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Bladder Dysfunction in Wolfram Syndrome is Highly Prevalent and Progresses to Megacystis

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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.

Keywords: Wolfram syndrome; bladder dysfunction; urodynamics; diabetes mellitus; diabetes insipidis; megacystis

Level of Evidence: Level II (National cohort study of prognosis)

Introduction

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 colour 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 aetiology 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.

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 paediatric endocrinologist, ophthalmologist, neurologist and a paediatric urologist. Routinely, Wolfram patients would have non-invasive urodynamics (NIU) performed during their clinic review.

A prospectively maintained database was used and interrogated for symptoms (e.g. incontinence, urgency and urinary tract infections), bladder capacity, voided volume, post-void residual and uroflow pattern.

Uroflow was measured using the Dantec Danflow 1000, and post-void residual was measured using the Ecoson bladder scanner. Bladder capacity was then calculated in milliliters as the volume voided added to the post void residual and then measured as a percentage of the predicted bladder capacity (PBC) (calculated using the formula [age in years+1)x30mls] (6). Uroflow was characterized as Normal (bell-shaped), Precipitous (Suggesting OAB), Staccato or Interrupted. Maximum flow rate (Qmax) in ml/s was recorded and the predicted Qmax was taken as the square root of the volume voided (7). Precipitous uroflows had actual Qmax greater than 150% of the predicted value.

Bladders were divided into normal, overactive (OAB), underactive (UAB) by pattern of the uroflow, (Figure 1). Megacystis was defined as >150% of predicted bladder capacity. Symptoms, bladder behavior and genotyping were correlated in each patient. Bladders were then compared by classification of behavior for capacity (given as percentage of predicted bladder capacity (%PBC) using the ICCS formula), voiding efficiency (defined as bladder volume-post void residual/bladder volume, normal >90%), ages of patients and presence of symptoms.

Genotyping was performed by the NHS West Midlands Regional Genetics Laboratory.

Data were expressed as median (interquartile range) unless otherwise indicated, and analyzed by Fisher exact test or Kruskal-Wallis test. A P value of ≤0.05 was taken as significant.

Results

Of 40 Wolfram children seen in clinic, 38 had undergone NIU at a median age of 14 (range 3.24-22.9) years. Normal bladder function was present in 4 (11%), with the remaining 34 (89%) having demonstrable bladder dysfunction. This was characterized as an overactive (n=9) or underactive bladder (n = 25). Only 11 children were symptomatic by enquiry.

There was no significant difference between the staccato and interrupted uroflow groups in terms of %PBC [98(83-193)% vs. 105(80-229)%] or voiding efficiency (%Emptying) [71(50-93)% vs. 62(38-81)%], so these were grouped

together as under active bladders (UAB). The different patterns of bladder behavior (OAB vs. normal vs. UAB) were significantly associated with different percentage of median predicted bladder capacity (%PBC) [36(29-59)% vs. 105(93-233)% vs. 100(77.5-337)% ; P<0.001 (Figure 2A) and % emptying [100(80-100)% vs. 100(87-100)% vs. 69(48-93)% ; P<0.05] (Figure 2B).

Genotype was available in 33 Wolfram patients, but did not correlate with bladder behavior or symptoms, (Table 1).

Symptoms were recorded in 11 children with Wolfram syndrome (Table 2). There were no episodes of urinary tract infection. Daytime urinary incontinence was present in 7, and 3 further children were on clean intermittent catheterization (CIC) (Mitrofanoff, n=1 and urethral, n = 2). Diurnal incontinence (n= 3), or nocturia (n=1) were noted. Daytime frequency was present in 3 and urgency in 1. 3 suffered from nocturia. These symptoms did not correlate with age. There were no symptomatic patients in the normal uroflow group. Symptoms were noted in OAB (1/9), UAB staccato uroflow (7/17) and UAB interrupted uroflow (3/8) (P=0.05 Fisher exact test).

Children with megacystis were significantly older than those without [13.4 (9.7-16.1) years vs. 15.4 (13.9-18.7) years ; P<0.05] (Figure 2C). Similarly there was a significant age progression with different bladder behaviors: normal uroflow [10.0 (4.8-11.5) vs. OAB 13.5 (9.3-17.9) vs. staccato uroflow 13.9 (12.8-16.0) vs. interrupted uroflow 19.0 (15.1-21.0) years; P<0.001 (figure 2D).

