Review

Lower urinary tract dysfunction following stroke: From molecular mechanisms to clinical anatomy

Eleni Agapiou[1,2], Efstratios-Stylianos Pyrgelis[1,3], Ioannis N. Mavridis[1,4]*, Maria Meliou[1], Welege Samantha Buddhika Wimalachandra[1]

[1]C.N.S. Alliance Research Group, 19400 Athens, Greece
[2]Department of Physical Medicine and Rehabilitation, Asklipieion Voulas General Hospital, Voula 16673, Athens, Greece
[3]First Department of Neurology, School of Medicine, National and Kapodistrian University of Athens, Eginition Hospital, 10679 Athens, Greece
[4]Department of Neurosurgery, School of Medicine, Democritus University of Thrace, University General Hospital of Alexandroupolis, 68100 Alexandroupolis, Greece

Abstract

Bladder dysfunction is a common clinical problem in stroke patients and a strong prognostic factor of disability and exerts an enormous impact on health and economy. The aim of this narrative review was to examine the pathophysiological mechanisms of lower urinary tract symptoms after stroke, as well as the relevant clinical anatomy. Normal micturition is achieved through complex coordination between brain regions, spinal cord, and peripheral nerves, and anatomic brain connectivity is crucial to lower urinary tract physiology. The most important neurotransmitters involved in bladder control include γ-aminobutyric acid, opioids, glutamate, dopamine, norepinephrine, acetylcholine, and nitric oxide. The precise correspondence between brain damage and relevant urinary symptoms is not well understood. Urodynamic changes after stroke include detrusor overactivity, dyssynergia, and uninhibited sphincter relaxation. Several brain regions could be implicated in post-stroke urinary dysfunction. Brainstem lesions can cause various urinary symptoms. A lesion superiorly to the pontine micturition center (PMC) results in an uninhibited bladder, whereas a lesion between the sacral spinal cord and PMC leads to either a spastic bladder or sphincter-detrusor dyssynergia. Supra-pontine lesions usually cause bladder storage dysfunction. Frontoparietal lesions have been associated with urinary incontinence and insular lesions with urinary retention. Understanding the mechanisms underlying the dysfunction of the lower urinary tract following stroke can aid in the development of new therapeutic strategies for these patients.

Keywords: Bladder dysfunction, Lower urinary tract dysfunction, Neurotransmitters, Stroke, Underlying mechanisms

1. INTRODUCTION

Cerebral stroke represents the second most common cause of death and is among the most important causes of disability [1-3]. Bladder dysfunction is a well-known common problem in these patients [4-6] and can severely impair their quality of life [2,7,8]. The prevalence of urinary symptoms has been reported to be as high as 94% [9], while the two most reported manifestations are urinary incontinence (UI) and voiding difficulty [2]. UI is the most common urinary symptom [4] affecting approximately 1/3 of patients with acute stroke [4,9-11] and persisting in as much as 15–25% 1 year after stroke [11-14]. Its prevalence stands somewhere between 28% and 79% [12,13,15-17], and its causes are multifactorial [16].

Spasticity, namely, muscle tightness due to prolonged contraction, is a common stroke complication which can have a detrimental effect on bladder control [18]. Dysfunction of the lower urinary tract may be part of a neurological syndrome, neurogenic bladder [14,19], or a result of associated deficits, that is, immobility and cognitive dysfunction, a situation known as "functional." Neurogenic

***Corresponding author:**
Ioannis N. Mavridis (pap-van@otenet.gr)

Received: 01 July 2024; Revision received: 28 July 2024; Accepted: 14 August 2024; Published: 13 September 2024

How to cite this article: Agapiou E, Pyrgelis E, Mavridis IN, Meliou M, Wimalachandra WSB. Lower urinary tract dysfunction following stroke: From molecular mechanisms to clinical anatomy. *J Biol Methods*. 2024;11(3):e99010024. DOI: 10.14440/jbm.2024.0022

as well as functional bladder dysfunction may co-exist [14]. In many cases, pre-existing urological issues can exacerbate urinary symptoms [20]. Despite its prognostic importance, social impact, and remarkable economic burden [21], bladder dysfunction is often overlooked and receives insufficient attention. In light of the impact of urinary problems on the victims of cerebrovascular incidents, the primary purpose of this review article was to explore the currently available knowledge regarding the mechanisms of bladder dysfunction following stroke and their relevant anatomy.

