Neurogenic Bladder Dysfunction Presenting as Urinary Retention in Neuronopathic Gaucher Disease

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Abstract Neuronopathic Gaucher disease can present as a continuum of clinical findings, including somatic symptoms of anemia, thrombocytopenia, hepatosplenomegaly, and bone disease as well as neurologic sequelae. There is a spectrum of neurologic symptoms ranging from oculomotor apraxia to severe convulsions. The heterozygosity of phenotypes makes it difficult to predict the disease course. We describe an 8-year-old male with neuronopathic type III Gaucher disease who developed bladder dysfunction and was unable to completely void. He also presented with hypertension and acute renal insufficiency, most likely secondary to urinary retention. A complete evaluation was done for causes of urinary retention and bladder dysfunction. A renal bladder ultrasound demonstrated marked hydroureteronephrosis. There was no clinical evidence of infection and cystoscopy revealed no anatomic obstruction. In addition, MRI showed no spinal abnormalities. His bladder dysfunction was managed operatively by creating a

catheterizable stoma, using his appendix, to empty his bladder, and surgical findings were consistent with neurogenic bladder. He continues to be managed for his Gaucher disease and neurogenic bladder by genetics, nephrology and urology. This is the first clinical report of neurogenic bladder dysfunction in neuronopathic Gaucher disease.

Introduction

Gaucher disease is an autosomal recessive lysosomal storage disease caused by a deficiency of the enzyme glucocerebrosidase. The accumulation of glucosylceramide within the macrophage-monocyte system causes the signs and symptoms of this disease (Grabowski 2008). Gaucher disease presents as a continuum of clinical findings; patients with no primary central nervous system disease are classified as type I/non-neuronopathic, and patients with both somatic symptoms and primary neurologic disease are classified as types II and type III, neuronopathic, with type II being more severe.

The neuronopathic subtypes occur in less than 1/100,000 births and are characterized by both somatic symptoms of anemia, thrombocytopenia, fatigue, hepatosplenomegaly, and bone disease and neurologic sequelae. Neuronopathic symptoms may be limited to oculomotor apraxia but can also manifest with progressive myoclonic epilepsy, cognitive impairment, bulbar signs, and pyramidal signs (Pastores and Hughes 2000). While there have been reports of urinary retention and neurogenic bladder in other lysosomal storage disorders, there have been no such reports to date in non-neuronopathic or neuronopathic Gaucher disease (Koyama et al. 1994; Gografe et al. 2009).

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Herein we present a case of a young boy with neuroopathic Gaucher disease who developed chronic urinary retention requiring surgical intervention.

Case Presentation

An 8-year-old African-American male with Gaucher disease presented to the pediatric urology clinic with three-week history of dysuria, urinary urgency, frequency, dribbling, and incontinence. He had several emergency room (ER) visits with normal urinalyses, renal/bladder sonogram, and voiding cystourethrogram. He was thought to be in urinary retention and had been catheterized in the ER for 250 cc of urine (expected bladder capacity for age = 300 cc) and was discharged home with terazosin, an alpha-blocker to potentially relax the internal urinary sphincter, and phenazopyridine, a urinary analgesic. He was able to void in clinic, but sonogram revealed a post-void residual of at least 185 cc.

He had been diagnosed with neuronopathic Gaucher disease at 26 months of age. At 27 months he began enzyme replacement therapy (ERT) with IV Cerezyme (imiglucerase injection) at a dose of 60 units/kg every 2 weeks. Given both his clinical presentation and genotype (L444P/L444P), he was classified as having neuronopathic disease. As suggested by preliminary data outlined in a 2001 European consensus statement for management of neuronopathic disease indicating that “high-dose” ERT could perhaps reverse, stabilize, or slow neurologic involvement, his dose was increased to 120 units/kg every 2 weeks before the age of 33 months (Vellodi et al. 2001). The family has been highly compliant with every other week infusions since his diagnosis. His infusion dose has been adjusted for growth over time and has remained above 60 units/kg/infusion as is advised by the revised management guidelines for neuronopathic disease published in 2009 (Vellodi et al. 2009).

Despite ongoing treatment of his Gaucher disease, before the age of 8 years, he demonstrated multiple clinical symptoms of neuronopathic disease. These symptoms include:

- History of swallowing difficulties, abnormal swallowing studies, and aspiration
- Abnormal EEG consistent with a nonspecific diffuse brain dysfunction/encephalopathy
- Abnormal BAER consistent with severe diffuse brain-stem conduction delay and mild conductive hearing loss
- Two abnormal sleep studies demonstrating obstructive events with accompanying O₂ desaturations
- Significant esotropia
- Developmental delay

After the initial urologic evaluation, the dose of terazosin was increased from 1 to 2 mg. Over the next 4 weeks, he was noted to have worsening constipation, which was treated, and the urinary symptoms were mildly improved without further episodes of retention.

Two weeks later, he returned to the clinic with increasing abdominal pain and was found to have a markedly distended bladder and BP of 138/118 mmHg. The patient had no other somatic complaints at this time. A renal bladder ultrasound showed bilateral moderate hydroureteronephrosis as well as a distended bladder with thickened wall consistent with functional or anatomic bladder outlet obstruction (Fig. 1). Serum chemistry was normal except for an elevated creatinine of 1.5 mg/dL. He was catheterized for a volume of 500 cc of urine; however, the hydronephrosis and hypertension did not resolve. He was, therefore, admitted for management of hypertension, acute renal insufficiency, and urinary retention. Serum creatinine returned to normal baseline value with continuous bladder drainage, and blood pressure normalized with IV and then oral medication. Attempts were made to initiate clean intermittent catheterization, but he was unable to tolerate catheterization due to normal urethral sensation. He was taken to surgery for further evaluation. Cystourethroscopy did not show posterior urethral valves or any other obstructive lesions. The bladder was noted to be normal except for signs of chronic distention. A suprapubic catheter was placed to allow regular and complete bladder emptying without the discomfort of a urethral catheter. A total spine MRI was obtained and revealed no abnormalities.

