CASE REPORT

Diffuse esophageal spasm and detrusor spasm: Combined visceral neuromuscular disorders in a patient with William's Syndrome

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Abstract

William's Syndrome is a rare genetic disorder associated with developmental delay, gregarious personality, characteristic facies, multiple medical complications and valvular heart disease. Urologic and gastrointestinal complications including motor abnormalities and diverticulosis of the bladder and colon are commonly present. We present a case of a 37 year old male with William's Syndrome who originally demonstrated typical bladder and bowel dysfunction associated with the condition, but also later developed severe dysphagia and associated weight loss. An esophagram revealed the presence of three large distal (epiphrenic) esophageal diverticula. These are most often caused by the presence of an underlying esophageal motility disorder. High-resolution esophageal manometry was performed and showed multiple simultaneous contractions and non-propagated contractions with swallowing maneuvers, consistent with the diagnosis of diffuse esophageal spasm (DES). This is the first case of an esophageal motor disorder described in a patient with William's Syndrome and supports the concept that there is a generalized visceral neuromuscular dysfunction present in these patients.

Key words

William's Syndrome, Congenital disorder, Diffuse esophageal spasm, Gastrointestinal motility disorders, Bladder diverticulosis, Esophageal diverticula

1 Introduction

William's Syndrome is a rare congenital disorder caused by deletions at chromosomal band 7q11.23 [1]. Clinical aspects of William's Syndrome include characteristic facies [2], the presence of a gregarious personality [3, 4], developmental delay, medical complications and valvular heart disease [5]. Facial anomalies include flattening of the nasal bridge and the presence of epicanthal folds. Dental anomalies are present, including loss of dental enamel and widely spaced teeth [2]. The condition has attracted interest among behavioral psychologists because patients with William's Syndrome have been found to have an unusual trust of strangers and acquaintances, as well as interest and ability in music [6]. Thus, William's Syndrome provides proof that genetic abnormalities can result in specific personality traits [7].

A variety of secondary medical complications have been described in patients with William's Syndrome. These include an increased risk of hypertension and the development of symptomatic altered calcium homeostasis. Blood pressure screening and measurement of serum electrolytes has been advised for these patients [2]. Supravalvular aortic stenosis as well as stenosis of the pulmonic valve and pulmonary artery also may be present. Urologic complications of the condition, including disordered motility and diverticulosis of the bladder are often seen [8]. Abdominal pain, constipation, gastroesophageal reflux, and colonic diverticulosis are common gastrointestinal manifestations of William's syndrome [9]. However, spastic motility disorders of the esophagus have not previously been described.

2 Case description

The patient is a 37-year-old male diagnosed with William's Syndrome. He exhibited neonatal failure to thrive, encountered in infants with William's Syndrome. Nocturnal enuresis was reported until the age of 4 years old and was corrected by training with an enuresis alarm. At age 25, the patient developed a poor urinary stream, straining with urination and incomplete bladder evacuation. A urodynamic study was performed and demonstrated the presence of detrusor spasm. A suprapubic catheter was placed at age 27. When the patient was 33 years old, he underwent a medical evaluation for diffuse severe abdominal pain and progressive dysphagia. Physical examination revealed a short statured individual with characteristic facial appearance of William's syndrome. The height was five feet two inches (157.5 cm) and weight was 120 pounds. The facial features included upturned nose, a long philtrum, perorbital pufiness, prominent chin and wide mouth. Further, the patient was noted to have a developmental disability. Labs and neurologic exam were reported to be normal. Cardiac exam reveal no cardiac enlargement or murmurs. Examination of the abdomen showed nonspecific tenderness to deep and light palpation, including tenderness of the abdominal wall. Electrocardiogram was normal. A computed tomography (CT) scan of the abdomen revealed dilation of the esophagus above the esophageal hiatus. An upper endoscopy showed esophageal diverticulosis. This was confirmed by an esophagram displaying a large epiphrenic esophageal diverticulum (4-5cm in diameter) and two additional proximal diverticula that were 2-3cm in diameter (see Figures 1 and 2). The patient began to experience worsening dysphagia and weight loss. His weight declined from 120 pounds to 100 pounds over several months. In addition, vomiting occurred after eating. A high-resolution esophageal manometry performed at a tertiary care center showed simultaneous contractions, non-conducted swallows, and normal lower esophageal sphincter (LES) relaxation. These findings are consistent with the manometric diagnosis of diffuse esophageal spasm (see Figure 3). Botulinum toxin A (Botox) injection and esophageal myometry were recommended but declined by the patient and his family. A pureed diet was initiated with subsequent weight gain and marked improvement of dysphagia.