2. LITERATURE SEARCH

Methodologically, a literature search was conducted in the PubMed database using the terms "bladder dysfunction" and "stroke," and the search retrieved 272 articles. The authors screened all articles published until March 2021 for potential suitability. English language publications, including foreign language publications with English abstracts, were included in this non-systematic review. Articles concerning bladder dysfunction after stroke with information on molecular mechanisms and relevant clinical anatomy were further analyzed. Our exclusion criteria were as follows: (1) non-relevant to our topic/theme, (2) lesions not affecting the brain, and (3) non-stroke brain lesions. The remaining articles (n = 57) were finally used for this narrative review. Data were collected by five independent investigators and then synthesized in a narrative format to thoroughly review this subject.

3. FUNCTIONAL ANATOMY

Normal micturition is essentially a spinal reflex involving complex coordination between peripheral ganglia, spinal cord, and brain [13,22,23]. Functional neuroimaging studies have contributed a lot to the understanding of brain control over bladder [13,24,25]. Brain regions involved in urinary dysfunction are as follows: frontal [14,17,23,26-28], parietal [27-29], temporal [28], and lobes and cerebellum [14,30,31]. More specifically, the anteromedial frontal lobe and its descending pathways [14], medial and dorsolateral prefrontal cortex, cingulate gyrus [13,24,28], paracentral lobule, orbital cortex [28], basal ganglia [14,22,27,28], precentral gyrus, inferior frontal gyrus, supplementary motor area, insula, periaqueductal gray matter (PAG), hypothalamus [13,24], and pontine micturition center (PMC) (Barrington's nucleus) [13, 23, 24, 28, 32, 33] are particularly significant in micturition control. In neuroimaging studies, the function of bladder filling shows a right hemisphere predominance [31,34].

Anatomic brain connectivity is crucial for lower urinary tract physiology [7,30]. Normal urethral and bladder afferents gather in PAG and end up in the insula, enabling sensation during urine storage. The anterior cingulate gyrus provides control and monitoring, whereas the prefrontal cortex controls voiding decisions [7]. Thus, PAG has a critical role in the storage and voiding of urine, projecting signals through the spinal cord to higher centers [13,25]. Close to PMC, the pontine storage center activates the external urethral sphincter during continence. During micturition, PMC stimulates bladder motor neurons in the sacral cord and inhibits the external sphincter of the urethra [33]. Following input from the frontal lobe and limbic system, information is transmitted to PMC and promotes urination [13]. Consequently, the location of the stroke can affect the type of detrusor dysfunction [7].

4. NEUROTRANSMITTERS IN BLADDER CONTROL

Autonomic and somatic peripheral nerves, coordinated by the brain and spinal cord, innervate the lower urinary tract. The striated muscle of the external urethral sphincter receives somatic innervation from the pudendal nerve. Parasympathetic fibers stimulate the detrusor, primarily through the pelvic nerve by releasing acetylcholine (ACh), whereas sympathetic fibers, through the hypogastric nerve, stimulate contraction of the smooth urethral and bladder neck muscles by releasing norepinephrine (NE) [17].

