Urodynamic evaluation of patients with autosomal dominant pure spastic paraplegia linked to chromosome 2p21-p24

L Neerup Jensen, T Gerstenberg, E B Kallestrup, P Koefoed, J Nordling, J E Nielsen

Abstract

Objectives—There are at least three clinically indistinguishable but genetically different types of autosomal dominant pure spastic paraplegia (ADPSP). Lower urinary tract symptoms are often present but have not been described in a homogeneous patient population. In this study lower urinary tract symptoms, cystometrical, and neurophysiological characteristics are described in patients with ADPSP linked to chromosome 2p21-p24.

Methods—Lower urinary tract symptoms were recorded at an interview and according to a formalised questionnaire. Eleven patients were clinically evaluated and cystometry, measurements of the cutaneous perception threshold, bulbocavernous reflex latency, and somatosensory evoked potentials (SSEPs) of the pudendal nerve were performed.

Results—All patients experienced urinary urgency or urge incontinence. Rectal urgency and sexual dysfunction were reported by most patients. The cystometrical findings showed a mixed pattern of bladder dysfunction. The SSEPs were normal in all but the bulbocavernous reflex latency was significantly prolonged in seven patients and the cutaneous perception threshold was raised in five patients.

Conclusions—Lower urinary tract symptoms and probably also bowel and sexual dysfunction in patients with ADPSP linked to chromosome 2p21-p24 are due to a combination of somatic and autonomic nervous system involvement which support the proposed multisystem affection in ADPSP linked to chromosome 2p21-p24.

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Keywords: autosomal dominant pure spastic paraplegia linked to chromosome 2p; voiding; bowel; sexual dysfunction; urodynamics; neurophysiology

Hereditary spastic paraplegia is a heterogeneous group of rare neurodegenerative disorders of the motor system characterised by slowly progressive spasticity and weakness of the lower limbs.

Based on the clinical features they are divided into two groups, depending on whether the disorder is a pure spastic paraplegia or a more complex syndrome with other codominating signs such as atrophy, mental retardation, eye symptoms, epilepsy, ataxia, dystonia, and peripheral neuropathy. Additional but not obligatory features seen in the pure form which predominantly affects legs may be hyperreflexia and weakness of the upper limbs, disturbance of sphincter function, and mild sensory impairment. In pure hereditary spastic paraplegia, inheritance is most commonly autosomal dominant.

By linkage analyses autosomal dominant pure spastic paraplegia (ADPSP) has been mapped to the chromosomes 14q, 2p, and 15q. By the “spastic paraplegia” is likely to be a symptom due to variable mutations of various genes in the CNS involving more components of the corticospinal tracts (neuron, axon, myelin, interneuron, synapse, and receptors).

A dynamic CAG repeat expansion has recently been identified as the most likely disease causing mutation in ADPSP linked to chromosome 2p21-p24. The neuropathological feature of ADPSP is axonal degeneration that is maximal in the terminal portions of the longest descending and ascending tracts (crossed and uncrossed corticospinal tracts to the legs, fasciculus gracilis fibres, and to a lesser extent, spinocerebellar fibres) whereas the neuronal cell bodies of the degenerating fibres are preserved. Dorsal root ganglia, posterior roots, and peripheral nerves are normal.

Lower urinary tract symptoms are often present, but most reports on voiding symptoms in hereditary spastic paraplegia are descriptive and only few patients of unknown inheritance and family history have been urodynamically evaluated. Urodynamic evaluation of patients from families with ADPSP with known genetic localisation assuring a homogeneous patient group has not previously been reported. Here we describe the urodynamic findings in 11 patients from five different families with ADPSP linked to chromosome 2p21-p24.

Patients and methods

In six of eight families with ADPSP linked to chromosome 2p21-p24, lower urinary tract symptoms were present in 16 of 44 definitely affected members. Family details and clinical features as well as neurophysiological and MRI findings in five of these families are previously described. After informed consent was obtained, two patients from family A, four from family C, three from family E, and one patient from each of the families K and L were studied. Five patients refused participation.

Genitourinary symptoms were recorded both at an interview and according to a formalised questionnaire. Each patient filled in a frequency/volume chart at home during 48 hours to assess the voiding symptoms. Urody-
Table 1. Clinical data of the patients with ADPSP and LUTS

