Bladder dysfunction in distal autonomic neuropathy of acute onset

ROGER S KIRBY, CLARE J FOWLER, JOHN A GOSLING, ROGER BANNISTER

From the Department of Urology, the Middlesex Hospital, the National Hospital for Nervous Diseases, London, and the Department of Anatomy, University of Manchester, UK

SUMMARY A patient with cholinergic dysautonomia and a patient with pandysautonomia have each been investigated for disturbances of bladder and urethral function. Both patients suffered from an inability to develop or sustain a detrusor contraction, while retaining normal bladder sensation. Biopsy specimens of bladder muscle stained for acetylcholinesterase revealed a significant reduction in cholinergic nerves compared with controls; however, the prominent cholinergic subepithelial plexus was strikingly preserved. These findings lend support to the view that acetylcholinesterase-containing nerves in the bladder muscle are motor fibres responsible for detrusor contraction, while those located in the subepithelium are sensory in function. Urethral sphincter electromyography revealed no abnormality of individual motor units, confirming that motor unit integrity in this muscle is dependent upon somatic rather than autonomic innervation. In the patient with pandysautonomia the proximal urethra was incompetent, while in the patient with cholinergic dysautonomia the bladder neck remained closed, as in controls. This suggests that sympathetic rather than parasympathetic efferent activity is necessary for the maintenance of proximal urethral competence.

Bladder dysfunction in distal autonomic neuropathy

Selective autonomic neuropathy of acute onset was first reported by Young *et al.*^{1,2} Since then 13 other cases of acute or subacute pandysautonomia have been described³⁻¹⁴ (table 1), with or without associated peripheral sensory, and motor nerve involvement. It is now recognised¹⁵ that a rare variant of this condition may occur, in which peripheral parasympathetic nerves alone are affected. Five cases of this disorder, which has been termed cholinergic dysautonomia, have been reported^{4,16-19} (table 2). In both pandysautonomia and pure cholinergic dysautonomia of acute onset disturbances of micturition are prominent; however, there have been no previous studies concerning the nature of the vesical dysfunction that these patients suffer. The results of a detailed urodynamic, electromyographic and neurohistochemical study in two patients with distal autonomic neuropathy of acute onset are now presented and compared with results obtained in a series of age-matched controls.

Address for reprint requests: Roger S Kirby, FRCS, Department of Urology, Middlesex Hospital, London W1N 8AA, UK.

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Patients

Two patients with distal autonomic neuropathy were investigated and the results compared with those obtained in 10 female patients (age range 21-45 yrs) who had been admitted for renal or ureteric surgery and who complained of no lower urinary tract symptoms. Written informed consent was obtained in every case.

Case 1 Cholinergic dysautonomia

This female patient presented in 1969, aged 11 years, with an acute onset of abdominal pain and blurred vision. After a period of urinary frequency, she developed painful acute retention and required catheterisation. On examination the pupils were dilated, the abdomen was distended and bowel sounds were absent. At laparotomy, performed to exclude intestinal obstruction, distended loops of bowel were found, but there was no localised intra-peritoneal pathology. The paralytic ileus persisted for almost a month and removal of the catheter failed to restore normal micturition. Six weeks after the onset of the illness, 100 µg of carbachol (one-fifth the usual dose) was given subcutaneously. This produced severe abdominal pain, vomiting, profuse sweating and a desire to micturate. After further physiological investigation, as reported previously (by Hopkins *et al.*) and subsequent studies by methods described by Bannister,¹⁵ a diagnosis of pure cholinergic dysautonomia was made. Although the patient had normal sensation of bladder distension, micturition was never