Neurotransmitters associated with bladder control have been extensively studied, mainly in animal models [35-38]. Specifically, γ-aminobutyric acid (GABA), glutamate, opioid, serotonin, NE, and dopamine are known to influence micturition [39]. Opioid receptor subtypes μ and δ1, which are present in the brain cortex, take part in the micturition reflex [40]. Infusion of GABA agonists into animal models inhibits bladder contraction [41]. Administration of a non-selective inhibitor of the nitric oxide synthase [35] increased the capacity of bladder in infarcted rats. Glutaminergic activity exerted an excitatory effect on bladder contractility [36]. Dopaminergic–glutaminergic interactions caused bladder dysfunction in rat models [17,42]. Bladder overactivity induced by cerebral ischemia was partially mediated by N-methyl-D-aspartate (NMDA) glutamatergic [34] and D2 dopaminergic excitatory mechanisms [34,38,43-45] in rats, and accompanied by increased c-fos and zif268 mRNA expression in the tegmental area of the pons [34]. In fact, the impaired balance between excitatory NMDA glutamatergic neurons and inhibitory glycinergic or GABAergic neurons in infarcted rats may contribute to bladder overactivity [17]. Reactivation of two major modulatory cholinergic systems, in the basal forebrain and pons/midbrain, using acetylcholinesterase inhibitors, could theoretically improve detrusor muscle overactivity. However, regulatory systems in the human brain are actually more complex [7].

In human and animal studies, urinary nerve growth factor levels were increased after cerebral infarction [46,47]. Furthermore, bladder capacity was reduced after stroke [35,37,41] and was correlated with the infarcted area [48]. This decrease was mediated by excitatory pathway upregulation and downregulation of a forebrain's tonic inhibitory pathway [44]. Table 1 summarizes the most important neurotransmitters implicated in bladder control.

5. CLINICAL ANATOMY

The precise correspondence between brain damage and relevant urinary symptoms is not well understood. Neural locations, physiological pathways, neurotransmitters, and receptors implicated in bladder control are schematically illustrated in Figure 1. UI seems to be caused by frontoparietal lesions, the insula plays a role in urinary retention, and various urinary symptoms develop after brainstem lesions [51].

Table 1. Neurotransmitters and receptors implicated in bladder control

Neurotransmitter	Receptor	Bladder control	References
GABA	GABA receptors	Inhibition of bladder contraction	[41]
Opioids	μ and δ1 receptors of the cerebral cortex	Micturition reflex and bladder overactivity	[40]
Glutamate	NMDA receptors	Bladder contractility dysfunction-bladder overactivity	[34]
Dopamine	D1 receptors D2 receptors	Suppression of bladder activity Voiding facilitation	[34,38,43-45]
Serotonin	5-HT_{1A}, 5-HT_2, 5-HT_3 receptors	Facilitation of micturition Facilitation of urine storage	[39]
NE	β3 adrenergic receptors in detrusor smooth muscle α1 adrenergic receptors in the urethral smooth muscle	Facilitation of urine storage	[49]
ACh	Nicotinic receptors Muscarinic receptors	Contraction of the detrusor muscle Direct (M_3) and indirect (M_2) contraction Increase (M_1) or decrease (M_4) the release of ACh and NE	[50]
NO	Soluble guanylyl cyclase	Decrease in intraurethral pressure, increase in bladder capacity	[35]

GABA: γ-aminobutyric acid; NMDA: N-methyl-D-aspartate; 5-HT: 5-hydroxy-tryptamine, NE: norepinephrine, Ach: Acetylcholine; NO: Nitric Oxide.

5.1. Brain lesions

As aforementioned, various brain regions could be involved in urinary dysfunction after stroke. More specifically, cerebellar stroke [14] and damage of the right frontal lobe may predominantly result in bladder overactivity, often expressed as urgency or UI [17]. In parietal strokes, urinary symptoms might be due to disruption of the afferent pathways of the micturition of the regulation of the micturition reflex [27]. Patients with parietal lobe involvement tended to have disturbed awareness of their need to void, and they suffered from reduced or absent bladder sensation and often denied leakage [29]. Urinary retention was associated with strokes in the frontal lobe, PMC, insula, and dominant hemisphere [26]. Lesions of the thalamus, basal ganglia, internal capsule, and frontoparietal area, have been found to be associated with detrusor areflexia (i.e., the inability of the bladder to contract) [23]. Bilateral infarcts were also associated with multiple micturition disorders [46].

