Lower urinary tract function in patients with pituitary adenoma compressing hypothalamus

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Objective: To investigate LUT function in patients with pituitary adenomas.

Methods: Urodynamic studies were carried out in three patients with LUT symptoms who had pituitary adenomas extending upwards to the hypothalamus.

Results: All three male patients (age 28 to 62 years) developed LUT symptoms (urinary urgency and frequency; urinary incontinence; voiding difficulty and retention) along with weight loss, psychiatric symptoms, unsteady gait, and/or visual disturbances. One had the syndrome of inappropriate secretion of antidiuretic hormone, but none had diabetes insipidus. Two had resection of the tumour and subsequent radiation therapy, but LUT dysfunction persisted. The third patient had partial resection of the tumour to ameliorate hydrocephalus. Urodynamic studies showed detrusor overactivity during the storage phase in all patients; during the voiding phase there was underactive detrusor in two and non-relaxing sphincter in one.

Conclusions: Hypothalamic lesions can cause severe LUT dysfunction in both the storage and voiding phases of micturition. This may reflect the crucial role of the hypothalamus in regulating micturition in humans.

Background: The micturition reflex is under the tonic influence of suprapontine structures including the anteromedial frontal cortex, basal ganglia, and hypothalamus. However, there have been few reports about the role of the hypothalamus on the lower urinary tract (LUT) function in humans.

Objective: The micturition reflex is under the tonic (mainly inhibitory) influence of several suprapontine structures, including the anteromedial frontal cortex (frontal micturition centre), the basal ganglia, and the hypothalamus. However, there have been few reports on clinical LUT dysfunction resulting from hypothalamic lesions. Ten years ago we had two such patients who presented with LUT dysfunction. Each had a pituitary adenoma extending upwards to the hypothalamus, which was detected by brain computed tomography (CT) with positive contrast enhancement. Recently, we encountered a third patient with the same brain lesion, detected by a magnetic resonance imaging (MRI). In this report, we describe the LUT function of these three patients, with a brief review of the literature.

CASE REPORT

Case 1

A 28 year old previously healthy man began to have progressive anorexia and weight loss (86 kg to 61 kg within four months). A month later, his family noticed that he had night time urinary frequency, urinary urgency, and dysarthria. In the next month, he was admitted to a local gastroenterology hospital. Fibreoptic examination of both upper and lower gastrointestinal tracts was carried out, but the results were normal. On admission to our department the next month, his LUT symptoms included night time urinary frequency (two to three times), urinary urgency, and reflex urinary incontinence (once or twice a day), but without daytime urinary frequency, nocturnal enuresis, or difficulty in voiding. He had no episodes of postural hypotension or constipation.

On examination, he was markedly emaciated (172 cm; 54.5 kg). His conjunctivae were pale, and his skin was dry. His pubic hair was thin. Mild gynaecomastia was observed, and the development of the penis and testes was poor. His state of consciousness was normal. However, he was depressed and a suicidal tendency was suspected. He had bitemporal hemianopia. Other cranial nerves were normal except for mild dysarthria. He showed bradykinesia and muscle rigidity, along with mild bilateral weakness of the flexor muscles in the lower extremities. The deep tendon reflexes were brisk, but Hoffman and Babinski signs were negative. Sensory examination was normal, including the genital area.

