Review Article

Int Neurourol J 2018;22:2-8
https://doi.org/10.5213/inj.1836040.020
pISSN 2093-4777 · eISSN 2093-6931

INTERNATIONAL NEUROUROLOGY JOURNAL
INJ
OPEN ACCESS

Central Regulation of Micturition and Its Association With Epilepsy

Hyun-Jong Jang[1], Min Jung Kwon[2], Kyung-Ok Cho[3]

[1]Department of Physiology, The Catholic Neuroscience Institute, College of Medicine, The Catholic University of Korea, Seoul, Korea
[2]College of Medicine, The Catholic University of Korea, Seoul, Korea
[3]Department of Pharmacology, The Catholic Neuroscience Institute, College of Medicine, The Catholic University of Korea, Seoul, Korea

Micturition is a complex process involving the bladder, spinal cord, and the brain. Highly sophisticated central neural program controls bladder function by utilizing multiple brain regions, including pons and suprapontine structures. Periaqueductal grey, insula, anterior cingulate cortex, and medial prefrontal cortex are components of suprapontine micturition centers. Under pathologic conditions such as epilepsy, urinary dysfunction is a frequent symptom and it seems to be associated with increased suprapontine cortical activity. Interestingly, micturition can also trigger seizures known as reflex epilepsy. During voiding behavior, frontotemporal cortical activation has been reported and it may induce reflex seizures. As current researches are only limited to present clinical cases, more rigorous investigations are needed to elucidate biological mechanisms of micturition to advance our knowledge on the process of micturition in physiology and pathology.

Keywords: Micturition; Central regulation; Epilepsy; Reflex epilepsy; Urinary dysfunction

- **Grant/Fund Support:** This work was supported by the Korea Health Technology R&D Project (HI15C2854) through the Korea Health Industry Development Institute (KHIDI) funded by the Ministry of Health & Welfare, Republic of Korea.
- **Conflict of Interest:** The authors have no potential conflict of interest relevant to this article to report.

INTRODUCTION

Micturition is a complex process finely controlled by the brain and the spinal cord [1]. The bladder functions by either storing or emptying urine. Considering that a normal voiding process takes only less than 5 minutes, the bladder is in the storage mode for most of the time. Switching from one state to the other of the bladder can be modulated by the central neural program. It is known that higher micturition centers including pons and suprapontine brain regions decide whether to void after comprehensive integration of information such as bladder fullness and social appropriateness [2]. This information is then transmitted to the spinal cord and subsequent peripheral nerves so that bladder function is under normal control. Since the voiding behavior transits from involuntary to voluntary processes during the postnatal periods [3], complicated regulation of micturition at cellular and network level needs to be established for proper urination. Thus, it is critical to understand how neurophysiological control of the bladder function takes place.

Many neurological diseases affecting the brain, spinal cord and the peripheral nervous system can manifest urinary dysfunction [4]. For example, cerebral palsy, stroke, head injury, multiple sclerosis, Parkinson disease, dementia, spinal cord injury, and peripheral neuropathy show various urinary symptoms, including urinary incontinence, urgency, hesitancy, and urinary retention [4,5]. This can further help us identify important central nervous system regions for micturition and understand how the voiding process is dysregulated under pathologic

Corresponding author: Kyung-Ok Cho https://orcid.org/0000-0002-1314-7584
Department of Pharmacology, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 06591, Korea
E-mail: kocho@catholic.ac.kr / Tel: +82-2-2258-7329 / Fax: +82-2-536-2485
Submitted: February 8, 2018 / **Accepted after revision:** March 20, 2018

circumstances. However, there have been no comprehensive reviews of urinary dysfunction in relation to epilepsy, one of the most common neurological disorders affecting more than 50 million people worldwide [6]. As seizures are abnormal and excessive neuronal excitation that can occur in any brain regions, physiologic micturition pathways can be disrupted in epilepsy. Therefore, we will review physiologic mechanisms of micturition first. The current status of the researches reporting urinary dysfunctions in epilepsy and micturition-induced reflex epilepsy is also then discussed.