Discussion

This study describes the bladder function in a national cohort of children and young adults with Wolfram syndrome. It suggests a progression of bladder dysfunction to megacystis as these patients age, together with an association between older age and change in pattern from normal, to UAB with staccato uroflow, then interrupted uroflow.

Bladder dysfunction in Wolfram syndrome is a common occurrence with most of our national cohort having some degree of bladder dysfunction and is consistent with other studies (5). Strikingly, however, less than 30% were actually symptomatic and none showed any UTIs. This is surprising given the degree of objective bladder dysfunction. It may be that the polyuria seen in these patients is important in reducing their UTI risk.

Overactive bladders were present in 25% and was the main feature of the urodynamic findings with significant reduction in their predicted bladder capacity. Most however emptied normally. Underactive bladders were significantly larger than the OAB, but had markedly reduced emptying efficiency. There was a significant age–related progression in bladder behaviour from normal through OAB to UAB with staccato uroflow, and finally UAB interrupted uroflow. This was mirrored by the older age of Wolfram patients with megacystis. This progression to ultimate atonia has been reported previously (8) .

The aetiology for this bladder dysfunction may be a polyuric stretch injury, or autonomic nerve dysfunction. Polyuria due to diabetes insipidus and diabetes mellitus may result in a recurrent stretch injury to the bladder (9) (10). Acute over-distension due to post-operative urinary retention may cause ongoing problems due to a similar stretch injury to the bladder (11). This could suggest the use of desmopressin in Wolfram syndrome, not just to reduce urine output and improve continence, but also as a therapeutic intervention to reduce the progression of bladder dysfunction due to stretch injury associated with polyuria. Diabetic neuropathy causing bladder dysfunction has been well described, but generally occurs in patients >50 years of age (12). Wolfram syndrome patients are particularly susceptible to neuropathy. In those in whom electromyography has been reported, an axonal sensorineural polyneuropathy has been the predominant pattern (13) .

As <30% of our cohort developed symptoms we feel it is a testament to their ability to cope with bladder dysfunction. But, it does also suggest a hidden

morbidity for the future. This study used non-invasive urodynamics to asses and monitor these patients. This has the advantages of being quick and non-invasive, but bladder compliance, detrusor overactivity or lack of contractility, and bladder neck function (or dysfunction) have not been measured. Staccato uroflows are typical of underactive bladder, and it is very likely that these have progressed with myogenic failure to in the interrupted pattern. Most patients have not had invasive urodynamics however (as they are asymptomatic), so this possibility of myogenic failure cannot be proven. It is possible that some of these Wolfram patients have a combination of OAB and detrusor sphincter dyssynergia (DSD). Detrusor pressure measurements or electromyography of the pelvic floor during voiding would be required to do this.

Eventual progression to severe megacystis with upper tract dilatation requiring continent reconstruction (such as a Mitrofanoff) has been described (14) but was not a common outcome in our series.

In conclusion, bladder dysfunction in children and young adults with Wolfram syndrome is common and progressive mandating the need for careful monitoring and urological follow-up, even in those who are asymptomatic.

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Legends:

Figure 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.

Figure 2: Analysis of bladder function in Wolfram Syndrome: Bladder capacity in Wolfram patients categorized by non-invasive urodynamics, A. Voiding efficiency measured by emptying post void expressed as a percentage of bladder capacity, (% emptying post void) B. Megacystis (>150% predicted bladder capacity (PBC)), C. Age comparison of Wolfram patients categorized by uroflow pattern, D.

Table 1: Genetic mutations and the types of bladder dysfunction seen in Wolfram patients