Routine laboratory investigations showed mild sideropenic anaemia. Cerebrospinal fluid examination revealed a mildly increased cell count of 7/mm³ (all mononuclear cells; no malignant cells were seen), a total protein of 85 mg/dl, but normal values of glucose (2.94 mmol/l) and chloride (126 mmol/l). Endocrine examination showed low values in serum testosterone (1.08 ng/ml), oestrogen E1 (20.3 IU/l), E2 (126 IU/l), and E3 (<5 IU/l). Baseline levels of thyroid stimulating hormone (TSH), adrenocorticotrophic hormone (ACTH), growth hormone (GH), and prolactin (PRL) were normal. However, tolerance tests showed low secretion of hormones in responses to insulin, thyroid hormone releasing hormone (TRH), bromocriptine, and luteinising hormone releasing hormone (LHRR). Serum antidiuretic hormone (ADH) was normal and there were no signs of diabetes insipidus or nocturnal polyuria. Analysis of the chromosomal pattern showed 47XXY. Brain CT revealed a pituitary tumour (8×8×20 mm) extending upward to the hypothalamus with positive contrast enhancement, which seemed to compress the hypothalamus, optic chiasm, stria terminaIs, septal area, and suprapoetic area (fig 1A). A diagnosis of Klinefelter’s syndrome was made on the basis of the physical signs.

Abbreviations: LUT, lower urinary tract; PAG, periaqueductal grey matter; PMC, pontine micturition centre; SIADH, syndrome of inappropriate secretion of antidiuretic hormone
endocrine examination, and chromosomal pattern. In addition, the rapid progressive weight loss, psychiatric symptoms, visual field defect, and the LUT dysfunction were thought to be caused by the pituitary adenoma compressing the hypothalamus.

Subtotal resection of the tumour and subsequent radiation therapy (total 61 Gy) were undertaken. Pathology revealed a pituitary adenoma. As a result, though visual field disturbance continued to progress mildly, the weight loss halted and the psychiatric symptoms improved. However, nocturnal urinary frequency and urge incontinence persisted, so urodynamic studies were carried out. Rectal examination and urethrocystography showed no evident prostatic hyperplasia or urethral stricture. He had no urinary tract infection at the time of urodynamic studies, nor was he taking a drug that would influence LUT function. The methods and definitions used for the urodynamic studies conformed to the standards proposed by the International Continence Society. The normal range of urodynamic variables is as follows:

- residual urine volume under 30 ml;
- first sensation more than 100 ml but less than 300 ml;
- bladder capacity more than 200 ml but less than 600 ml.

After voluntary voiding, residual urine measurement in case 1 showed a minimum post-void residual volume of 40 ml. Electromyography (EMG)-cystometry was undertaken with an 8 F double lumen urethral catheter, a rectal catheter, and a concentric needle electrode that was inserted into the anal sphincter. He had normal first sensation of 100 ml, but a small maximum bladder capacity of 140 ml. Detrusor overactivity was noted at the end of bladder filling. When asked to void, following the detrusor overactivity his detrusor

![Figure 1](http://jnnp.bmj.com/)

**Figure 1** Brain imaging in the patients described. (A) Brain computed tomography (CT) of case 1 (coronal and axial planes with contrast enhancement), showing a pituitary tumour (8 x 8 x 20 mm) extending upward to the hypothalamus, seeming to compress the hypothalamus, optic chiasm, stria terminalis, septal area, and suprachiasmatic area. (B) Magnetic resonance imaging (MRI) (sagittal plane, proton weighted image) and CT (axial plane with contrast enhancement) of case 2, showing a similar sized pituitary tumour (10 x 10 x 25 mm). (C) MRI in case 3 (coronal and sagittal planes, gadolinium-DTPA images), showing a pituitary tumour (35 x 25 x 20 mm) extending upward to the third ventricle and compressing the hypothalamus bilaterally.
pressure increased moderately. There was no detrusor–sphincter dysynergia. These results indicated the presence of neurogenic LUT dysfunction.

**Case 2**

A 62 year old man began to have mild fever (38.0°C), general weakness, and symptoms of upper respiratory infection. A week later, administration of an anti-inflammatory drug improved his pyrexia. However, general weakness progressed and he developed gait disturbance. He also experienced voiding difficulty, but not urinary frequency, urgency, or incontinence. He had no episodes of postural hypotension or constipation. A week later, he was admitted to our hospital.