PHYSIOLOGIC CONTROL OF MICTURITION

In human, voiding happens involuntarily until 3 to 5 years after birth. It then becomes a voluntary process [3]. Bladder switches between filling and voiding modes depending on signals from the spinal cord and the brain. At early stages of bladder filling, signals from the spinal cord are main determinants of bladder filling (Fig. 1B, C lower parts). Spinal cord receives sensory signals from the bladder via pelvic and hypogastric nerves informing the tension of bladder wall. It then sends sympathetic, para-

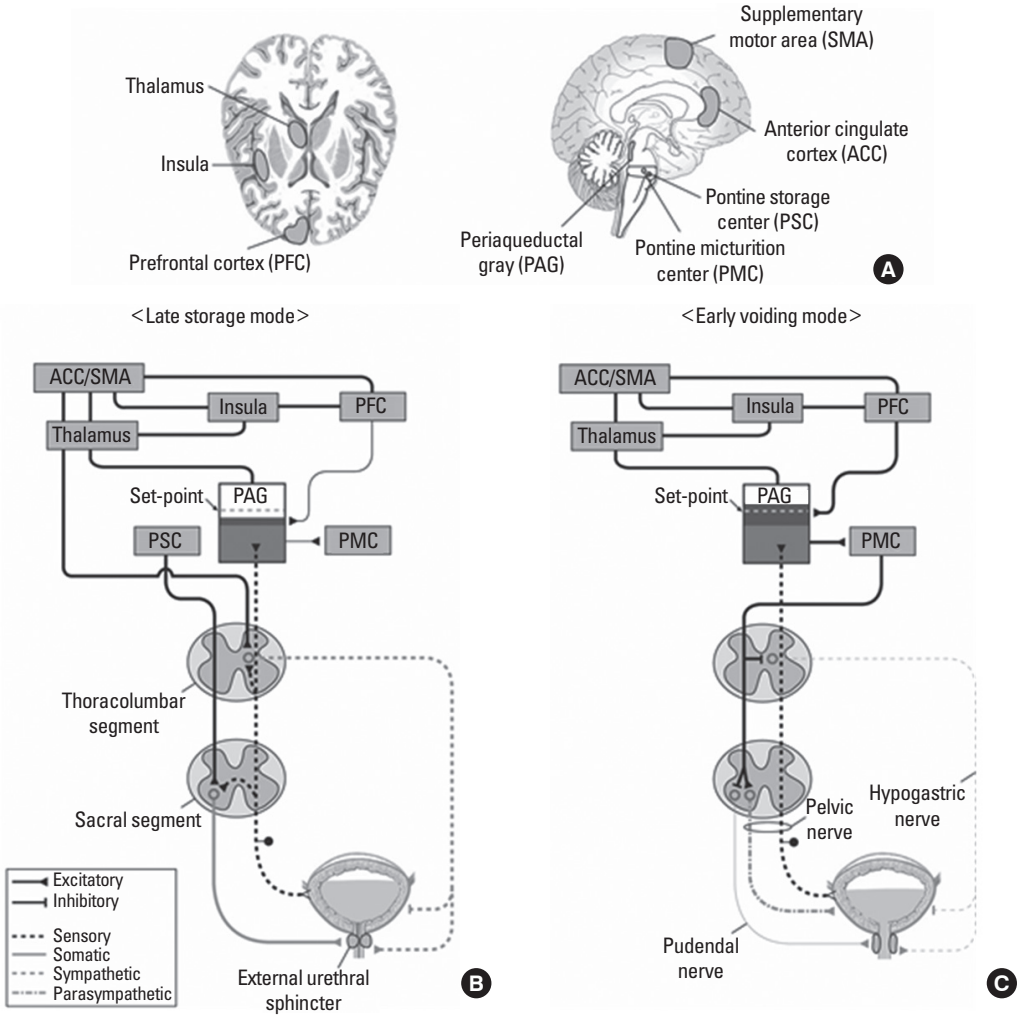

Fig. 1. Brain and spinal networks involved in the regulation of bladder filling and voiding. (A) Major brain regions responsible for micturition are marked on the horizontal section (left) and the sagittal section (right) of the brain. (B) Brain and spinal networks involved in the late phase of bladder filling are shown schematically. Thickness of lines roughly represents the relative strength of signal. Dark grey and grey rectangles in periaqueductal gray represent the contribution of signal inputs from prefrontal cortex and the bladder, respectively. (C) Brain and spinal networks involved in the initiation of voiding are shown schematically. Thickness of lines roughly represents the relative strength of signal. Dark grey and grey rectangles in PAG represent the contribution of signal inputs from PFC and the bladder, respectively. Note the change in relative contribution of signal inputs from the PFC.

sympathetic, and somatic outputs back to bladder [7]. Sympathetic output leaves the spinal cord at the level of thoracolumbar segments as the hypogastric nerve, inhibiting the contraction of detrusor muscles and promoting the contraction of urethral outlet. With regard to somatic outputs, the pudendal nerve leaving the spinal cord from the sacral segment promotes the contraction of the external urethral sphincter. Finally, the pelvic nerve corresponds to parasympathetic output of the spinal cord and it comes from the sacral segment. In general, increase in both sympathetic and somatic signaling results in inhibition of voiding so that bladder can be filled. These signaling pathways comprise the basic spinal reflex mechanism to inhibit involuntary voiding [1]. On the contrary, increase in parasympathetic tone can cause voiding by promoting contraction of detrusor muscles and inducing relaxation of urethral outlet simultaneously.

At the early stage of bladder filling, sympathetic and somatic signals from the spinal cord are the main stimuli to fill the bladder that is rarely affected by brain activity [8]. However, as the bladder gets further distended, sensory signals can ascend the spinal tract and reach higher micturition centers where multiple brain regions interact with each other to sophisticatedly control bladder filling and voiding (Fig. 1A) [9,10]. In detail, spinal afferent