5.2. Brainstem lesions

After brainstem stroke, urinary dysfunction occurred in 50–95% [32,46] of patients, usually manifested as voiding difficulties [46], with weak stream, nocturia, straining, intermittency, incomplete emptying, urgency, and UI. Detrusor overactivity has been observed after midbrain or medullary strokes, whereas detrusor underactivity developed after pontine stroke [32]. In the latter case, detrusor-sphincter dyssynergia (i.e., disturbance of muscular coordination) was attributed to PMC damage [33]. Pontine lesions might disrupt inhibitory descending fibers from the midbrain's tegmentum and medulla lesions could disrupt stimulatory descending fibers from the pons' tegmentum [28].

5.3. Connectivity between micturition centers

The PMC excitability is controlled by the medial frontal lobe's inhibitory input. Thus, a lesion above the PMC resulted in an uninhibited bladder, whereas a lesion between the sacral spinal cord and PMC caused a spastic bladder [28] or sphincter-detrusor dyssynergia [23]. In general, supra-pontine lesions caused bladder storage dysfunction [52]. Prefrontal deactivation seemed to cause detrusor overactivity, similar to lesions in other areas. Thus, lesion localization is not always correlated with the type of urinary dysfunction [7]. Furthermore, stroke patients might show higher activity in the cerebellum and PAG during the bladder's filling and voiding, reflecting a stronger reliance on primitive centers, probably due to the loss of their connections with the latter [30].

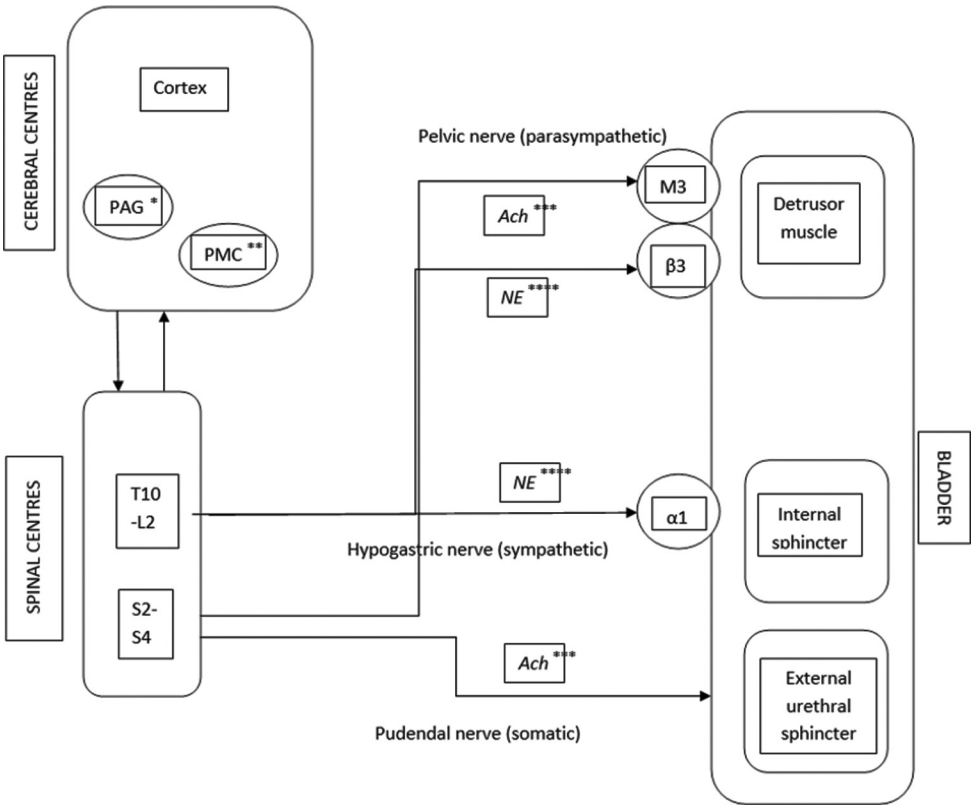

Figure 1. Locations of the nervous system, physiological pathways, neurotransmitters, and receptors implicated in bladder control
Ach: Acetylcholine; PAG: Periaqueductal Gray Matter; PMC: Pontine micturition center; NE: norepinephrine; T10: 10th thoracic myelotome, S2-4: 2nd-4th sacral myelotome, M3: M3 muscarinic acetylcholine receptor, β: Beta adrenoreceptor, α: Alpha adrenoreceptor

