PAPER

Micturition disturbance in acute idiopathic autonomic neuropathy

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Objective: To define the nature of micturition disturbance in patients with acute idiopathic autonomic neuropathy (AIAN).

Methods: Micturitional symptoms were observed during hospital admissions and the in outpatient clinics in six patients with clinically definite AIAN (typical form in four, cholinergic variant in one, autonomic-sensory variant in one). Urodynamic studies included medium-fill water cystometry, external sphincter electromyography, and a bethanechol test.

Results: Four patients had urinary retention and two had voiding difficulty as the initial presentation. Patients with retention became able to urinate within a week (two to seven days). The major symptoms at the time of urodynamic studies (three weeks to four months after disease onset in most cases) were voiding difficulty and nocturnal frequency. None had urinary incontinence. Complete recovery from the micturition disturbance took from three months to >18 years. The recovery period was shorter in a patient with cholinergic variant, and it was longer in two patients who had a longer duration of initial urinary retention. Micturition disturbance tended to improve earlier than orthostatic hypotension. The major urodynamic abnormalities were detrusor areflexia on voiding (5), denervation supersensitivity to bethanechol (3); low compliance detrusor (1); and impaired bladder sensation (2). None had neurogenic motor unit potentials of the external sphincter muscles.

Conclusions: In patients with AIAN, urinary retention and voiding difficulty are common initial presentations. The underlying mechanisms seem to be pre- and postganglionic cholinergic dysfunction with preservation of somatic sphincter function. The bladder problems tend to improve earlier than orthostatic hypotension.

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cute idiopathic autonomic neuropathy (AIAN),12 or pure pandysautonomia, is a rare but distinct clinical entity first described by Young et al in 1969.3 4 The disorder involves both sympathetic and parasympathetic nervous systems, with an acute onset, a monophasic course, and partial recovery with relative preservation of sensory function.5 Somatic motor function is almost completely preserved. The site of lesions is the pre- and postganglionic autonomic fibres, 15 and the disorder is thought to have an autoimmune aetiology similar to the Guillain-Barré syndrome.67 Variant forms may also occur,5 in which sensory fibres are involved8 9 or cholinergic autonomic fibres alone are affected.10 The most common presenting symptoms of AIAN are orthostatic hypotension (postural dizziness, syncope), gastrointestinal (nausea, vomiting, diarrhoea, constipation, intestinal pseudo-obstruction), and sudomotor (failure to sweat, causing heat intolerance and flushing).5 Disturbances of micturition are known to occur in this disorder, and most patients suffer from voiding difficulty and retention, which often requires an indwelling urinary catheter.1-4 6 8-10 However, few studies have attempted to follow up the bladder symptoms and investigate the underlying mechanism, though Kirby et al investigated two patients with this condition.11 In this paper we outline our findings relating to the micturition histories in six patients with AIAN, and describe the urodynamic studies that were done.

METHODS

Patients

This was a retrospective study in which we reviewed the records of six patients with AIAN, all of whom satisfied the inclusion and exclusion diagnostic criteria.^{1 2 5} Two were male

and four were female, median age of onset 30 years (range 9 to 46). All the patients experienced acute exacerbations of autonomic abnormalities during the first two to four weeks, but motor function was almost completely preserved. On the basis of the neurological and neurophysiological findings and the autonomic function tests (done within a month of onset except in two cases) (table 1),⁷ ^{12–15} four patients (cases 2, 3, 4, and 5) were considered to have the typical form of the disease and the other two to have variant forms (case 1, acute cholinergic autonomic neuropathy; case 6, acute autonomic-sensory neuropathy).

Procedures

Micturitional and other autonomic symptoms were observed during hospital admission and in the follow up outpatient clinic. The follow up period was six months in one patient and more than four years (4 to 18) in five. Micturition status of the patients with an indwelling urinary catheter was evaluated at least one week after removal of the catheter. Patients with urinary symptoms did not have urinary tract infection. One patient under 10 years of age (case 2) did not have a recent history of enuresis. In four patients, urodynamic studies were done three weeks to four months after the onset of disease, while in the remaining two patients, urodynamic and autonomic function tests were done four and 18 years after the onset of disease. In one patient (case 3) the urodynamic studies were repeated. None of the male patients studied had prostatic hypertrophy on abdominal ultrasonography. Informed consent was obtained from all the patients before the urodynamic studies were done.

