Lower urinary tract function in patients with pituitary adenoma compressing hypothalamus

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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: 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.

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 depressive 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 (10 IU/l), E2 (<10 IU/l), and E3 (<5 IU/l). Baseline levels of thyroid stimulating hormone (TSH), adrenocorticotropic 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 (LHRH). 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 terminalis, septal area, and supraoptic area (fig 1A). A diagnosis of Klinefelter’s syndrome was made on the basis of the physical signs, and the development of the penis and testes was poor. His state of consciousness was normal. However, he was depressive 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.

CASE REPORT

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. 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. 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. 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. 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. 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.
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  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 × 8 × 20 mm) extending upward to the hypothalamus, seeming to compress the hypothalamus, optic chiasm, stria terminalis, septal area, and supraoptic 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 × 10 × 25 mm). (C) MRI in case 3 (coronal and sagittal planes, gadolinium-DTPA images), showing a pituitary tumour (35 × 25 × 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, stria terminalis, septal area, and preoptic area.
Cervical x ray showed mild spondyloctic change in the third
and fourth vertebrae. On rectal examination and urethrocytos-
tography 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 hemi-
anopia. Though he could void by himself, micturition
difficulty persisted and night time urinary frequency (two
to three times) and urinary urgency (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 hormones, SIADH, visual field disturbance,
and subsequently 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 dis-
orientation 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 (second-
ary 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 ame-
liorated 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 no evidence of prostatic hypertrophy on the examina-
tion 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 (PdetQmax) 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 neuro-
genic 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 treat-
ment, 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.6–8 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, Brouwer9 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 Nathan1 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 Nathan10 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 cervical spondylosis at the C3 and 4 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 (polyuria), postvoid residual urine, posterior pituitary insufficiency. Rectal examination, cystourethrography, and ultrasound echography 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 terminalis, 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).1 The spino-bulbo-spinal micturition reflex is under tonic (mainly inhibitory) influence from several suprapontine structures including the hypothalamus.2,9 It is well known that cerebral diseases can lead to a loss of the brain’s inhibitory influence on the micturition reflex.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.15 Previously, Andrew and Nathan1 also described detrusor overactivity in a patient with a third ventricular cyst. In an experimental setting, chemical stimulation of the medial hypothalamus in freely moving rats elicits defence-like reactions such as locomotion, rearing, and micturition,18 which are akin to those elicited by PAG stimulation (the emotional motor system).19 20 This is presumably because the hypothalamus has fibre connections with the limbic brain (the anterior frontal cortex, cingulate cortex, and amygdala).21 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.22 23 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 animals24 and humans.25 The hypothalamus and the preoptic area also have dense fibre connections with the PAG and the PMC,24 26 both of which are crucial for the spino-bulbo-spinal micturition reflex arc. The hypothalamus also projects to Onuf’s (sacral) nucleus, which innervates the urethral sphincter muscles (pudendal nerves).2 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.27 In addition, one patient (case 2) had an unrelaxing sphincter on voiding, though it normally relaxes completely,27 which suggests incoordinate neural control of the bladder and urethra.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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