Table 1 *Pandysautonomia*

Author	Age (yr)	Sex	Cholinergic/Adrenergic	Site of neural Injury	Other neurological deficit	Urological problem	Recovery/duration
Appenzeller and Kornfield ³	6	M	Both	Post-ganglionic	—	Retention. Voids by straining	Complete (16 yr)
Hopkins <i>et al.</i> (Case 1)	28	F	Both	Post-ganglionic	—	No urological history recorded	Complete (4 mon)
Yahr & Frontera ⁵	13	F	Both	Post-ganglionic	Decreased reflexes	No urological history recorded	Good
Okada <i>et al.</i> ⁶	43	M	Both	Post-ganglionic	Decreased reflexes	"Hypotonic" bladder	Moderate (31 mon)
Ibid. (Case 2)	37	M	Both	Pre-ganglionic	—	Impotence	Complete (1 yr)
Wischer <i>et al.</i> ⁷	47	F	Both	Post-ganglionic	—	No urological history recorded	Partial (14 mon)
Young <i>et al.</i> ²	49	M	Both	Post-ganglionic	—	Areflexic bladder	Complete (17 mon)
Yee <i>et al.</i> ⁸	39	M	Both	Post-ganglionic	—	"Incomplete" micturition	Partial (6 yr)
Low <i>et al.</i> ⁹	46	F	Both	Post-ganglionic	Impaired thermal sensation	Retention	Poor (5 yr)
Ibid (Case 2)	74	F	Both	Post-ganglionic	—	Retention	Not recorded
Estanol-Vidal <i>et al.</i> ¹⁰	20	F	Both	Post-ganglionic	Decreased reflexes	Retention	Poor (1 yr)
Goulon <i>et al.</i> ¹¹	40	M	Both	Post-ganglionic	Opthalmoplegia Ataxia (L) Babinski sign	Retention of urine	Good (3 mon)
Colan <i>et al.</i> ¹²	9	M	Both	Post-ganglionic	Sensory loss	Retention of urine	Autonomic: Good; Sensory: Poor
Fagius <i>et al.</i> ¹³	31	M	Both	Post-ganglionic	Sensory loss	Retention of urine	Poor (45 mon)
Edelman <i>et al.</i> ¹⁴	46	F	Both	Post-ganglionic	Sensory + Motor Impairment	Retention of urine	Fair (5 mon)

Table 2 *Cholinergic dysautonomia*

Author	Age	Sex	Cholinergic/Adrenergic	Site of neural injury	Other neurological deficit	Urological problem	Recovery/duration
Thomaschevsky <i>et al.</i> ¹⁶	6	F	Cholinergic	Post-ganglionic	—	Retention of urine	Moderate (2 yr)
Hopkins <i>et al.</i> ⁴ (Case 2)	11	F	Cholinergic	Post-ganglionic	—	Retention of urine	None (16 yr)
Anderson <i>et al.</i> ¹⁷	19	F	Cholinergic	Post-ganglionic	—	Retention of urine	Incomplete (2 yr)
Harik <i>et al.</i> ¹⁸	9	M	Cholinergic	Post-ganglionic	—	Retention of urine	Moderate (18 yr)
Hopkins <i>et al.</i> ¹⁹	11	M	Cholinergic ? some adrenergic	Post-ganglionic	—	Frequency of micturition	Incomplete (9 mon)

re-established and could only be achieved by suprapubic manual compression (Credé manoeuvre).

The patient had now been followed up for 15 years and during this time her clinical condition has remained static. She is only able to empty her bladder by use of the Credé manoeuvre, and this has resulted in pressure marks on the lower abdomen.

Case 2 *Pandysautonomia*

The female patient presented in 1980, aged 52 years, with a subacute onset of difficulty with micturition, culminating in urinary retention. She also complained of an excessively dry mouth, severe constipation, and a sensation of dizziness on standing. On examination, both pupils were dilated, there was a total absence of sweating and the blood pressure fell from 160/80 mm Hg in the supine position to 130/60 on standing. Detailed physiological tests of autonomic function were undertaken according to the methods described by Bannister¹⁵ and a diagnosis of pandysautonomia of subacute onset was made. Urinary retention persisted after a prolonged period of urethral catheterisation, and the patient was therefore taught intermittent self-catheterisation. She has continued to practise this four to six times per day, for the past four years. Although she is able to perceive when her bladder is full, she is quite

unable to void. At the time of the present investigation she was receiving no medication.