fibers convey signals of bladder filling states to the periaqueductal grey (PAG) (Fig. 1B, C upper parts) [11,12]. PAG acts as a relay center for bladder sensory input [13]. PAG then distributes the information about the bladder filing status to higher brain centers via thalamus. Insula is one of first targets of bladder sensory signals reaching higher brain centers. It is a core part of the interoception [14] and the degree of bladder filling is encoded here. The signal from the insula can be transmitted to anterior cingulate cortex (ACC) that interprets the subjective sensation on how much the bladder is filled [15,16]. Although both insula and ACC can cooperate for generating the desire to void and emotional responses to bladder filling [17], the feeling of urgency is believed to be mediated by ACC. However, the urgent feeling does not instantly lead to urination because the prefrontal cortex (PFC) usually suppresses the voiding behavior until the socio-emotional situation is acceptable for voiding. To hold voiding, multiple brain regions can be recruited to enhance sympathetic and somatic outflow to the bladder. For instance, ACC and supplementary motor area are activated to increase thoracolumbar sympathetic outflow [17]. Pontine storage center (PSC) located at the ventrolateral part of the pons can also send signals to stimulate striated urethral sphincter activity [1]. Together, these signals eventually enhance the spinal reflex to inhibit voiding as described earlier.

Final decision to void can be mediated by PFC, especially medial PFC (mPFC) that can act through the default mode network (Fig. 1A) [18]. When the bladder is not full without strong need to suppress voiding, mPFC sends the signals to PAG as a default mode of action. This signal is summated in PAG together with sensory inputs from the bladder [17]. When the bladder is further filled with desire to void, mPFC will determine whether to void or not. If the situation is inadequate to void, mPFC is deactivated with decreased signal to PAG (shown as thin dark grey rectangle). Thus, total neural inputs to PAG fail to reach the set-point (Fig. 1B). On the other hand, when it is good to void, mPFC is activated to stimulate PAG (shown as thick dark grey rectangle) (Fig. 1C). Finally, summated signals from mPFC (shown as dark grey rectangle) and the bladder (shown as grey rectangle) can exceed the set-point in PAG, thus activating pontine micturition center (PMC) located in the medial part of the pons (Fig. 1C) [17,19]. PMC then activates parasympathetic nucleus in the spinal cord and inhibits sympathetic outflow to the bladder. Parasympathetic input to the bladder can initiate voiding by inducing both detrusor muscle contraction and urethral outlet relaxation [1]. Once the urine starts to flow through the urethra, a secondary reflex in the spinal cord continuously enhances further bladder emptying.