5.4. Detrusor overactivity and underactivity

Urodynamic patterns after stroke include detrusor overactivity, dyssynergia, and uninhibited sphincter relaxation [46]. Detrusor overactivity/overactive bladder syndrome [39,53], manifested as urgency and frequency of micturition along with urge UI [14], is the result of loss of supraspinal control, which produces a hyper-excitability state of the sacral cord's neuronal activity [54] and is the predominant finding after stroke [9,13,16,23,36,39,53,55-57]. This can lead to leakage [9,13] accompanied or preceded by urgency [9,13,53]. Extended cerebral lesions (>40 mm in diameter) have been found in most patients with bladder overactivity [22].

During the acute stroke period (cerebral shock), detrusor underactivity was usually observed [9,14,23,32,57]. After that, detrusor underactivity was far less common [16,23,57] and caused urinary retention and overflow incontinence [13]. Pontine infarction has been described to play a role in the process, but specific causes remain unclear and pre-existing comorbidities might be involved as well [13]. Comorbidities are an important consideration in clinical practice, not only due to the potential effect of other diseases on bladder function (e.g., diabetic neuropathy) but also because the patient's medication could directly or indirectly affect bladder function (e.g., drugs acting on the autonomous nervous system). Intriguingly, symptoms of overactive bladder have been reported among patients with detrusor underactivity after stroke [56]. Finally, post-stroke conditions could interfere with bladder control as well, such as secondary urinary infections, a frequent entity in these patients.

6. CONCLUSION

Following a stroke, bladder function is frequently affected, which exerts an enormous impact on the patient's quality of life and care. Normal micturition is achieved through involved coordination among brain regions, spinal cord, and peripheral nerves, and anatomic brain connectivity is crucial for lower urinary tract physiology. The most important neurotransmitters involved in bladder control include GABA, opioids, glutamate, dopamine, NE, ACh, and nitric oxide. Urodynamic changes after stroke include detrusor overactivity, dyssynergia, and uninhibited sphincter relaxation. Several brain regions could be involved in urinary dysfunction after stroke. Brainstem lesions can cause various urinary symptoms. A lesion superiorly to the PMC results in an uninhibited bladder, whereas a lesion between the sacral spinal cord and PMC leads to either a spastic bladder or sphincter–detrusor dyssynergia. Supra-pontine lesions usually cause bladder storage dysfunction. Frontoparietal lesions have been

associated with UI and insular lesions are linked to urinary retention. Understanding the pathophysiological mechanisms of lower urinary tract dysfunction following stroke can aid in the development of new therapeutic approaches for stroke patients.

ACKNOWLEDGMENTS

None.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Conceptualization: All authors
Writing – original draft: All authors
Writing – review and editing: All authors

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA

Not applicable.