Physical examination on admission showed no abnormal findings. Neurological examination showed some degree of disorientation in time and space. He had enlargement of the blind spot and temporal narrowing of the visual fields bilaterally. The other cranial nerves were normal. There was mild weakness of the left arm and leg. The deep tendon reflexes were exaggerated, but Hoffman and Babinski signs were not observed. Sensation, including that in the genital area, was normal.

Two days after admission, he suddenly developed urinary retention without any precipitating cause, and an indwelling balloon catheter was inserted. Routine laboratory tests were normal except for marked hyponatraemia (Na 114 mmol/l) and low serum chloride (82 mmol/l). Endocrine examination showed that basic secretion of most of the anterior pituitary hormones was decreased, but secretion of posterior pituitary hormone (ADH) was increased. A diagnosis of the syndrome of inappropriate secretion of ADH (SIADH) was therefore made. Brain CT and MRI showed a pituitary tumour (10 × 10 × 25 mm) extending upward to the hypothalamus with positive contrast enhancement (fig 1B). The tumour extended from the pituitary gland to the optic chiasm, hypothalamus, sistra terminals, septal area, and preoptic area. Cervical x ray showed mild spondyloitic change in the third and fourth vertebrae. On rectal examination and urethrocytography there was no evident prostatic hyperplasia or urethral stricture. He had no urinary tract infection at the time of urodynamic studies, nor was he taking any drug that would influence LUT function.

On EMG-cystometry, the first sensation was 230 ml and the maximum bladder capacity was 510 ml (both in the normal range). Minor detrusor overactivity was observed during bladder filling. When asked to void, following slight detrusor overactivity, he was unable to contract the detrusor at all (underactive detrusor). He could not relax the sphincter on voiding. These results indicated neurogenic LUT dysfunction.

After admission to our hospital, his visual disturbance gradually progressed, and he developed bitemporal hemianopia. Though he could void by himself, micturition difficulty persisted and night time urinary frequency (two to three times a week) became apparent. We considered that hyposcretion of anterior pituitary hormones, SIADH, visual field disturbance, and the LUT dysfunction were likely to be caused by the pituitary adenoma compressing the hypothalamus. We prescribed 20 mg/day of prednisolone to counter the anterior pituitary hyposcretion, and his water intake was limited to 800 ml/day to ameliorate the SIADH. Partial resection of the tumour and subsequent radiation therapy (total 40 Gy) were carried out. Pathology of the resected specimen showed a pituitary adenoma. Following surgery, his visual disturbance improved somewhat on the left and he became able to urinate. However, right sided visual disturbance persisted, and he still had night time frequency (two to three times), urinary urgency (two to three times a week), and mild voiding difficulty.

**Case 3**

A 60 year old man gradually developed an unsteady gait, which was followed by disorientation, urinary urgency/ frequency, and voiding difficulty which were present for four months before his admission to hospital. On admission to our hospital, his LUT symptoms included daytime frequency (10 times), night time frequency (four times), urinary urgency, and urgency/functional incontinence, but without nocturnal enuresis, delay in initiating urination, prolongation of urination, straining, or the sensation of post-void residual urine. He had no postural hypotension or constipation.

On examination, he was uncooperative and had disorientation and dementia. On Hasegawa’s dementia rating scale (equivalent to the mini-mental state examination), he scored 15/30. He was also uncooperative to complete visual field examination. He had no apparent motor weakness. Deep tendon reflexes were normal, with negative Babinski sign. He had mild postural tremor and rigidity in both hands. There was a slight lack of coordination and a mildly broad based gait. Sensation was normal. Routine laboratory data were normal. Gonadotropins (LH, FSH, prolactin), GH, and TSH were normal. He did not have diabetes insipidus.

Brain MRI showed a pituitary mass (35 × 25 × 20 mm) which extended upward to the hypothalamus and appeared with low signal intensity on T1 weighted images and with high signal intensity on T2 weighted images. Gadolinium-DTPA images showed positive contrast enhancement. Brain MRI also showed mildly enlarged lateral ventricles (secondary hydrocephalus), most probably caused by obstruction of the foramina of Monro by the mass lesion.