Methods

Urodynamic assessment was carried out by cystometry at a filling rate of 100 ml/s with simultaneous radiography of the bladder.²⁰ In addition, the intravesical pressure response to 100 µg of carbachol was assessed, after the bladder had been filled to a volume of 100 ml with saline; a pressure rise of more than 20 cms of water is taken to indicate denervation supersensitivity.²¹ A coaxial needle was inserted percutaneously into the striated muscle of the urethral sphincter and 10 individual motor units were isolated and their amplitude and duration measured from film.²² At cystoscopy bladder muscle biopsies were taken; the tissue was rapidly frozen in liquid nitrogen and subsequently processed for both acetylcholinesterase²³ and tissue catecholamines.²⁴ The density of enzyme-positive nerves was assessed using a point-counting technique. An eye-piece graticule with a grid divided into 1 mm squares was used. At each point of intersection the underlying tissue (that is smooth muscle cell or nerve) was noted. Different areas of tissue were examined, far enough apart to preclude counting any point twice. A minimum of 500 and

Table 3

	Controls (n = 10)	Cholinergic dysautonomia	Pandysautonomia
Bladder capacity (ml)	447 (± 119)	500	500
Proximal urethral configuration	Competent	Competent	Incompetent
Intravesicular pressure during filling (cm of water)	10 (± 8)	10	27
Voiding pressure (cm of water)	44 (± 18)	0	40
Flow rate (ml/s)	21 (± 13)	8	0
Intravesicular pressure in response to carbachol (cm of Water)	8 (± 4.4)	38	30
Mean motor unit amplitude	2 mV	2 mV	2 mV
Mean motor unit duration	6 ms	6 ms	6 ms
Polyphasic units	0%	0%	0%
Cholinergic nerve density (nerves/square mm)	470 (± 134)	5 (± 2)	287 (± 2.0)
Sub-epithelial plexus	normal	normal	normal

a maximum of 2000 points were counted in every case, and a mean value for the density of innervation per square mm was calculated for each patient.

Results (Summarised in Table 3)

Both the patient with cholinergic dysautonomia (Case 1) and the patient with pandysautonomia (Case 2) appeared to have normal sensation of bladder filling. The bladder capacity in both cases was 500 ml, a value not significantly different from the mean value found in controls (447 mls $\pm$ SD 119). During filling, the proximal urethra appeared competent in Case 1, as in controls; but in the patient with pandysautonomia, the bladder neck was widely dilated. The mean intravesicular pressure rise in response to filling in the control group was 10 cm of water (± 8.0), and in no control subject did this exceed 15 cm of water. In the patient with pure cholinergic dysautonomia, intravesicular pressure rose to 10 cm during filling, while in the patient with pandysautonomia, there was a pressure rise to 27 cm of water.

On request to void, all the control patients were able to comply, achieving a mean intravesicular pressure of 44 cm of water (± 18) and a mean flow rate of 21 ml/s (± 13). By contrast, the patient with cholinergic dysautonomia was unable to generate any measurable detrusor contraction, and voided by means of the Credé manoeuvre, leaving a residual volume of only 50 ml. In the patient with pandysautonomia an intravesicular pressure rise to 40 cm of water was recorded, but she was unable to void at all.

None of the control patients responded to subcutaneous carbachol with an intravesicular pressure rise of more than 15 cm of water. By contrast, both the patient with cholinergic dysautonomia and the patient with pandysautonomia exhibited supersensitive response to this drug, with intravesicular pressure rises of 38 cm and 30 cm of water respectively. In association with the rise of intravesicular pressure, both patients experienced a marked desire to

void, as well as a marked meiosis, profuse salivation and sweating, together with severe abdominal colic.

Individual motor units isolated from the striated muscle of the urethral sphincter of both patients with dysautonomia were within the normal range of measured range of amplitude and duration and no units were polyphasic.²²

Fig. 1 Bladder muscle biopsy specimen from a female control patient, aged 35 yrs, processed to demonstrate tissue cholinesterases. Note the rich plexus of darkly staining cholinergic nerves distributed among the smooth muscle bundles. ($\times 50$).

Fig. 2 Bladder muscle biopsy from the patient with cholinergic dysautonomia (case 1). There is a striking absence of acetylcholinesterase-positive nerves among the smooth muscle bundles ($\times 50$).

Fig. 3 Bladder biopsy from the patient with cholinergic dysautonomia (case 1). The subepithelial plexus of enzyme positive nerves is preserved in spite of the almost complete absence of similarly staining nerves in the muscularis. ($\times 40$).