Although we described key brain and spinal circuits responsible for the voiding process in this review, it remains unclear how continence and micturition are delicately controlled by the central nervous system. As new brain regions such as parahippocampal complex and hypothalamus that play roles in complicated voiding processes are being discovered [17], it will be interesting to identify critical components of higher micturition centers and their contributions to bladder control for better understanding of voiding mechanisms.

DYSREGULATION OF MICTURITION UNDER PATHOLOGIC CONDITIONS

Urinary Dysfunction in Epilepsy

Patients with epilepsy often show urinary dysfunction [20-22]. Despite urinary complaints can be regarded as autonomic signs accompanied with epileptic seizures, one cross-sectional study has examined the prevalence of urinary symptoms in epilepsy [20]. They found that approximately 39% of patients with epilepsy had at least one urinary symptom. Specifically, incontinence was the most common problem, followed by urinary ur-

Table 1. Urinary dysfunction in patients with epilepsy

Case No.	Age (yr)	Sex	Urinary symptom	Seizure focus by EEG monitoring	CT or MRI	Treatment	Classification of epilepsy	Reference number
1	42	Male	Enuresis (incontinence)	Right frontal region	Not indicated	Not indicated	Juvenile myoclonic epilepsy	23
2	41	Female	Urinary urge	Left temporal region	Left hippocampal atrophy	Not indicated	Temporal lobe epilepsy	24
3	32	Female	Urinary urge	Right temporal region	Right hippocampal atrophy	Not indicated	Temporal lobe epilepsy	24
4	14	Male	Urinary urge	Right temporal region	Normal	Not indicated	Temporal lobe epilepsy	24
5	25	Female	Urinary urge	Right temporal region	Bilateral hippocampal atrophy	Not indicated	Temporal lobe epilepsy	24
6	44	Male	Urinary urge	Right temporal region	Right temporal focal cortical dysplasia	Not indicated	Temporal lobe epilepsy	24
7	61	Male	Urinary urge	Temporal region, nonlateralized	Right hippocampal atrophy	Not indicated	Temporal lobe epilepsy	24
8	19	Female	Urinary urge	Left temporal region	Cortical dysplasia of the left temporal lobe	Left temporal lobectomy	Temporal lobe epilepsy	25
9	64	Male	Urinary retention	Frontotemporal region	Old ischemic lesions in left occipital lobe, right basal ganglia, and pons	Diazepam	Stroke-induced epilepsy	26
10	56	Male	Urinary retention	Bitemporal region	Brain atrophy with no focal lesion	Diazepam	Not classified	26
11	35	Male	Urinary retention	Not indicated	Normal	Diazepam	Not classified	26

EEG, electroencephalogram; CT, computed tomography; MRI, magnetic resonance imaging.

Table 2. Micturition-induced reflex epilepsy

Case No.	Age (yr)	Sex	Stimuli	Seizure focus by EEG monitoring	CT or MRI	Treatment	Developmental disorder	Reference number
1	7	Male	Micturition	Left frontotemporal region	Normal	Valproic acid	Mental retardation, microcephaly	27
2	5	Male	Micturition, immersion of feet in hot water	Central midline region (C3 and Cz)	Normal	Valproic acid, carbamazepine	Mental retardation	28
3	12	Female	Micturition, emotional response to prayer	Anterior cingulate cortex	Normal	No treatment	Developmental delay	29
4	8	Female	Micturition	Frontal region	Normal	Phenytoin	Normal	30
5	6	Female	Micturition, defecation	Frontal and central region	Normal	Clobazam, phenytoin	Delay in language development	31
6	14	Male	Micturition	Right anterior temporal and temporal region	Not indicated	Primidone	Normal	32
7	21	Female	Micturition	Left frontal region	Normal	Lamotrigine	Normal	33
8	11	Female	Micturition	Bilateral occipital region	Normal	Clobazam	ADHD, developmental delay	34
9	6	Male	Micturition	Central midline region (Cz)	Normal	Not indicated	Not indicated	35

