hypoglycemia and inflammatory bowel disease (presumed to be GSD1b-related), requiring recurrent hospitalization. His current GSD management includes nocturnal elemental feeds. He is known to have multiple hepatic adenomas stable on serial imaging. At age 19, a 6 mm hypodensity, and a 2.1 × 2.1 cm focus were seen by CT. MRI at age 23 showed multiple liver lesions with the largest measuring 2.4 × 1.6 cm, a second lesion of

1.2 cm, and at least 7 subcentimeter lesions, consistent with adenomas which were unchanged at follow-up imaging 1 year later.

BMD at age 23 showed low bone mass, with lower BMD at the lumbar spine (L1–L4 BMD 0.748 g/cm², Z-score −2.8) relative to hip (BMD 0.739 g/cm², Z-score −2.1). In addition, he had short stature, measuring 151 cm (<1st percentile), decreased body and facial hair, and he reported low energy. At the same time, investigations revealed a low total testosterone and inappropriately normal FSH and LH. Prolactin, TSH, ferritin, and iron saturation were normal (Table 1). Testosterone cypionate therapy was initiated at 100 mg IM every 2 weeks with improvement in energy and well-being.

Case 4

A 30-year-old male with GSD1b diagnosed in infancy has had a history of erratic metabolic control with persistent hyperlactatemia. He is currently managed with frequent meals. Over the course of his life, his GSD has been complicated by unilateral renomegaly (stable over time), hepatomegaly, and hepatic adenomas.

When he was investigated at the age of 12 years for poor growth, IGF-1 and IGF-binding protein 3 (IGF-BP3) were low, but GH stimulation testing was appropriate. LH and FSH were low with correspondingly low total testosterone, at pre-pubertal levels. ACTH stimulation test was adequate and free T4 was normal (Table 1). Ferritin was normal, with a hemoglobin 114 (130–170 g/L) with an MCV of 94.7 fL (80–100).

Ongoing monitoring for clinical signs of puberty continued until age 16 and 17, but he remained pre-pubertal so at 17 years, testosterone was initiated with testosterone cypionate 50 mg monthly. After 1 year, height velocity was 10 cm/year with progression of puberty (Tanner stage 3 pubic hair and genitalia, coarsening facial hair). Testosterone was increased by 50 mg every year to 200 mg monthly and he reached Tanner stage 5 at age 22. Liver enzymes remained stable. Hepatic imaging at age 27 and 28 showed multiple focal lesions which remained stable in size in both lobes of liver (measuring 2.1 × 1.5 cm, and 1.3 × 0.9 cm, and several subcentimeter lesions), consistent with adenomas.

Low bone mass was also noted. At age 19, he had a low LS BMD (LS 0.39 g/cm², Z-score −4.1) and TBLH (0.761 g/cm², Z-score −3.4, 71st percentile). At age 21 he had a disproportionately low LS BMD at 0.845 g/cm² (Z-score −3.3), in comparison to his TH BMD of 0.856 g/cm² (Z-score −1.8). Over the years, this gap closed with his most recent LS BMD at LS 0.945 g/cm² (Z-score −2.3) and TH BMD 0.789 g/cm² (Z-score −2.3) at age 27.

Discussion

We present four patients with suboptimal metabolic control of GSD and hypogonadotropic hypogonadism. Within minutes of onset of hypoglycemia, there is a decrease in insulin secretion and an increase in glucagon and epinephrine secretion in a homeostatic effort to increase serum glucose levels by promoting delivery of substrates to the liver for gluconeogenesis, increasing hepatic glycogenolysis, and inhibiting peripheral utilization of glucose. Following this immediate response, cortisol and growth hormone are secreted to further promote gluconeogenesis and reduce rates of glucose utilization (Santiago et al. 1980).

Cortisol is known to suppress both the GH/IGF-1 axis and the hypothalamic–pituitary–gonadal axis (Gaillard and Wehrenberg 1996). Specifically in GSD1, poor linear growth has been documented caused by GH deficiency which improves with GH therapy. This abnormality may be related to the counterregulatory response, specifically recurrent surges in cortisol, in response to hypoglycemia (Noto et al. 2003; Wolfsdorf et al. 1999; Dunger et al. 1982). In untreated GSD1 patients, serum cortisol levels are elevated, up to 810 nmol/L, and subsequently decrease with a glucose load (Dunger et al. 1982). It is known that hypercortisolemia can lead to hypogonadism. Patients with Cushing syndrome have decreased LH and FSH levels (Luton et al. 1977) and even short-term hydrocortisone therapy in normally menstruating women results in suppression of gonadotropin levels (Saketos et al. 1993).

These physiological processes provide a basis for our hypothesis that recurrent hypoglycemia in GSD1 patients could potentially contribute to hypogonadotropic hypogonadism. In GSD1 patients with suboptimal metabolic control, hypogonadism may be secondary to chronic recurrent elevations of cortisol in response to hypoglycemia, with resulting suppression of GnRH, LH, and FSH release (Gore et al. 2006; Breen and Karsch 2006).

Clinical symptoms of hypogonadism in males include delayed puberty, decreased libido and spontaneous erections, gynecomastia, small testes, infertility, hot flushes, and low BMD (Bhasin et al. 2010).