In 10 control patients, bladder muscle biopsy specimens processed for tissue acetylcholinesterases revealed the presence of numerous enzyme-positive nerves in the muscularis (mean density = 470 nerves/square mm (± 134) (fig 1). There was, in addition, a rich plexus of acetylcholinesterase-positive nerves present in the lamina propria, adjacent to the epithelium. By contrast, in the patient with cholinergic dysautonomia, the bladder muscularis was almost devoid of enzyme-containing nerves (density = 5 nerves/square mm (± 2.0) (fig 2), while that of the patient with pandysautonomia had a significantly reduced density of nerves compared with controls (287 nerves/square mm ± 2.0). Despite this deficit, acetylcholinesterase-positive nerve fibres were present in the lamina propria of both patients with dysautonomia and, as in controls, appeared particularly numerous adjacent to the epithelium (fig 3).

In specimens from controls and the two patients with dysautonomia, catecholamine-containing nerves were exceedingly sparse, and in

many cases were not observed even after extensive searching of the sections.

Discussion

The present study serves to define the nature of the bladder dysfunction that occurs in pandysautonomia and cholinergic dysautonomia. The cases are of especial interest because they not only cast light upon the differential roles played by sympathetic and parasympathetic nerves in the lower urinary tract but also provide a means of distinguishing afferent from efferent nerve endings in the bladder.

Urodynamic studies confirmed that the principal defect of bladder function in both patients with dysautonomia was a failure to initiate and sustain an adequate detrusor contraction during attempted micturition. In this context, our finding of an almost complete absence of acetylcholinesterase-positive nerves in Case 1, and a marked reduction in Case 2, is significant: similar depletion in those nerves has also been reported in patients who have suffered

injury to their peripheral parasympathetic nerves at the time of pelvic surgery²⁵ with impairment of detrusor contractility as a result. Clearly, these findings lend weight to the view that the acetylcholinesterase-containing nerves distributed to bladder muscle are predominantly responsible for detrusor contraction during micturition.

In spite of the loss of neurally-mediated detrusor contraction in our two patients, both exhibited an abnormal intravesicular pressure rise in response to 100 μ g of carbachol. This indicates that their bladder smooth muscle receptor sites remain intact, and indeed are supersensitive, and that the muscle fibres themselves maintain their ability to contract in response to agonist agents, even after many years of profound denervation.

Both these patients had normal sensation of bladder filling, and it therefore seems significant that both patients appeared to have striking preservation of acetylcholinesterase-positive nerves in the suburothelial plexus, similar to that found in controls. The function of these subepithelial nerves has been the subject of some debate: while Gosling and Dixon²⁶ have argued that they may be sensory nerves, Uemura *et al.*²⁷ suggested that they are motor in function. The results of the present study are clearly consistent with the view that these nerves are responsible for conveying the sensation of bladder distension.

There are also widely differing opinions concerning the innervation of the striated muscle of the urethral sphincter. Elbadawi and Shenck²⁸ have reported that in the dog, this muscle has a triple parasympathic/sympathetic/somatic nerve supply, although Wein *et al.*²⁹ have only been able to demonstrate somatic nerves and motor end plates. The observation that the urethral sphincter electromyography in our two patients revealed entirely normal motor units, and that there was no incontinence, would appear to indicate that, provided somatic nerve function is unimpaired, the striated muscle of the urethral sphincter is able to function normally in spite of a deficit of peripheral autonomic nerve supply.

A further area of controversy is the mechanism by which proximal urethral competence is maintained. Although Barbalias and Blaivas³³ have argued that sympathetic neural activity is essential, Nordling *et al.*³¹ maintain that parasympathetic efferent activity is the critical factor. The fact that proximal urethral competence was maintained in our patient with cholinergic dysautonomia, who clearly had complete loss of parasympathetic activity, would appear to support the former view, and implies that the parasympathetic efferent nerves play little or no part in maintaining bladder neck closure.

The cause of the autonomic neuropathy in these and other cases is unknown. An autoimmune aetiology has been suggested on the basis that an experimental autonomic neuropathy may be induced in rabbits by immunisation with human sympathetic tissue.³² Furthermore, immunofluorescence studies on skin biopsy specimens from a case with pure cholinergic dysautonomia¹⁸ revealed the presence of IgG antibodies in association with sudomotor postganglionic cholinergic fibres; similar antibodies were absent from control material. It remains to be determined why the autonomic nerves should be selectively involved in these disorders, and why, in the two cases reported here and in others in the literature, recovery was incomplete.

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