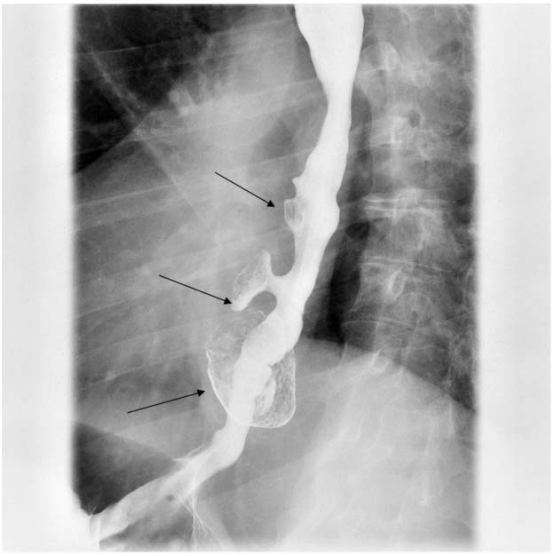

Figure 1. Radiologic demonstration of three esophageal diverticula in a patients with William's Syndrome as seen on an esophagram (arrows)

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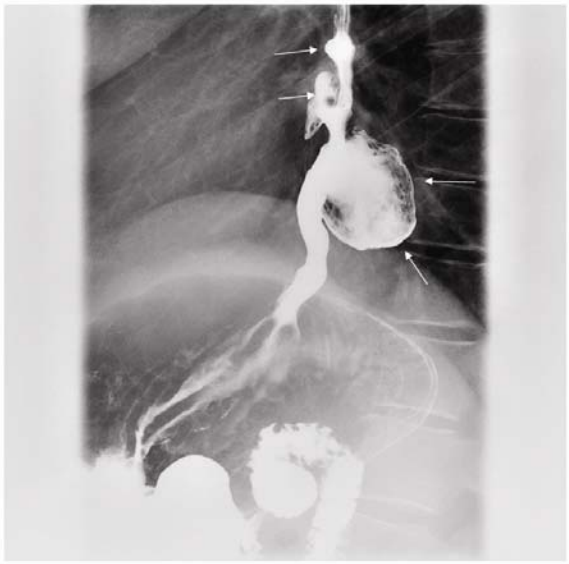

Figure 2. Additional radiographic views of esophageal diverticula occurring in a patient with William's Syndrome, dysphagia and weight loss (arrows)