In the patients, we also undertook peripheral nerve examinations including nerve conduction studies and sural nerve biopsy.

	Patient							
Variable	1 (KA)	2 (TO)	3 (TO)	4 (MM)	5 (CK)	6 (ET)		
Age of onset (years)/sex	46/M	9/M	23/M	34/M	37/F	28/F		
Initial symptoms	Anhidrosis, urinary retention	Diarrhoea, vomiting,	Abdominal distension,	Syncope	Vomiting, urinary retention	Abdominal pain, diarrhoea		
Clinical form	Cholinergic variant	urinary retention Typical form	vomiting Typical form	Typical form	Typical form	Autonomic-sensor variant		
Autonomic signs and symptoms								
Orthostatic syncope	-	+	+	+	+	+		
Pupillary abnormality	-	Tonic pupil	Tonic pupil	Tonic pupil	-	-		
Anhidrosis	+	+	+	+	+	+		
Paroxysmal coughing	+	-	+	+	+	_		
Constipation/intestinal pseudo-obstruction	+	+	+	+	+	+		
Erectile dysfunction	+	+ (afterwards)	+	+				
Urinary dysfunction	Retention (3 days), voiding difficulty		Voiding difficulty, nocturia	Voiding difficulty	Retention (2 days), voiding difficulty	Retention (7 days voiding difficulty		
Deep tendon reflexes	Normal	Absent	Absent	Absent	Decreased	Absent		
Sensory signs and symptoms								
Tingling sensation/numbness	+ (hands, feet)	-		+ (hands)	+ (generalised)	+ (generalised)		
Decrease in pain, touch Decrease in position,	-	-	+ (hands)	+ (hands)	-	+ (generalised)		
vibration/sensory ataxia, Romberg sign						+ (generalised)		
sign	_	_	_	_	_	+ (generalisea)		
Autonomic function tests Cardiovascular function Systolic pressure fall (mm Hg) in head		<18 years later>				<4 years later>		
up tilt (70°, 10 min) (normal <20) Supine plasma noradrenaline	Normal	Normal*	50 (30°)	76	18 (30°)	58		
(NA) (pg/ml) (normal >100) Supersensitivity to NA infusion	291	np	40	50	20	30		
(0.1 mg/kg, 5 min) Sudomotor function	Np	np	+	+	+	+		
Thermal/sympathetic sweat response Pupillary responses	Absent	Absent	Absent	np	Absent	Absent		
Supersensitivity to 1.25% NA instillation (60 min) Supersensitivity to 0.125% pilocarpine	Normal	+	+	Normal	+	+		
instillation (30 min)	Normal	+	+	+	+	np		
Peripheral nerve examination Nerve conduction studies								
Median, ulnar, tibial, sural nerves Sural nerve biopsy ight microscopy: decreased	Normal	Normal	Normal	Normal	Normal	Decreased SNAP		
fibre density	+	np	+	+	+	np		
Electron microscopy (compared with control)	Np	np	Small myelinated 7%, unmyelinated 3%		Small myelinated 26%, unmyelinated 9%	np		

Urodynamic studies

The urodynamic studies consisted of uroflowmetry, measurement of residual urine, urethral pressure profilometry, medium-fill (50 ml/min) water cystometry, and external sphincter electromyography (EMG) with a urodynamic computer (Urovision; Lifetech, Houston, Texas, USA) and an EMG computer (Neuropack Σ ; Nihon Kohden, Tokyo, Japan). Uroflow curves were evaluated according to Siroky's nomogram. The normal ranges of urodynamic variables were: residual urine volume under 30 ml; maximum urethral closure pressure more than 41 cm $\rm H_2O$ and less than 82 cm $\rm H_2O$; first sensation at the bladder volume more than 100 ml but less than 300 ml; and bladder capacity more than 200 ml but less than 600 ml. Increased first sensation and/or bladder capacity indicates impaired bladder sensation.