<table>
<thead>
<tr>
<th>Family, patient No</th>
<th>A1</th>
<th>A2</th>
<th>C3</th>
<th>C4</th>
<th>C5</th>
<th>C6</th>
<th>E7</th>
<th>E8</th>
<th>E9</th>
<th>K10</th>
<th>L11</th>
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<td>F</td>
<td>M</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>M</td>
<td>M</td>
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<td>M</td>
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<tr>
<td><strong>Age (y)</strong></td>
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<td>37</td>
<td>58</td>
<td>33</td>
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<td>41</td>
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<td>34</td>
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<td><strong>Age at onset (y):</strong></td>
<td>30</td>
<td>1</td>
<td>42</td>
<td>23</td>
<td>43</td>
<td>33</td>
<td>35</td>
<td>20</td>
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<td>18</td>
<td>42</td>
<td>23</td>
<td>50</td>
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<td>43</td>
<td>35</td>
<td>24</td>
<td>47</td>
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</tr>
<tr>
<td><strong>Symptoms:</strong></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Urgency</td>
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<td>++</td>
<td>+++</td>
<td>++</td>
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<td>-</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Urge incon tinence</td>
<td>++</td>
<td>+</td>
<td>+</td>
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<td>+</td>
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<td>Nocturia</td>
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<td>-</td>
<td>-</td>
<td>+</td>
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<td>++</td>
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<td>Hesitancy</td>
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<td>+++</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>++</td>
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<tr>
<td>Diminished stream</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
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<td>-</td>
<td>-</td>
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<td>++</td>
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<tr>
<td>Rectal urge</td>
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<td>+</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>++</td>
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<tr>
<td>Rectal urge incon tinence</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

**+, ++, +++; −, −+, −++, −++ = mild; ++, +++, +++ = moderate; ++++, ++++, ++++ = severe; −, −−−−, −−−−−− = absent; ±, ±±±± = indeterminant

Dynamic evaluation was performed with patients in the supine position using a double lumen transurethral catheter, rectal pressure balloon, and two EMG surface electrodes placed in the region of the external anal sphincter. If possible a free flow study was performed on arrival. Patients were then catheterised and postvoid residual urine volume measured. Cystometry was performed using body warm saline infused at 50 ml/min. Intravesical and rectal pressures were recorded simultaneously with the EMG activity on a multichannel recorder (MMS UD-2000). Definitions conform to the International Continence Society (ICS) standards.12 The sensory threshold was defined as the lowest current perceptible. A mean of three measurements was used for calculation.

A detailed description of lower urinary tract symptoms in the remaining 10 patients is shown in table 1.

Urinary urgency and frequency were the dominant complaints and six patients regularly experienced urge incontinence. Other lower urinary tract symptoms included nocturia, hesitancy, and diminished force of stream. Rectal urgency was reported by all patients but one, and eight patients occasionally experienced rectal urge incontinence.

Sexual dysfunction was reported by seven patients (two women and five men). The male complaints varied from slightly reduced erection to totally loss of the ability to obtain erection. The women reported reduction or lack of lubrication and reduction in orgasmic capacity. One woman did not answer the questions concerning sexual function.

The cystometrical findings are shown in table 2. We found a mixed pattern of bladder dysfunction; six patients demonstrated normal detrusor activity (patient Nos 1–4, 6, and 11), patient No 5 was found to have detrusor hyperreflexia and no detrusor-sphincter dyssynergia; having failed a trial of several anticholinergic drugs, he preferred suprapubic catheter drainage.

An accurate description of the symptoms was not possible in the patient with the indwelling catheter.
patients but two. Seven patients had an early first sensation; the capacity being almost normal in all but one patient (No 8). In the male patients rectal examination showed normal prostate size and consistency for age. Clinically, the bulbocavernosus reflex was absent in six patients and only normal in one (patient No 10), as the anal and anocutaneous reflexes were reduced in all but patient No 10 (table 3). The anal sphincter tone was decreased in the same 10 patients. The cutaneous perception threshold was raised in five patients. SSEPs were normal in all patients. The bulbocavernosus reflex latency was significantly prolonged in seven patients with an obvious correlation between a clinically absent bulbocavernosus reflex and prolongation of the bulbocavernosus reflex latency. There were no correlations between the duration of symptoms, the three point functional grading score, urological symptoms, and cystometrical and neurophysiological findings.

### Discussion

The frequency of urinary symptoms in our patients (36%) correlates well with the frequency of 34% reported by Dürr et al in 83 patients with definite ADPSP linked to chromosome 2. However, they reported a sex difference, the women more often having sphincter disturbances than men. In our patients there was a higher proportion of men reporting lower urinary tract symptoms but this difference is probably due to the relatively few patients and most certainly does not rely on a real biological variation. Urinary symptoms most often are late manifestations but in three patients, those symptoms were present from the onset of the disease. In agreement with other reports the most common symptoms were urinary urgency, urge incontinence, and frequency. Urinary urgency has been extensively reported, but rectal urgency/urge incontinence. This finding may suggest an autonomic component which, in combination with the weak pelvic floor, might cause the rectal urgency/urge incontinence; however, in the very few studies trying to uncover other changes in autonomic function—for example, sweat regulation and vasomotor function—the results were normal.

In the eight patients showing raised postvoid residual urine volumes, an obstructive aetiology or detrusor weakness might be proposed. Bushman et al reported detrusor-sphincter dyssynergia in one of three patients with hereditary spastic paraplegia of unknown inheritance and family history. The EMG recording was not satisfactory in four of our patients; however, hyperreflexia was not disclosed in those cases, therefore the raised postvoid residual urine volumes cannot be explained by detrusor-sphincter dyssynergia. In the three patients in whom hyperreflexia was noted a spinal pathology could be responsible for the unstable detrusor without evidence of an organic or neurogenic increase in outlet resistance.