Table 2: Symptom patterns seen in the 11 symptomatic patients

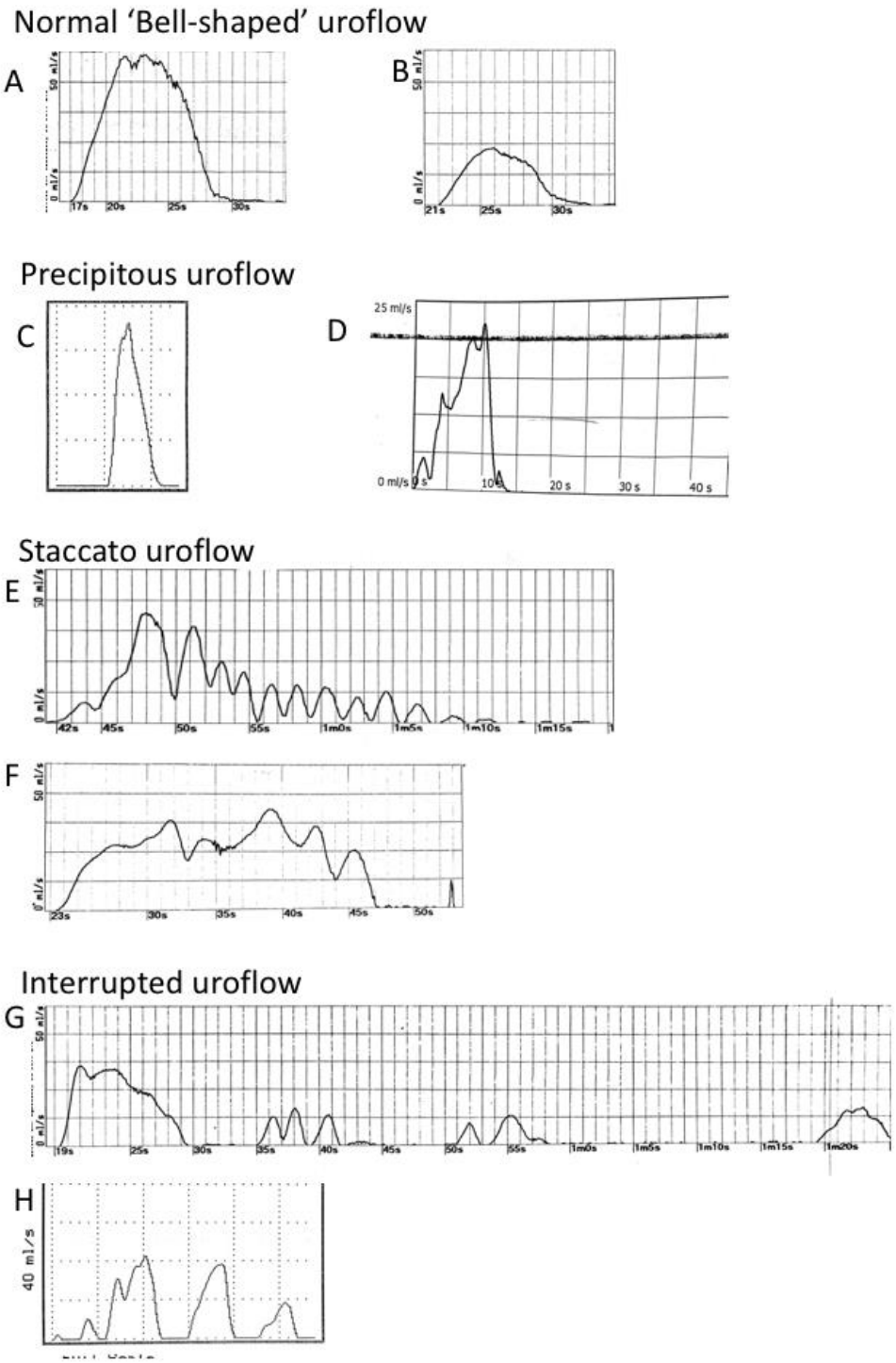

Figure 1

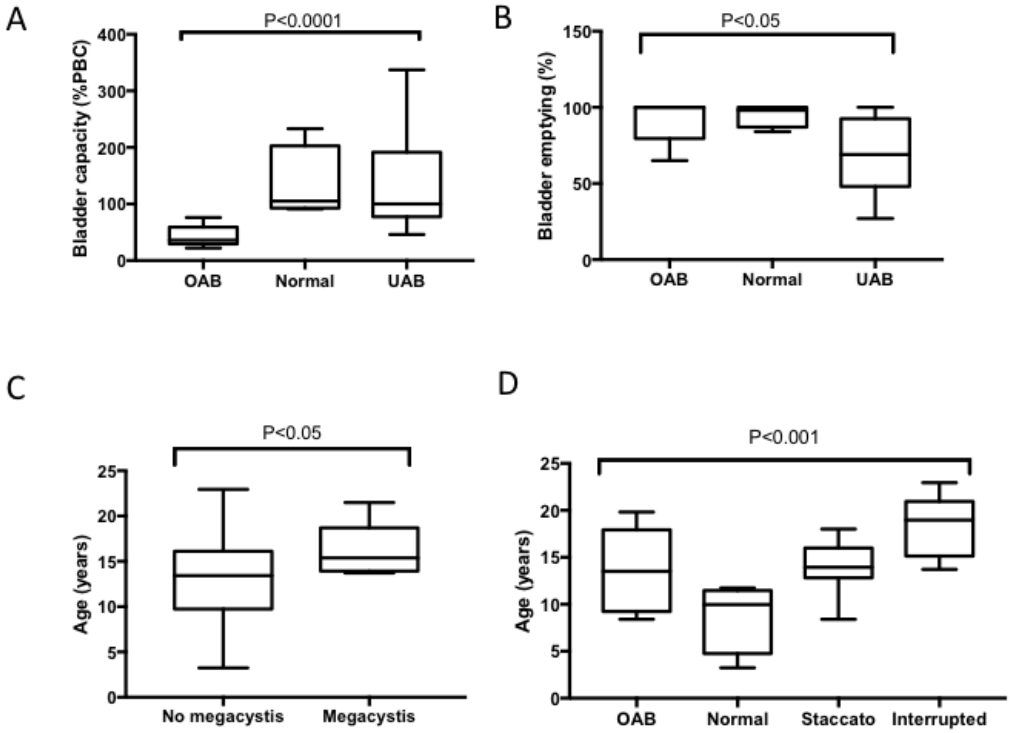

Figure 2

Patient	Nucleotide change 1	Protein 1	Nucleotide change 2	Protein 2	Bladder Behaviour
1	c.2051C>G	p.Ala684Gly	c.2051C>G		Overactive Bladder
2	c.2099G>A	p.Trp700*	c.2099G>A	p.Trp700*	Overactive Bladder
3	c.1338G>A		c.2327A>T	p.Glu776Val	Overactive Bladder
4	homozygous loss of function		homozygous loss of function		Overactive Bladder
5	homozygous loss of function		homozygous loss of function		Overactive Bladder
6	loss of function		no second mutation detected		Overactive Bladder
7	missense change		no second mutation detected		Overactive Bladder
8	Not recorded				Overactive Bladder
9	homozygous loss of function		homozygous loss of function		Normal
10	heterozygous loss of function		heterozygous loss of function		Normal
11	homozygous loss of function		homozygous loss of function		Normal
12	c.2099G>A	p.Trp700*	c.2099G>A	p.Trp700*	Normal
13	heterozygous loss of function		heterozygous loss of function		Underactive Bladder
14	homozygous loss of function		homozygous loss of function		Underactive Bladder
15	homozygous loss of function		homozygous loss of function		Underactive Bladder
16	homozygous loss of function		homozygous loss of function		Underactive Bladder
17	c.911_914dupTTGA				Underactive Bladder
18	c.911_914dupTTGA				Underactive Bladder
19	c.2206G>A	p.Gly236Ser	c.1049_1051delTCT	p.Phe350del	Underactive Bladder