Analysis of sphincter motor unit potentials was done in four patients using a concentric needle electrode. According to the criteria proposed by Palace *et al*,¹⁷ neurogenic sphincter EMG was diagnosed when either of the following abnormalities was present: average duration of motor unit potentials >10 ms; >20% of motor unit potentials with a duration of >10 ms. A bethanechol test was done in five patients. After an infusion of 100 ml of water, 2.5 mg of bethanechol chloride was injected subcutaneously and detrusor pressure was measured for 30 minutes. A detrusor pressure increase of >15 mm H₂O during the test is considered high.¹⁸ The methods and definitions used for the urodynamic studies conformed to the standards proposed by the International Continence Society.¹⁹

RESULTS

Initial presentation

All the patients had urinary dysfunction at the onset of their disease (table 1). Four patients had transient urinary

retention which required urinary catheterisation; the other two had voiding difficulty with or without nocturnal urinary frequency. All patients with urinary retention became able to urinate within a week (two to seven days), including those who underwent steroid pulse treatment. While three patients needed midodrine or L-threoDOPS for the treatment of orthostatic hypotension, none needed drug treatment for the micturition disturbance.

With respect to other autonomic disturbances, all the patients except one (case 1, cholinergic variant) had frequent episodes of orthostatic dizziness and syncope. All patients had intestinal pseudo-obstruction or severe constipation, and four also had vomiting, abdominal distension, and pain. All patients had anhidrosis, four had intractable paroxysmal coughing, three had tonic pupils, and all four male patients had erectile dysfunction (which developed later in a young patient).

Urodynamic studies

When the urodynamic studies were done, all patients still had moderate micturition disturbance (table 2). The major symptoms were voiding difficulty and nocturnal urinary frequency. However, none of the patients developed urinary incontinence or recurrent urinary retention.

Post-void residual urine volume was measured in all the patients. Residual urine of more than 30 ml was noted in three (median volume, 50 ml) but none had a residual volume of more than 100 ml. Water cystometry was done in all cases. Bladder volume at first sensation, bladder capacity, or both were decreased in one patient and increased in two: one patient had increased first sensation (340 ml); another had increased bladder capacity (>750 ml; water infusion stopped to avoid overdistension). During bladder filling, one patient showed a low compliance detrusor. During voiding, five patients had detrusor areflexia.

The bethanechol test was done in five patients, three of whom showed supersensitivity of the bladder. External sphincter EMG showed unrelaxing sphincter on voiding in one patient. Analysis of sphincter motor unit potentials was done in four patients, and none had neurogenic changes in the sphincter motor unit potentials.

In addition to the above urodynamic abnormalities, one patient (case 2) with diurnal frequency had polyuria (>2200 ml/day) because of an excessive water intake, as he had heat intolerance caused by generalised anhidrosis.