REFERENCES

1. Kim BR, Lee J, Sohn MK, *et al*. Risk factors and functional impact of medical complications in stroke. *Ann Rehabil Med*. 2017;41(5):753-760. doi: 10.5535/arm.2017.41.5.753
2. Liang CC, Shaw SW, Huang YH, Lin YH, Lee TH. Bladder transplantation of amniotic fluid stem cell may ameliorate bladder dysfunction after focal cerebral ischemia in rat. *Stem Cells Transl Med*. 2017;6(4):1227-1236. doi: 10.1002/sctm.16-0212
3. Tekeoğlu Y, Adak B, Göksoy T. Effect of transcutaneous electrical nerve stimulation (TENS) on barthel activities of daily living (ADL) index score following stroke. *Clin Rehabil*. 1998;12(4):277-280. doi: 10.1191/026921598672873816
4. Kuptniratsaikul V, Kovindha A, Suethanapornkul S, Manimmanakorn N, Archongka Y. Complications during the rehabilitation period in Thai patients with stroke: A multicenter prospective study. *Am J Phys Med Rehabil*. 2009;88(2):92-99. doi: 10.1097/PHM.0b013e3181909d5f
5. Lorish TR, Sandin KJ, Roth EJ, Noll SF. Stroke rehabilitation. 3. Rehabilitation evaluation and management. *Arch Phys Med Rehabil*. 1994;75:S47-S51.
6. Olai L, Borgquist L, Svärdsudd K. Health problems in elderly patients during the first post-stroke year. *Ups J Med Sci*. 2012;117(3):318-327. doi: 10.3109/03009734.2012.674572
7. Yoo KH, Lee SJ, Chang SG. Predictive value of the ischemic stroke lesion to detrusor function. *Neurourol Urodyn*. 2010;29(7):1355-1356. doi: 10.1002/nau.20885
8. Salehi-Pourmehr H, Hajebrahimi S, Rahbarghazi R, *et al*. Stem cell therapy for neurogenic bladder dysfunction in rodent models: A systematic review. *Int Neurourol J*. 2020;24(3): 241-257. doi: 10.5213/inj.2040058.029
9. Akkoç Y, Bardak AN, Ersöz M, *et al*. Post-stroke lower urinary system dysfunction and its relation with functional and mental status: A multicenter cross-sectional study. *Top Stroke Rehabil*. 2019;26:136-41. doi: 10.1080/10749357.2018.1555389
10. Gelber DA, Good DC, Laven LJ, Verhulst SJ. Causes of urinary incontinence after acute hemispheric stroke. *Stroke*. 1993;24(3):378-382. doi: 10.1161/01.str.24.3.378
11. Mehdi Z, Birns J, Bhalla A. Post-stroke urinary incontinence. *Int J Clin Pract*. 2013;67(11):1128-1137. doi: 10.1111/ijcp.12183
12. Guo GY, Kang YG. Effectiveness of neuromuscular electrical stimulation therapy in patients with urinary incontinence after stroke: A randomized sham controlled trial. *Medicine* (*Baltimore*). 2018;97(52):e13702. doi: 10.1097/MD.0000000000013702
13. Panfili Z, Metcalf M, Griebling TL. Contemporary evaluation and treatment of poststroke lower urinary tract dysfunction. *Urol Clin North Am*. 2017;44(3):403-414. doi: 10.1016/j.ucl.2017.04.007
14. Sakakibara R. Lower urinary tract dysfunction in patients with brain lesions. *Handb Clin Neurol*. 2015;130:269-287. doi: 10.1016/B978-0-444-63247-0.00015-8
15. Kohler M, Mayer H, Battocletti M, Kesselring J, Saxer S. Wirksamkeit von nichtmedikamentösen interventionen zur förderung der urinkontinenz bei menschen nach einem cerebrovaskulären Insult-eine systematische Literaturübersicht [Effectiveness of non-pharmacological interventions to promote urinary continence in stroke survivors-a systematic literature review]. *Pflege*. 2016;29(5):235-245. [In German]. doi: 10.1024/1012-5302/a000493
16. McKenzie P, Badlani GH. The incidence and etiology of overactive bladder in patients after cerebrovascular accident. *Curr Urol Rep*. 2012;13(5):402-406. doi: 10.1007/s11934-012-0269-6
17. Miyazato M, Kadekawa K, Kitta T, *et al*. New frontiers of basic science research in neurogenic lower urinary tract dysfunction. *Urol Clin North Am*. 2017;44(3):491-505. doi: 10.1016/j.ucl.2017.04.014

