Journal of Pediatric Surgery 53 (2018) 321–325

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.elsevier.com/locate/jpedsurg

Bladder dysfunction in Wolfram syndrome is highly prevalent and progresses to megacystis

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ARTICLE INFO

Article history:
Received 6 November 2017
Accepted 8 November 2017

Key words:
Wolfram syndrome
Bladder dysfunction
Urodynamics
Diabetes mellitus
Diabetes insipidis
Megacystis

ABSTRACT

Aim: Wolfram syndrome is a rare genetic defect in WFS1 or WSF2(CISD2). It includes diabetes mellitus and insipidis, sensorineural deafness, optic atrophy, but not bladder dysfunction. However, this has appeared a common finding in our national referral clinic, and we sought to quantify this problem.
Methods: Data were collected from a multidisciplinary team managing all Wolfram patients in the UK. The following was analyzed: age, date of non-invasive urodynamics (NIU), symptoms, bladder capacity, voided volume, post-void residual and uroflow pattern. Bladder capacity was given as percentage predicted bladder capacity (PBC). Bladders were divided into normal, overactive (OAB), and underactive (UAB). Symptoms, bladder behavior, and genotyping were correlated. Data were expressed as median (interquartile range).
Main results: Forty patients with Wolfram syndrome were identified, and 38 underwent NIU. This showed normal bladder function (n = 4), OAB (n = 9), UAB (n = 25). Symptoms were present in only 11 children. The different patterns of bladder behavior (OAB vs. normal vs. UAB) were significantly associated with different %PBC (36 (29–59)% vs. 105 (93–233)% vs. 100 (77.5–337)%; $p < 0.001$), and percentage emptying (100 (80–100)% vs. 100 (87–100)% vs. 69 (48–93)%; $p < 0.05$). There was no association of genotype, symptoms and bladder behavior. Patients with megacystis were older: [13.4 (9.7–16.1) vs. 15.4 (13.9–18.7) years; $p < 0.05$).
Conclusion: Bladder dysfunction is very common in Wolfram syndrome (~90%), but most children cope (symptoms ~30%). With time there is a significant progression to megacystis, which may represent an underlying neuropathic myogenic failure and is likely to require intervention in the future.
Level of evidence: Level II (National cohort study of prognosis).

Wolfram syndrome is a rare genetic disorder comprising diabetes mellitus, diabetes insipidus, optic atrophy and sensorineural hearing loss. It is also known by the acronym DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, and deafness). Children present in early childhood with diabetes mellitus and then most often progress with optic atrophy characterized by initial loss of peripheral and color vision, progressing to blindness [1]. Eventual neurological degeneration in early adulthood with ataxia and dysphagia followed by brainstem atrophy and central apnoea is common, and results in a reduced life expectancy.

The genetic mutation for most patients with Wolfram syndrome is found in the WFS1 locus [2]. The inheritance pattern is usually autosomal recessive, but there are some dominant mutations reported [3], although dominant WFS1 mutations are also seen in patients with isolated low frequency sensorineural hearing loss, and occasionally those with isolated diabetes mellitus. Some patients, mainly from the Middle East, have a mutation in the WFS2 (CISD2) gene [4].

Bladder dysfunction and urological manifestations are commonly reported in Wolfram syndrome, although they are not officially part of the syndrome. These include upper tract dilatation, megacystis or an overactive bladder [5]. The etiology for this is unknown, however, it has been hypothesized to be due to either a stretch injury secondary to polyuria, or autonomic dysfunction.

The aim of our study was to quantify the problem of bladder dysfunction in children with Wolfram syndrome and identify a correlation with the genotype.