The patient returned to the ER 2 weeks after discharge with the suprapubic catheter dislodged and unable to void. Due to the persistence of urinary retention, the family elected to proceed with a more permanent intervention. Urodynamics were not performed at this time because he would not tolerate urethral catheterization and results were unlikely to affect management. An appendicovesicostomy (Mitrofanoff procedure) was performed to create a continent catheterizable channel from the umbilicus to the bladder using the appendix. The bladder was noted to be markedly thickened, consistent with a neurogenic bladder. The patient did well after surgery and was discharged home with normal renal function.

Follow-up renal bladder ultrasound 6 months postoperatively demonstrated complete resolution of hydroureteronephrosis. Urodynamic evaluation at 8 months postoperatively demonstrated normal bladder compliance and capacity (300 cc) with no detrusor overactivity. Bladder sensation was noted only at capacity. He was unable to void during the study.

Currently now 22 months after surgery, he remains on low amlodipine for hypertension. He has no proteinuria. His constipation is managed with polyethylene glycol 3350

Fig. 1 (a) Right Kidney, long. (b) Left Kidney, prone. (c) Bladder, long

as needed. He has had only one documented urinary tract infection. He continues to catheterize himself independently with a 12 French catheter without supervision and is completely dry during the day with only rare nocturnal enuresis. He can void spontaneously, but his elevated post-void residual urine volume mandates ongoing intermittent bladder catheterization twice daily.

While there continues to be some concern regarding neuropathic symptoms, recent evaluation demonstrated moderate oropharyngeal dysphagia; his somatic disease appears to be well controlled. On his most recent physical examination with the primary specialist following his diagnosis of Gaucher disease, his spleen was not palpable and his liver was just palpable below the right costal margin. The family has denied any bone fractures, pain, or crisis, and his laboratory parameters demonstrate normal hemoglobin and platelet levels at all evaluated time points since his surgery. Biomarkers used for monitoring disease progression and response to therapy (tartrate-resistant acid phosphatase, angiotensin-converting enzyme, and chitotriosidase) have been stable over this time period excepting one increase chitotriosidase level at a semi-annual evaluation. After dose adjustment of ERT for growth/weight gain initiated at that visit, a recheck one month later showed decrease in chitotriosidase trending in the direction of his previous baseline.

Discussion

This is the first case report of chronic urinary retention and neurogenic bladder in a patient with neuropathic Gaucher disease. The bladder dysfunction led to acute renal insufficiency that would have been progressive without definitive urologic management. There was no evidence for spinal cord abnormalities on the MRI in our patient;

however, this patient experienced severe bladder and bowel dysfunction that led to acute renal insufficiency and hypertension, requiring a permanent surgical intervention to address the bladder issues. While constipation is often linked to acute urinary retention, the urinary retention remained an issue after treatment of constipation, and the intraoperative findings of a thickened bladder wall were consistent with neurogenic bladder.

There are no reports of urinary sequelae of Gaucher disease, specifically the neuropathic type. A February 2011 query to the International Collaborative Gaucher Group (ICGG) Gaucher registry identified no other reported cases of patients with neuropathic Gaucher disease who also had symptoms of urinary retention, incomplete bladder emptying, and/or neurogenic bladder. At the time of the query, 488 of 5,943 patients enrolled in the Registry were identified as type II or III Gaucher disease.

There is scant literature on lysosomal storage disease and urinary sequelae in general. One preclinical study has shown mononuclear cell infiltrate in the lower urinary tract, specifically the bladder, of a mouse mucopolysaccharidosis type IIIB model that led to urinary retention, although this has not been demonstrated in humans (Gografe et al. 2009). There is one case report of neurogenic bladder in a patient with Hunter syndrome, but this was secondary to cervical myelopathy (Koyama et al. 1994).

This patient has had good somatic response to his ongoing enzyme replacement therapy with resolution of his anemia and thrombocytopenia within 8 months of treatment initiation. However, he continues to have ongoing neuropathic symptomatology despite high compliance with enzyme replacement therapy. We hypothesize that this is bladder autonomic dysfunction secondary to neurologic sequelae of type III Gaucher Disease. Bladder autonomic dysfunction can be seen in other neurologic diseases and can manifest as urinary retention. Gaucher disease may

affect the nerves that promote contraction of the detrusor muscle and/or relaxation of the internal (involuntary) and/or external (voluntary) sphincter(s)—simultaneous functions that are required for efficient bladder emptying—causing his neurogenic bladder.

Synopsis

A case report of neurogenic bladder that had to be managed surgically, presenting as urinary retention in an 8-year-old boy with neuronopathic Gaucher disease.

Compliance with Ethics Guidelines

Funding Source

No external funding was secured for this study.

Conflict of Interest

Dr. McNamara, Jennifer Sullivan, and Dr. Nagaraj do not have any conflict of interest, financial or otherwise, to disclose.

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Contribution

Erin R. McNamara—responsible for analysis and interpretation of data and drafting the article or revising it critically for important intellectual content

Jennifer Sullivan—responsible for revising the article critically for important intellectual content

Shashi K. Nagaraj—responsible for revising the article critically for important intellectual content

Drs. John S. Wiener, Priya S. Kishnani—responsible for conception and design as well as revising the article critically for important intellectual content. Provided expertise in their respective fields of pediatrics

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