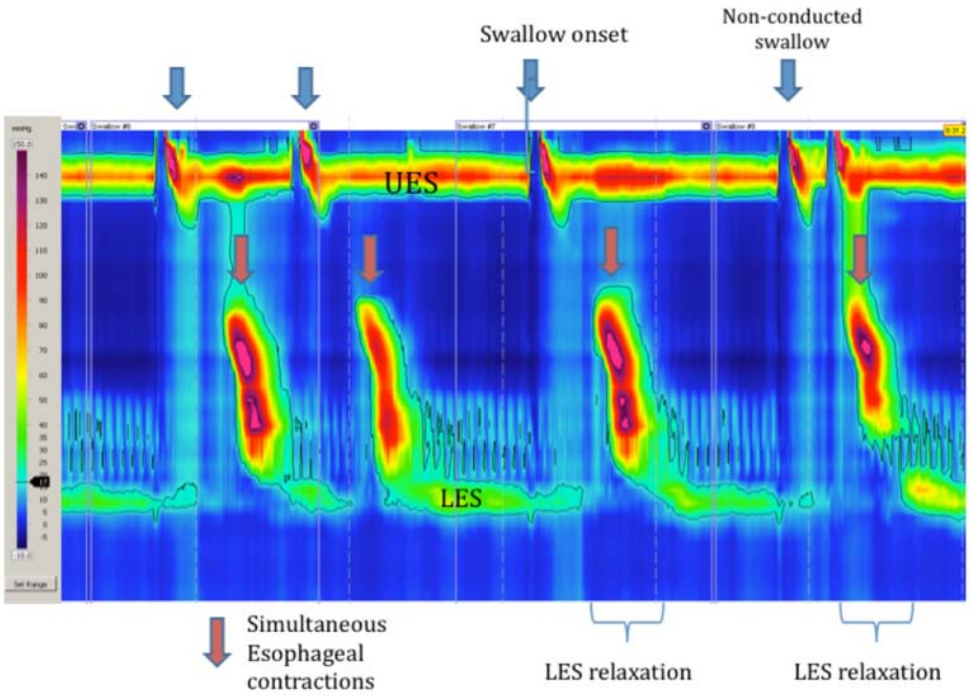

Figure 3. High resolution manometry showing simultaneous contractions with normal relaxation of the LES and a non-conducted swallow in a patient with William's Syndrome. These findings are consistent with diffuse esophageal spasm. Blue arrows show swallows including a non-conducted swallow, red arrows show simultaneous esophageal contractions. Mean resting pressure= 27mmHg, pressurized front velocity= 6.6cm/s, peak amplitude=165mmHg, duration=5.1s, retrograde escape=55%.

3 Discussion

William's Syndrome is a rare disorder affecting between 1/7500-1/50,000 persons [3]. Children with the syndrome are often diagnosed based on their distinct physical appearance as well as the development of characteristic medical problems. The unique facial appearance, which has been termed "elfin facies", is distinguished by a long philtrum, short up-turned nose, wide set eyes with a stellate pattern in the iris, and a small chin [2, 5]. A variety of dental anomalies also occur,

including widely spaced teeth and loss of enamel [2]. Also unique to individuals with William's Syndrome is a complex array of cognitive abilities. On the one hand, IQ tests show that patients with William's Syndrome are mild to moderately intellectually disabled, having special difficulties with visuo-spatial perception and diminished mathematical reasoning [1, 10]. On the other hand, many individuals with William's Syndrome are deemed to be immensely creative and often excel at music and language [1, 6]. Individuals with William's Syndrome are often described as having a "cocktail personality". This term comes from their excessive interest in socializing with others, their lack of social anxiety, and their empathy for others [9, 12]. In fact, recent research indicates that unlike normally developing children, children with William's Syndrome show no racial stereotyping when interacting with strangers and in fact, must be taught to fear strangers for their safety [11, 12]. Aside from the well-known neurocognitive abnormalities associated with this condition, patients with William's Syndrome also have characteristic medical complications. The most common cardiac valvular abnormality in these patients is supravavular aortic stenosis, although stenosis of the pulmonic valve and pulmonary artery have also been described [13]. Endocrine abnormalities such as hypothyroidism and alterations in calcium homeostasis are also associated with this syndrome [5]. Experts suggest that adult patients with William's Syndrome should be screened for calcium abnormalities [14].

The patient described in this case displays evidence of visceral neuromuscular abnormalities in several organ systems. Detrusor spasm and diverticulosis of the bladder are common occurrences in William's Syndrome [2]. Detrusor spasm is defined as spasm of the detrusor urinae muscle, the smooth muscle that controls filling of the bladder. The presence of detrusor spasm results in lack of bladder relaxation [15]. Patients with William's Syndrome likely have a congenital form [16] of bladder diverticulosis, with herniations of portions of the bladder mucosa occurring as a consequence of intense detrusor spasm. Congenital disorders, connective tissue disorders, and neurodegenerative disorders are also associated with bladder diverticulosis [15, 16]. In our patient, his abnormal bladder function eventually required placement of a suprapublic catheter to allow for urine flow.