Variable	Patient							
	1 (KA)	2 (TO)	3 (TO)	4 (MM)	5 (CK)	6 (ET)		
Clinical form	Cholinergic variant	Typical form	Typical form	Typical form	Typical form	Autonomic-sensor variant		
Interval between disease onset and urodynamic studies	4 Months	18 Years	2 Months	4 Months	3 Weeks	4 Years		
Micturition symptoms(at the time of urod	ynamic studies)							
Nocturnal frequency	+	-	+	-	+	+		
Diurnal frequency	-	+*	-	_	_	+		
Urgency	_	_	_	_	+	+		
Incontinence	_	_	_	_	_	_		
Hesitancy/prolongation	_	+/-	+	+/-	+	_		
Retention	-	_	-		-	-		
Urodynamic studies								
Decréased urinary flow Post-void residual urine (ml)	np	+	np	np	np	+		
(normal<30) Maximum urethral closure pressure	50	_	-	50	60	-		
(cm H_2O) (41 <normal<82)< td=""><td>>100</td><td></td><td>33</td><td>63</td><td>60</td><td></td></normal<82)<>	>100		33	63	60			
		np 80		200		np 160		
First sensation (ml) (100 <normal<300) (ml)<="" bladder="" capacity="" td=""><td>240</td><td></td><td>340</td><td></td><td>250</td><td></td></normal<300)>	240		340		250			
(200 <normal<600)< td=""><td>350</td><td>250</td><td>500</td><td>350</td><td>350</td><td>>750</td></normal<600)<>	350	250	500	350	350	>750		
Detrusor hyperreflexia during filling	-	-	-	-	-	-		
Low compliance detrusor during filling	-	-	-	+	-	-		
Detrusor areflexia on voiding	+/-	+	-	+	+/-	+		
Supersensitivity to bethanechol injection								
(2.5 mg, 30 min)	_	np	+	+	-	+		
Unrelaxing sphincter on voiding	_	+/-	-	_	-	-		
Neurogenic motor unit potentials								
of the external sphincter	-	-	np	np	_	-		
Treatment	Steroid pulse therapy, oral prednisolone	Steroid pulse therapy, oral prednisolone, dihydroergotamine for OH, sildenafil for ED	Oral prednisolone	L-threoDOPS, midodrine for OH	Laxative for constipation	Midodrine for OH		
Course	Nocturia disappeared (4 months), complete recovery (6 months)	Diurnal frequency persisted (18 years), OH changed to POTS, Sildenafil withdrawn because of POTS (18 years)	Urinary frequency, voiding difficulty disappeared (6 months), normal UDS (2 years); OH persisted (3 years)	persisted	Urinary frequency, voiding difficulty gradually disappeared (3 months); OH lessened but persisted (17 years)	Urinary frequency OH persisted (4 years)		

Follow up

The period for complete recovery of the micturition disturbance ranged widely, from three months to more than 18 years. There was no apparent correlation between the recovery period and the sex of the patient or the age of onset. However, the recovery period was shorter (four months) in one patient with acute cholinergic autonomic neuropathy (without orthostatic hypotension), and it was longer (more than four years) in two patients in whom the duration of initial urinary retention was longer (seven days). Comparing the recovery periods for the micturition disturbance and orthostatic hypotension, the micturition disturbance tended to improve earlier than the orthostatic hypotension (three months to four years for micturition disturbance, except in one cases, where it lasted for 18 years; three years to 18 years for orthostatic hypotension).

DISCUSSION

Although AIAN is rare,5 micturition disturbance is well recognised in this disorder. In the present study, all six patients showed micturition disturbance as the initial presentation, four of whom required urinary catheterisation for relief of urinary retention. The other two patients had voiding difficulty with or without nocturia. The high incidence of micturition disturbances reported here is in accordance with previous series of patients with AIAN, 1-4 6 11 including the variant forms (acute autonomic-sensory neuropathy⁸ and acute cholinergic neuropathy¹⁰ 11 20). All of our patients with urinary retention became able to urinate within a week (two to seven days). However, when the urodynamic studies were done (three weeks to four months in the majority), all patients still had moderate micturition disturbance. The major symptoms were voiding difficulty and nocturnal urinary frequency. However, none developed urinary incontinence, post-void residuals of more than 100 ml, or recurrent urinary retention. In our patients, the period for complete recovery of micturition disturbance ranged widely from three months to more than 18 years. The recovery period was shorter (four months) in one patient with acute cholinergic autonomic neuropathy (without orthostatic hypotension), and it was longer (more than four years) in the two patients who had a longer duration (seven days) of initial urinary retention. Thus the severity of micturition disturbance at the initial presentation may predict the duration of the subsequent disturbance. Though severe micturition disturbance appears to occur as often as orthostatic hypotension, it tended to resolve earlier in our series (within three months to four years, with one case lasting 18 years, versus three 3 years to 18 years).