1. Methods

Birmingham Children's Hospital is a national referral centre for all patients diagnosed with Wolfram syndrome in the UK and runs a regular multidisciplinary clinic including a pediatric endocrinologist, ophthalmologist, neurologist and a pediatric urologist. Routinely, Wolfram

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https://doi.org/10.1016/j.jpedsurg.2017.11.025
0022-3468/

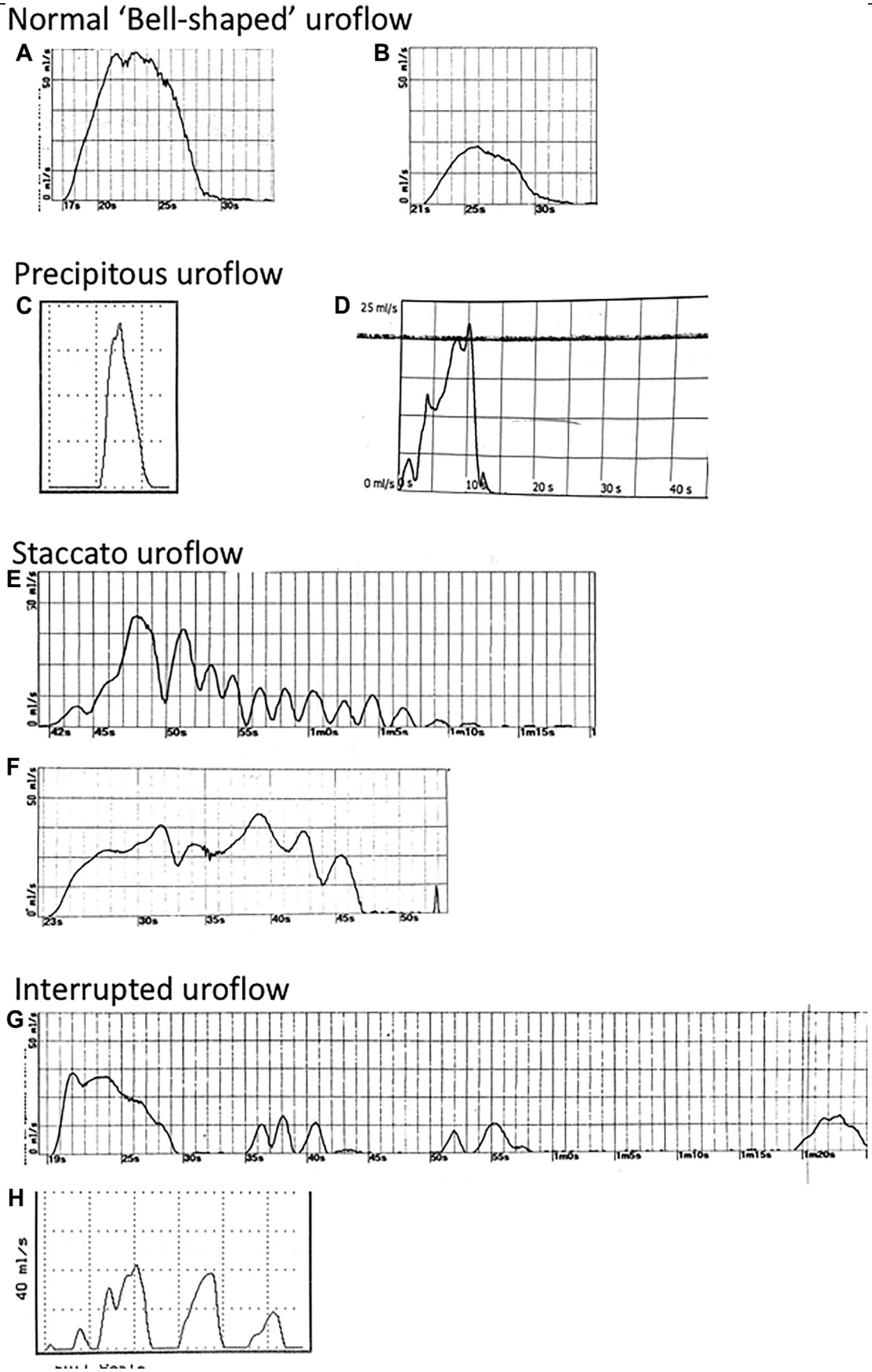

Fig. 1. Patterns of uroflow: Normal bell-shaped curve (A,B). Precipitous uroflow typical of OAB (C,D). Staccato uroflow, typical of UAB (E,F). Interrupted uroflow which may be severe UAB or detrusor sphincter dyssynergia (G,H).