EEG, electroencephalogram; CT, computed tomography; MRI, magnetic resonance imaging; ADHD, attention deficit hyperactivity disorder.

gency, frequency, retention, and hesitancy. However, except for this study, limited work has explored genitourinary complications in epilepsy.

It has been reported that urinary incontinence occurs at the end of the clonic phases of tonic-clonic generalized seizures when sphincter muscles are relaxed [20,22]. In an effort to elucidate neurophysiological mechanisms, Rosenzweig et al. [23] have described that a patient with more than 30 years of epilepsy history suffers from urinary incontinence following seizures (Table 1). Ictal electroencephalogram (EEG) indicated a seizure onset from posterior parts of the right middle and inferior frontal gyrus. Since the supracallosal part of the medial frontal cortex has been reported to be one of the suprapontine micturition centers, incontinence of this patient may be attributed to cortical seizures, supporting that the frontal lobe plays a significant role in the regulation of micturition.

Urinary urgency, a relatively rare symptom in patients with epilepsy compared to urinary incontinence, refers to having intense desire to urinate. It has been reported that several patients with temporal lobe epilepsy experience urinary urge during aura or at the beginning of seizures (Table 1) [24]. In addition, one recent case of ictal urinary urge originated from the non-dominant right temporal lobe has been described [25], further supporting previous case studies (Table 1). To localize seizure focus, closer analysis by single photon emission computed tomography has revealed hyperperfusion of the insula and the superior temporal gyrus [24,25]. Considering that insula in micturition plays a role as a relay region sensing the amount of bladder filling and sending a signal of voiding desire to PFC, ictal urinary urge in patients might be attributed to abnormal hyperactivity of the insula.

Urinary retention refers to lack of desire to urinate. Motamedi et al. [20] have reported that urinary retention is one of main postictal deficits, different from the urinary incontinence and urgency that are associated with peri-ictal periods. A study presenting 3 cases of patients with epilepsy [26] further supports that urinary retention is a postictal symptom (Table 1). Moreover, EEG monitoring discloses epileptiform activity in the frontotemporal or bitemporal regions, implying that alteration of cortical activity on suprapontine micturition-associated structures might result in postictal urinary retention.

Micturition-Induced Seizures

Micturition can trigger the genesis of seizures (called reflex epilepsy). Reflex seizures are provoked seizures caused by a specific sensory stimulus, including visual precipitants, reading, writing, eating, bathing, and thinking. Micturition is one of these stimulants. Although micturition-induced seizures are rare and seldom reported, several clinical cases affecting children and young adults have been reported (Table 2) [27-35]. The presence of normal consciousness was variable as three patients lost their awareness while 2 patients preserved consciousness [27,28,30,31,35]. All cases included variable motor components such as tonic posturing and clonic movements [27-35]. Semiology of seizures indicated that the seizure focus was midline or frontotemporal regions. These data suggest the following possible mechanism of micturition-induced seizures: while voiding, midline or frontotemporal lobe that plays a role in micturition might be excessively activated that seizures are generated shortly after the voiding process. Urodynamic studies can also be helpful to understand how micturition induces seizures as one study reported phasic detrusor overactivity with normal urinary flow despite seizures were not detected during the test [33]. Interestingly, of previously reported cases, many patients had developmental delay, raising the possibility that micturition-induced seizures might be associated with neurodevelopmental abnormalities [27-29,31,34]. To advance our understanding about how micturition is regulated by the central nervous system, more studies are needed to not only demonstrate the basic epidemiologic information, but also determine molecular and cellular mechanisms of micturition-induced reflex epilepsy.