The weakness of the pelvic floor correlates well with the finding of hyperreflexia, indicating

### Table 2 Cystometrical findings in the patients with ADPSP and LUTS

<table>
<thead>
<tr>
<th>Patient No</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
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<tbody>
<tr>
<td>PVR (ml)</td>
<td>90</td>
<td>110</td>
<td>80</td>
<td>60</td>
<td>150</td>
<td>100</td>
<td>±</td>
<td>60</td>
<td>0</td>
<td>180</td>
<td>15</td>
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<tr>
<td>First sensation (ml)</td>
<td>26</td>
<td>36</td>
<td>41</td>
<td>56</td>
<td>156</td>
<td>349</td>
<td>78</td>
<td>±</td>
<td>35</td>
<td>18</td>
<td>52</td>
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<tr>
<td>Capacity (ml)</td>
<td>480</td>
<td>180</td>
<td>161</td>
<td>353</td>
<td>471</td>
<td>325</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>±</td>
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<tr>
<td>Hyperreflexia</td>
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<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>DSD</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>±</td>
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</tbody>
</table>
| =indeterminant; PVR=post-void residual urine volume. DSD=detrusor-sphincter dyssynergia.

### Table 3 Clinical evaluation of reflexes, anal sphincter function and the neurophysiological findings in the patients with ADPSP and LUTS

<table>
<thead>
<tr>
<th>Patient No</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
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<td>0</td>
<td>0</td>
<td>0</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
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<tr>
<td>Anal reflex</td>
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<td>+</td>
<td>+</td>
<td>+</td>
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<td>+</td>
<td>++</td>
<td>0</td>
<td>++</td>
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<td>+++</td>
</tr>
<tr>
<td>Anocutaneous reflex</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>++</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Cutaneous perception</td>
<td>2.6</td>
<td>1.9</td>
<td>4.0</td>
<td>2.8</td>
<td>8.1</td>
<td>3.9</td>
<td>9.9</td>
<td>5.5</td>
<td>4.9</td>
<td>3.8</td>
<td>5.7</td>
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<tr>
<td>BC reflex latency</td>
<td>63</td>
<td>129</td>
<td>61</td>
<td>123</td>
<td>156</td>
<td>36</td>
<td>37</td>
<td>44</td>
<td>45</td>
<td>30</td>
<td>36</td>
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</tbody>
</table>
| BC=Cublcavernosus: 0=absent; + =weak; ++ =moderate; +++=normal. Cutaneous perception: normal values: men: median (range) 3.3 (3.0-4.2) mAmp/0.2 ms/2 Hz; women: 2.7 (2.0-3.8) mAmp/0.2 ms/2 Hz. BC latency: normal values: men and women: median (range): 36 (30-40) ms.
that a peripheral neuropathy may be part of the pathophysiological picture. This is in accordance with the finding of prolongation of the bulbocavernosus reflex latencies, suggesting dysfunction of the integrity of central and peripheral tracts of the sacral reflex arc that consist of the dorsal nerve of the clitoris or penis, the S2-S4 cord segments, and the motor branch of the pudendal nerve innervating the bulbocavernous muscles, and anal and urethral sphincter.\textsuperscript{a}\textsuperscript{21} The bulbocavernosus reflex has been evaluated clinically compared with the EMG demonstration of the reflex; the absence of a bulbocavernous reflex in male patients was found to be indicative of a neurological lesion involving the sacral cord and highly suggestive of such a lesion in female patients.\textsuperscript{a}\textsuperscript{22} The normal SSEPs are in accordance with the normal findings from upper and lower limbs previously reported in 16 patients with ADPSP linked to chromosome 2p21-p24.\textsuperscript{11} As the SSEPs were normal in all cases the prolonged bulbocavernous reflex latencies indicate affection of the motor part of the somatic pudendal nerve. The delay of the bulbocavernosus reflex, however, may also be located in the sacral cord, involving internurons connecting the afferent and efferent part of the bulbocavernosus reflex arc. The cutaneous perception threshold has been evaluated in males only. It is thought to give a semiquantitative measurement of sensory nerve fibres mediating pain, different from those of the dorsal columns responsible for the SSEPs; and the raised cutaneous perception thresholds therefore suggest an affection of those fibres of the sensory part of the pudendal nerve.\textsuperscript{21} A high incidence of multisystem subclinical involvement of the CNS has been proposed by different neurophysiological techniques and MRI of the brain also\textsuperscript{12}\textsuperscript{3} and the degenerative processes seem not only to be confined to the long motor and sensory tracts. We propose that lower urinary tract symptoms and probably also bowel and sexual dysfunction in patients with ADPSP linked to chromosome 2p21-p24 are due to a combination of somatic and autonomic nervous system involvement supporting the proposed multisystem affection in ADPSP. However, this study is the first on ADPSP linked to chromosome 2p21-p24 and therefore more studies are warranted to elucidate further aspects of the pathophysiological background of the bladder, bowel, and sexual dysfunction so obviously associated with the disease.

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