Although we have not done urodynamic studies during the initial retention period, "atonic bladder" was described in the original report by Young et al.3 4 We carried out our urodynamic studies three weeks to four months after the onset of disease except in two cases. Our major findings included detrusor areflexia on voiding in five patients, a positive bethanechol test in three, low compliance detrusor in one, and disturbed bladder sensation in two. Our findings support the earlier study by Kirby et al,11 who described two patients with AIAN: one cholinergic variant (case 1; an 11 year old girl) and one typical form (case 2; a 53 year old woman). Both initially had urinary retention. In case 1, the retention resolved a month later, but she still had voiding difficulty for the following 15 years. In case 2, urinary retention persisted for four years before urodynamic studies were done, and these showed detrusor areflexia on voiding. Detrusor areflexia is a common feature in diabetic polyneuropathy,21 and it also occurs in severely affected cases of Guillain-Barré syndrome. 7 22 It indicates a postganglionic type

of pelvic (parasympathetic cholinergic) nerve dysfunction which is the major cause of evacuation disorders.²³

Three of our patients showed supersensitivity to a minimal amount of bethanechol. Supersensitivity to carbachol was also noted by Kirby *et al* in both their cases.¹¹ These findings most probably reflect denervation of the detrusor smooth muscles owing to the postganglionic pelvic nerve lesion,¹⁸ which has been confirmed by a reduction of acetylcholinesterase containing nerves in biopsies of the bladder muscle.¹¹ One of our patients showed a low compliance detrusor, which was also noted in Kirby's case 2.¹¹ A low compliance detrusor commonly occurs in spinal conus or cauda equina lesions²⁴ ²⁵ and indicates a preganglionic type of pelvic nerve dysfunction.²³

There was a discrepancy in that impaired bladder sensation was noted in two of our patients but in none of Kirby's cases. Impaired bladder sensation indicates disturbance of afferent fibres from the bladder wall, although it might also be a result of potential overdistension injury during the initial retention period. Analysis of the sphincter motor unit potentials showed that none had denervation potentials, which is in agreement with the earlier study. 11 The external sphincter did not relax completely during voiding in only one of the five patients who had detrusor areflexia, suggesting mild sphincter dysfunction. Nerve conduction studies and sural nerve biopsy in the present study showed severe loss of small myelinated and unmyelinated nerve fibres, with preservation of somatic motor nerves, which is consistent with previous reports.^{1 5} Thus the external striated sphincter muscles (innervated by somatic pudendal nerves) tend to be preserved in this disorder.

Conclusions

In our patients with acute idiopathic autonomic neuropathy, urinary retention and voiding difficulty were common initial presentations. The underlying mechanisms seem to be preand postganglionic cholinergic dysfunction with preservation of somatic sphincter function. The problems tend to resolve earlier than orthostatic hypotension.

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ECHO...

Bladder dysfunction in Duchenne muscular dystrophy can be treated



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en and boys with Duchenne muscular dystrophy may be suffering with bladder problems unnecessarily, a UK study has found. Symptoms of detrusor hyperreflexia, at least, can be treated successfully.

A chance finding of reported urinary problems in the condition alerted doctors at a paediatric neurology unit to a need to investigate further.

More than half (46/74) of 88 males aged 3-31 years with Duchenne muscular dystrophy at one neuromuscular clinic had urinary problems not previously raised with their doctors. These included daytime and night time incontinence, frequency, urgency, hesitancy, and stress incontinence and covered young boys able to walk and older males using wheelchairs. Twenty one males with symptoms were offered kidney and bladder ultrasonography before and after bladder emptying and videourodynamic tests to isolate the nature of the problem. Of the 10 who opted for both investigations, nine had results suggesting detrusor hyperreflexia; seven of them had a small bladder. Five with similar symptoms opted just for ultrasonography. The ultrasonographic studies confirmed complete emptying of the bladder in all patients. All reported symptoms improved significantly and night time incontinence resolved with oxybutinin treatment in 10 males (seven and three, respectively, from each group). The neurological reasons for the urinary symptoms were unclear.

Urinary problems are not generally recognised with Duchenne muscular dystrophy among doctors, and parents assume they are part and parcel of the condition.

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