CONCLUSIONS

In this article, we reviewed neurophysiological regulation of the micturition and its disruption in pathologic conditions showing seizures. Voluntary control of the micturition can be executed by complex neuronal interactions among several brain regions and the spinal cord. For example, PAG, insula, ACC, and mPFC are known to influence PMC and PSC so that the bladder can switch between voiding and storage modes. Patients with epilepsy displayed various urinary dysfunctions, including incontinence, urgency, and retention, although the micturition itself can also trigger seizures. These patients showed increased activities in the frontal cortex, the insula, and the temporal cortex, supporting that suprapontine micturition centers have critical contribution to fine regulation of the voiding process. However, more extensive investigations are needed to reach comprehensive understanding of all central neural programs controlling micturition as our current knowledge is limited to identifying

major brain regions with a few pathologic cases.

AUTHOR CONTRIBUTION STATEMENT

- Full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis: *KO Cho*
- Study concept and design: *HJ Jang, KO Cho*
- Analysis and interpretation of data: *HJ Jang, KO Cho*
- Drafting of the manuscript: *HJ Jang, MJ Kwon, KO Cho*
- Critical revision of the manuscript for important intellectual content: *HJ Jang, KO Cho*
- Obtained funding: *KO Cho*
- Study supervision: *KO Cho*

REFERENCES

1. Fowler CJ, Griffiths D, de Groat WC. The neural control of micturition. Nat Rev Neurosci 2008;9:453-66.
2. Kitta T, Mitsui T, Kanno Y, Chiba H, Moriya K, Shinohara N. Brain-bladder control network: the unsolved 21st century urological mystery. Int J Urol 2015;22:342-8.
3. de Groat WC. Plasticity of bladder reflex pathways during postnatal development. Physiol Behav 2002;77:689-92.
4. National Institute for Health and Clinical Excellence: Guidance. Urinary incontinence in neurological disease: management of lower urinary tract dysfunction in neurological disease. urinary incontinence in neurological disease: management of lower urinary tract dysfunction in neurological disease. London: Royal College of Physicians; 2012.
5. Fowler CJ. Neurological disorders of micturition and their treatment. Brain 1999;122(Pt 7):1213-31.
6. World Health Organization. Epilepsy fact sheet [Internet]. Geneva (Switzerland): World Health Organization; 2016 [cited 2018 Jan 25]. Available from: http://www.who.int/mediacentre/factsheets/fs999/en/.
7. de Groat WC, Griffiths D, Yoshimura N. Neural control of the lower urinary tract. Compr Physiol 2015;5:327-96.
8. Zhang H, Reitz A, Kollias S, Summers P, Curt A, Schurch B. An fMRI study of the role of suprapontine brain structures in the voluntary voiding control induced by pelvic floor contraction. Neuroimage 2005;24:174-80.
9. Sugaya K, Roppolo JR, Yoshimura N, Card JP, de Groat WC. The central neural pathways involved in micturition in the neonatal rat as revealed by the injection of pseudorabies virus into the urinary bladder. Neurosci Lett 1997;223:197-200.
10. Shy M, Fung S, Boone TB, Karmonik C, Fletcher SG, Khavari R. Functional magnetic resonance imaging during urodynamic testing identifies brain structures initiating micturition. J Urol 2014;192:1149-54.
11. Holstege G. The emotional motor system and micturition control. Neurourol Urodyn 2010;29:42-8.
12. Athwal BS, Berkley KJ, Hussain I, Brennan A, Craggs M, Sakakibara R, et al. Brain responses to changes in bladder volume and urge to void in healthy men. Brain 2001;124(Pt 2):369-77.
13. Blok BF, De Weerd H, Holstege G. Ultrastructural evidence for a paucity of projections from the lumbosacral cord to the pontine micturition center or M-region in the cat: a new concept for the organization of the micturition reflex with the periaqueductal gray as central relay. J Comp Neurol 1995;359:300-9.
14. Craig AD. How do you feel? Interoception: the sense of the physiological condition of the body. Nat Rev Neurosci 2002;3:655-66.
15. Griffiths D, Tadic SD. Bladder control, urgency, and urge incontinence: evidence from functional brain imaging. Neurourol Urodyn 2008;27:466-74.
16. Ketai LH, Komesu YM, Dodd AB, Rogers RG, Ling JM, Mayer AR. Urgency urinary incontinence and the interoceptive network: a functional magnetic resonance imaging study. Am J Obstet Gynecol 2016;215:449.e1-449.e17.
17. Griffiths D. Neural control of micturition in humans: a working model. Nat Rev Urol 2015;12:695-705.
18. Raichle ME, Snyder AZ. A default mode of brain function: a brief history of an evolving idea. Neuroimage 2007;37:1083-90.
19. Nardos R, Gregory WT, Krisky C, Newell A, Nardos B, Schlaggar B, et al. Examining mechanisms of brain control of bladder function with resting state functional connectivity MRI. Neurourol Urodyn 2014;33:493-501.
20. Motamedi M, Nikoobakht MR, Aloosh M, Ebrahimi Nasrabady S, Afshin A, Orandi A, et al. Peri-ictal urinary dysfunction in patients with epilepsy: a cross-sectional study. Urol J 2011;8:222-6.
21. Baumgartner C, Lurger S, Leutmezer F. Autonomic symptoms during epileptic seizures. Epileptic Disord 2001;3:103-16.
22. Devinsky O. Effects of seizures on autonomic and cardiovascular function. Epilepsy Curr 2004;4:43-6.
23. Rosenzweig I, Varga ET, Akeson P, Beniczky S. Simple autonomic seizures and ictal enuresis. Seizure 2011;20:662-4.
24. Baumgartner C, Gröppel G, Leutmezer F, Aull-Watschinger S, Pataraia E, Feucht M, et al. Ictal urinary urge indicates seizure onset in the nondominant temporal lobe. Neurology 2000;55:432-4.
25. Gurgenashvili K, Massey SL, Grant M, Piatt J Jr, Legido A, Valencia