In adulthood, our patient presented with dysphagia and weight loss. Diagnostic evaluation with esophageal contrast radiography (esophagram) revealed the presence of multiple large distal epiphrenic esophageal diverticula. Epiphrenic esophageal diverticula often occur as a consequence of esophageal motility disorders, including achalasia and diffuse esophageal spasm [17]. In one study of 21 patients with epiphrenic diverticula, 17 patients (81%) had esophageal motility disorders [18]. Manometric abnormalities identified in the patients with esophageal motility disorders included achalasia in 2 patients, diffuse esophageal spasm in 5 patients, nonspecific esophageal motility disorder in 5 patients and nutcracker esophagus in 5 patients. Our patient was diagnosed with diffuse esophageal spasm using high-resolution esophageal manometry. The definitive treatment for symptomatic epiphrenic diverticula is surgical removal, (diverticulectomy) is often performed using a laparoscopic approach [19]. A myomectomy and fundoplication are additionally performed along with the diverticulectomy [20].

Diffuse esophageal spasm is a primary motility disorder of the esophagus. Microscopically, inflammatory infiltrates in the myenteric plexus, smooth muscle hypertrophy, and degeneration of the vagal fibers are seen, a presentation similar to that of esophageal achalasia [20]. Diffuse esophageal spasm occurs when there are uncoordinated contractions of the smooth muscle lining the lower portion of the organ, resulting in the disruption of normal peristalsis [21] and may also be characterized by the intermittent presence of normal progressive peristalsis. Discoordinated swallows develop from an imbalance existing between excitatory and inhibitory neurons that normally orchestrate rhythmic contraction and relaxation, causing clinical difficulties with swallowing [22]. Characteristic manometric findings in patients with diffuse esophageal spasm include non-propagated esophageal contractions and simultaneous esophageal contractions with swallowing maneuvers. Dysphagia is a cardinal symptom of both diffuse esophageal spasm and epiphrenic esophageal diverticula, both of which were found in our patient. A variety of pharmacotherapies have been suggested as treatments for diffuse esophageal spasm, but randomized controlled trials of these treatments are lacking [22]. Calcium channel blockers diminish the frequency and amplitude of contractions. Nitrates including sublingual nitroglycerin, isosorbide nitrate and amyl nitrite have been used. Tricyclic antidepressants probably have a role in reducing chest pain in patients with

esophageal spasm. Additional treatments used for diffuse esophageal spasm include endoscopic injection of Botulinum toxin B (Botox) into the LES [24], or esophageal myomectomy [24-26]. In the case presented, the patient and family chose to adhere carefully to a puréed diet. Dietary changes alone resulted in improvement of symptoms and weight gain.

In this case, the definitive diagnosis of diffuse esophageal spasm was made using high-resolution manometry [25]. Measurement of esophageal motility is performed using a catheter that has a group of pressure sensors that are placed into the esophagus for measurement of esophageal peristalsis. With high-resolution esophageal manometry, pressure data measured at rest and during swallowing is analyzed by a computer system that graphically represents esophageal pressures on a color spectrum as they are occurring during esophageal peristalsis [27, 28].

In our patient, the presence of bladder diverticulosis, destrusor spasm, and esophageal diverticula and diffuse esophageal spasm appear to be related to a generalized systemic neuromuscular abnormality. Gastroesophageal reflux (GERD), a condition occurring during childhood in our patient, is a common finding in a variety of congenital conditions, particularly in children with neurologic conditions and congenital heart disease [29]. GERD is likely related to esophageal dysmotility in some of these patients. To our knowledge, diffuse esophageal spasm (a rare esophageal motility disorder) and esophageal diverticula are new findings in William's Syndrome. We propose that esophageal and bladder motility disorders are part of an overall visceral neuromuscular defect related to the pathophysiology of William's Syndrome. Further investigation into the pathophysiological mechanism of these abnormalities is warranted. Physicians involved in the care of patients with William's Syndrome should recognize the potential for esophageal motility disorders and other visceral neuromuscular abnormalities associated with this condition.

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