As seen in our patients, hypogonadism leads to a preferential loss of trabecular bone. Two types of bone exist: cortical and trabecular. Cortical bone (such as the hip or pelvis) is dense and compact, forming the outer layer of most bones. Trabecular bone (such as the vertebrae and femoral neck) forms the inner layer and is honey-comb like, thereby providing flexibility. Importantly, trabecular bone has a higher surface area to mass ratio and is the site of frequent remodeling. Therefore, in hypogonadism, greater loss of BMD occurs at sites with predominantly trabecular bone than with predominantly cortical bone (Khosla et al. 2008). Acute losses in testosterone and therefore estradiol, as seen in patients with

prostate cancer treated with androgen deprivation therapy, leads to greater losses in trabecular bone than cortical bone (Greenspan et al. 2005). Bone loss in male hypogonadism is primarily due to loss of estradiol (produced by aromatization of testosterone) which accounts for about 70% of the effects on bone metabolism in men and testosterone itself is 30% of the effect (Clarke and Khosla 2010). Estradiol suppresses production of bone-resorptive mediators such as receptor activation of nuclear factor κ B ligand (RANKL), thereby promoting the formation of resorption pits on bone surfaces (Clarke and Khosla 2010).

Other factors also contribute to bone loss, both cortical and trabecular, to varying degrees. Elevated cortisol such as glucocorticoid therapy will also preferentially affect trabecular bone. Aging also leads to trabecular bone loss, although later in life, cortical bone loss also occurs due to increased cortical porosity (Bousson et al. 2001). Parathyroid (PTH) excess leads to cortical bone loss and may be anabolic for trabecular bone (Duan et al. 1999). Primary hyperparathyroidism has been shown to predominantly affect cortical bone loss with preservation of trabecular bone (Silverberg et al. 1989). Secondary hyperparathyroidism such as renal disease, vitamin D or calcium deficiency, will affect both cortical and trabecular bone as will malnutrition, such as protein (Weaver and Heaney 2013; Giannini et al. 1997).

Less specific findings of hypogonadism include fatigue, depression, anemia, reduced muscle mass, and increased body fat. Androgen deficiency is defined as a persistently low morning total testosterone level (Bhasin et al. 2010). Once confirmed, measuring LH and FSH will distinguish between a primary cause (high LH and FSH) and a secondary cause (low or inappropriately normal LH and FSH). If secondary hypogonadism, investigations should include iron studies to rule out hemochromatosis, prolactin, TSH, and free T4 to assess for pituitary dysfunction, and pituitary imaging to exclude a pituitary adenoma (Bhasin et al. 2010). Other less common etiologies include tuberculosis and sarcoidosis. If primary hypogonadism is suspected, then karyotype should be performed to rule out Klinefelter syndrome or other underlying genetic or chromosomal abnormality (Bhasin et al. 2010).

Hypogonadism itself can potentially exacerbate complications of GSD, such as osteoporosis, and therefore it is important to consider treating this. Treatment with testosterone is directed at restoring levels to normal.

Replacement results in development or maintenance of secondary sexual characteristics, increases in libido, lean body mass, muscle strength, and BMD. Therapeutic options include intramuscular injections, oral and transdermal preparations. Overall, rates of venous thromboembolism and cardiovascular events are not significantly elevated compared to placebo (Baillargeon et al. 2015; Corona et al. 2014); however, when

choosing amongst the different routes of administration, there is suggestion that oral testosterone, but not intramuscular or transdermal testosterone, may increase cardiovascular risk (relative risk = 2.20, 95% CI: 1.45–3.55, $p = 0.015$) (Borst et al. 2014). Most recent studies indicate that testosterone therapy does not increase the risk of prostate cancer, but long-term follow-up data are not yet available and testosterone therapy is considered contraindicated in men with advanced prostate cancer (Fernandez-Balsells et al. 2010). Given that GSD1 patients are at risk for hepatic adenomas with the potential for malignant transformation, testosterone therapy should be carefully monitored. Androgen receptors are expressed in the liver, and androgens can stimulate hepatocyte proliferation. Although rare, androgens have been shown in observational studies to induce adenoma development (Giannitrapani et al. 2006). Testosterone levels should be assessed for response 2–3 months after therapy is initiated.

To our knowledge, this is the first case series describing hypogonadotropic hypogonadism in patients with glycogen storage disease. Based on our observations ongoing assessment of the hypothalamic–pituitary–testicular axis function is important in managing such patients as treatment is available and may impact long-term outcome.

Take-Home Message

Hypogonadotropic hypogonadism is an important complication in glycogen storage disease (GSD) type 1 and incorporating clinical and/or biochemical screening of the hypothalamic–pituitary–gonadal axis may be important in the management of this disease.

Details of the Contributions of Individual Authors

All authors have been involved in the conception and design, analysis and interpretation of data, and drafting and revision of the article for important intellectual content.

Name of One Author Who Serves as Guarantor for the Article

SS accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Competing Interests

None of the authors have competing interests to declare.

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The patients have consented to the publication of their medical information.

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