20	c.1549delC	p.Arg57Alafs*5	c.2033G>A		Underactive Bladder
21	c.1549delC	p.Arg57Alafs*5	c.2033G>A		Underactive Bladder
22	c.2099G>A	p.Trp700*	c.2099G>A	p.Trp700*	Underactive Bladder
23	c.2648-2651delTCTT	p.Phe883Serfs*68	c.2146G>A	p.Ala715Thr	Underactive Bladder
24	c.2643_2646delCTTT	p.Phe883Serfs*69	c.2643_2646delCTTT	p.Phe883Serfs*69	Underactive Bladder
25	heterozygous loss of function		heterozygous loss of function		Underactive Bladder
26	heterozygous loss of function		heterozygous loss of function		Underactive Bladder
27	homozygous loss of function		homozygous loss of function		Underactive Bladder
28	homozygous loss of function		homozygous loss of function		Underactive Bladder
29	heterozygous loss of function		heterozygous loss of function		Megacystis
30	homozygous missense				Megacystis
31	c.937C>T	p.His313Tyr	Exon 1 variant unknown significance		Megacystis
32	homozygous loss of function		homozygous loss of function		Megacystis
33	homozygous loss of function		homozygous loss of function		Megacystis

Table 1: The genetic mutations and the types of bladder dysfunction seen in Wolfram patients

Incontinence		Bladder dysfunction		UTI
Day	Night	Day	Night	
Y	Y	No	No	No
Y	Y	.	.	.
Y	Y	Frequency	No	No
Y	N	No	Nocturia	No
Y	N	No	No	No
Y	N	.	.	.
Y	N	No	Nocturia	No
N	Y	Urgency	No	No
CIC Mitrofanoff	Overnight Drainage	Frequency	No	No
CIC	N	.	.	.
CIC	N	Frequency	Nocturia	No

Table 2: Symptom patterns seen in the 11 symptomatic patients