He underwent partial resection of the tumour, which completely reversed the hydrocephalus and gradually ameliorated his disorientation and unsteady gait. Pathology of the resected specimen revealed a pituitary adenoma. However, postoperatively he became unable to void and had to begin clean intermittent catheterisation (CIC) three times a day. His voided volume was 30 to 50 ml and the volume of post-void residual urine was 300 to 600 ml, showing urinary retention. The follow up brain MRI two weeks after surgery revealed tumour in the third ventricle still compressing the hypothalamus bilaterally (fig 1C). There was evidence of prostatic hypertrophy on ultrason examination or ultrasound echography. He had no urinary tract infection at the time of the urodynamic studies, nor was he taking a drug that would influence LUT function.

Urodynamic studies showed a voluntary voided volume of 80 ml with a low maximum flow rate (Qmax) of 4 ml/s and a low average flow rate (Qave) of 2 ml/s. He had a post-void residual volume of 220 ml. On EMG-cystometry, the first sensation was at 220 ml and the maximum bladder capacity was 235 ml, both in the normal range. However, detrusor overactivity was noted at the end of bladder filling. When asked to void, following the detrusor overactivity, his detrusor pressure (Pdet) increased only slightly, with poor urinary flow. There was no detrusor–sphincter dysynergia. We also carried out a pressure-flow analysis. The peak Pdet at Qmax (Pdet(Qmax)) indicated equivocal obstruction by the Abrams-Griffiths’ nomogram, and grade 2 (equivocal obstruction) with weak detrusor contraction by Schäfer’s nomogram. These results indicated the presence of neurogenic LUT dysfunction.

To ameliorate the voiding difficulty, the patient was started on 2 mg/day of oral urapidil hydrochloride, a selective α1 adrenergic antagonist. Two weeks after starting this treatment, the voiding difficulty had improved and the voiding
parameters were now as follows: voided volume, 110 ml; Qmax, 13 ml/s; Qave, 7 ml/s; Schäfer grade 1 (normal/equivocal obstruction); weak detrusor contraction; residual urine volume, 10 ml.

**DISCUSSION**

Until recently, few reports have been available on the role of the hypothalamus in LUT function in humans.\textsuperscript{10–12} This is probably because a critical illness such as disturbance of consciousness in the patients with hypothalamic lesions could easily mask any LUT dysfunction that might be present. In 1950, Brouwer\textsuperscript{13} reported a patient initially presenting with urinary incontinence. Necropsy proved that he had a glioma located in the hypothalamus and the third ventricle. In 1965, Andrew and Nathan\textsuperscript{1} described a patient presenting with loss of visual acuity, urinary frequency, urge urinary incontinence, and nocturnal enuresis. Surgical exposure of the brain revealed a cystic lesion compressing the optic chiasm, anterior hypothalamus, and septal area. In the following year, Andrew and Nathan\textsuperscript{14} reported five patients with LUT symptoms appearing after a ruptured cerebral aneurysm. All patients had motor paresis or exaggerated deep tendon reflexes. Surgical procedures carried out in these patients included ligation of the anterior cerebral artery and resection of the frontal rectal gyrus. Although these investigators speculated that the site of lesion responsible for the LUT dysfunction was the anterior hypothalamus, the lesions seemed to be much more widespread than the anterior hypothalamus alone.