I. Intracranial localisation of ictal urinary urge epileptogenic zone to the non-dominant temporal lobe. Epileptic Disord 2011;13:430-4.
26. Vander T, Ifergane G. Transient postictal urinary retention: presentation of three cases. Eur J Neurol 2004;11:207-8.
27. Rho YI. Reflex seizures induced by micturition: a pediatric case and ictal EEG finding. Korean J Pediatr 2008;51:1346-9.
28. Bourgeois BF. A retarded boy with seizures precipitated by stepping into the bath water. Semin Pediatr Neurol 1999;6:151-6.
29. Glass HC, Prieur B, Molnar C, Hamiwka L, Wirrell E. Micturition and emotion-induced reflex epilepsy: case report and review of the literature. Epilepsia 2006;47:2180-2.
30. Okumura A, Kondo Y, Tsuji T, Ikuta T, Negoro T, Kato K, et al. Micturition induced seizures: ictal EEG and subtraction ictal SPECT findings. Epilepsy Res 2007;73:119-21.
31. Higuchi T, Fukuyama T, Misawa Y, Inaba Y, Ichikawa M, Koike K. Reflex seizures induced by micturition and defecation, successfully treated with clobazam and phenytoin. Epileptic Disord 2011;13:166-71.
32. Zivin I, Rowley W. Psychomotor epilepsy with micturition. Arch Intern Med 1964;113:8-13.
33. Seth JH, McLaughlin C, Eriksson S, Fowler CJ, Walker MC, Panicker JN. Blackouts in the toilet: a case of micturition-induced reflex epilepsy. Pract Neurol 2014;14:261-3.
34. Whitney R, Callen DJ. Micturition-induced seizures: a rare form of reflex epilepsy. Pediatr Neurol 2013;49:61-3.
35. Rathore C, Radhakrishnan A, Nayak SD, Radhakrishnan K. Teaching video neuroimage: electroclinical characteristics of micturition-induced reflex epilepsy. Neurology 2008;70:e86.