Our three patients had various combinations of LUT symptoms (case 1, nocturnal frequency, urinary urgency, reflex incontinence; case 2, nocturnal frequency, urgency incontinence, voiding difficulty, and urinary retention; case 3, diurnal and nocturnal frequency, urgency incontinence, and urinary retention), together with visual disturbances, anorexia, psychiatric symptoms, and SIADH. Case 1 had Klinefelter syndrome, and case 2 had mild cerebral spongiosis at the C3 and C4 vertebrae. However, the LUT symptoms appeared along with symptoms suggestive of hypothalamic lesions. In case 3, LUT symptoms were accompanied by disorientation and gait difficulty caused by secondary hydrocephalus. After resolution of the hydrocephalus following partial resection of the tumour, the patient’s disorientation and gait difficulty improved. However, the LUT symptoms persisted and he developed complete urinary retention. None of the three patients had diabetes insipidus (pseudo-Wilson syndrome) or posterior pituitary insufficiency. Rectal examination, cystourethrography, and ultrasonography showed no evidence of prostatic hyperplasia. They had no urinary tract infections and were taking no drugs that would influence LUT function. Brain MRI or CT in each case revealed a mass lesion in the pituitary gland and the hypothalamus extending to the optic chiasm, stria terminals, septal region, and the preoptic area. Pathology revealed a pituitary adenoma in all cases. Thus the LUT symptoms in our patients can be attributed to the pituitary adenoma compressing the hypothalamus.

Information arising from the LUT reaches the midbrain periaqueductal grey matter (PAG), then descends back to the pontine micturition centre (PMC), which activates the descending pathway to the sacral parasympathetic preganglionic neurones innervating the bladder (pelvic nerves).\textsuperscript{9} The spino-bulbo-spinal micturition reflex is under tonic (mainly inhibitory) influence from several suprapontine structures including the hypothalamus.\textsuperscript{9,10} It is well known that cerebral diseases can lead to a loss of the brain’s inhibitory influence on the micturition reflex.\textsuperscript{17} Filling phase cystometry in the present study showed detrusor overactivity—which is a phasic increase in the detrusor pressure—in all three patients studied. Detrusor overactivity is the major cause of storage disorder.\textsuperscript{17} Previously, Andrew and Nathan\textsuperscript{1} also described detrusor overactivity in a patient with a third ventricular cyst. In an experimental setting, chemical stimulation of the mediobasal hypothalamus in freely moving rats elicited defence-like reactions such as locomotion, rearing, and micturition,\textsuperscript{10} which are akin to those elicited by PAG stimulation (the emotional motor system).\textsuperscript{10,13} This is presumably because the hypothalamus has fibre connections with the limbic brain (the anterior frontal cortex, cingulate cortex, and amygdala).\textsuperscript{12} Under anaesthesia, electrical stimulation of the hypothalamus in cats and dogs elicits either facilitation (particularly in the anterolateral part and the preoptic area) or inhibition (in the medial part and Ford’s H1 area) of the micturition reflex.\textsuperscript{14} In our three patients, however, we could not analyse the detailed location of lesions within the hypothalamus.

During urinary storage, the hypothalamic neurones are known to be activated in both experimental animals\textsuperscript{22} and humans.\textsuperscript{23} The hypothalamus and the preoptic area also have dense fibre connections with the PAG and the PMC,\textsuperscript{24,25} both of which are crucial for the spino-bulbo-spinal micturition reflex arc. The hypothalamus also projects to Omuñ’s (sacral) nucleus, which innervates the urethral sphincter muscles (pudendal nerves).\textsuperscript{17} During the voiding phase, two of our patients (cases 2 and 3) showed an underactive detrusor, though both patients had detrusor overactivity during bladder filling. This condition is known to occur in various types of neurogenic bladder dysfunction.\textsuperscript{17} In addition, one patient (case 2) had an unrelaxing sphincter on voiding, though it normally relaxes completely,\textsuperscript{17} which suggests incoordinated neural control of the bladder and urethra.\textsuperscript{17} Hence, a lesion in the hypothalamus may cause various types of LUT dysfunction, reflecting the crucial role of the hypothalamus in regulating micturition in humans.

**Conclusions**

Our results show that pituitary adenomas compressing the hypothalamus can cause severe LUT dysfunction in both the storage and the voiding phases, reflecting the crucial role of the hypothalamus in regulating micturition in humans.

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**REFERENCES**


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