18. Satkunam LE. Rehabilitation medicine: 3. Management of adult spasticity. *CMAJ*. 2003;169(11):1173-1179.
19. Amarenco G. Troubles vésico-sphinctériens d'origine nerveuse Vesico-sphincter disorders of nervous origin. *Rev Prat*. 1995;45(3):331-335. [In French].
20. Chartier-Kastler E, Mozer P, Ayoub N, Richard F, Ruffion A. Hypertrophie bénigne de la prostate et neuro-urologie Benign prostatic hyperplasia and neurourology. *Prog Urol*. 2007;17(3):529-534. [In French].
doi: 10.1016/s1166-7087(07)92363-5
21. Kasyan GR, Dreval RO, Krivoborodov GG, *et al*. Socio-economic aspects of neurogenic dysfunctions in urology. *Urologiia*. 2020;(5):127-132. [In Russian].
22. Feder M, Heller L, Tadmor R, Snir D, Solzi P, Ring H. Urinary continence after stroke: Association with cystometric profile and computerised tomography findings. *Eur Neurol*. 1987;27(2):101-105.
doi: 10.1159/000116140
23. Wu MN, Guo YC, Lai CL, Shen JT, Liou LM. Poststroke detrusor hyporeflexia in a patient with left medial pontine infarction. *Neurologist*. 2012;18(2):73-75.
doi: 10.1097/NRL.0b013e318247b9d9
24. Khavari R, Boone TB. Functional brain imaging in voiding dysfunction. *Curr Bladder Dysfunct Rep*. 2019;14(1):24-30.
doi: 10.1007/s11884-019-00503-0
25. Zare A, Jahanshahi A, Rahnama'i MS, Schipper S, Van Koeveringe GA. The role of the periaqueductal gray matter in lower urinary tract function. *Mol Neurobiol*. 2019;56(2): 920-934.
doi: 10.1007/s12035-018-1131-8
26. Smith CE, Schneider MA. Assessing postvoid residual to identify risk for urinary complications post stroke. *J Neurosci Nurs*. 2020;52(5):219-223.
doi: 10.1097/JNN.0000000000000536
27. Tateno F, Sakakibara R, Aiba Y, *et al*. Bladder autonomic dysfunction after a parietal stroke. *J Stroke Cerebrovasc Dis*. 2020;29(4):104620.
doi: 10.1016/j.jstrokecerebrovasdis.2019.104620
28. Yum KS, Na SJ, Lee KY, *et al*. Pattern of voiding dysfunction after acute brainstem infarction. *Eur Neurol*. 2013;70(5-6): 291-296.
doi: 10.1159/000352040
29. Pettersen R, Stien R, Wyller TB. Post-stroke urinary incontinence with impaired awareness of the need to void: Clinical and urodynamic features. *BJU Int*. 2007;99(5): 1073-1077.
doi: 10.1111/j.1464-410X.2007.06754.x
30. Kreydin EI, Gad P, Gao B, Liu CY, Ginsberg DA, Jann K. The effect of stroke on micturition associated brain activity: A pilot fMRI study. *Neurourol Urodyn*. 2020;39(8):2198-2205.
doi: 10.1002/nau.24473
31. Sakakibara R. Editorial comment to effect of dominant hemispheric stroke on detrusor function in patients with lower urinary tract symptoms. *Int J Urol*. 2010;17(7):660.
doi: 10.1111/j.1442-2042.2010.02549.x
32. Lee HS, Choi JG, Shin JH. Urological disturbance and its neuroanatomical correlate in patients with chronic brainstem stroke. *Neurourol Urodyn*. 2017;36(1):136-141.
doi: 10.1002/nau.22889
33. Shukla R, Giri P, Bhandari A, Shankhwar SN. Pontine stroke and bladder dysfunction. *BMJ Case Rep*. 2014;2014:bcr2013200787.
doi: 10.1136/bcr-2013-200787
34. Yotsuyanagi S, Yokoyama O, Komatsu K, Kodama K, Niikura S, Namiki M. Expression of neural plasticity related gene in the pontine tegmental area of rats with overactive bladder after cerebral infarction. *J Urol*. 2001;166(3): 1148-1155.
35. Kodama K, Yokoyama O, Komatsu K, Yotsuyanagi S, Niikura S, Namiki M. Contribution of cerebral nitric oxide to bladder overactivity after cerebral infarction in rats. *J Urol*. 2002;167(1):391-396.
36. Yokoyama O, Ishiura Y, Komatsu K, *et al*. Effects of MK-801 on bladder overactivity in rats with cerebral infarction. *J Urol*. 1998;159(2):571-576.
doi: 10.1016/s0022-5347(01)63986-7
37. Yokoyama O, Komatsu K, Ishiura Y, Nakamura Y, Morikawa K, Namiki M. Change in bladder contractility associated with bladder overactivity in rats with cerebral infarction. *J Urol*. 1998;159(2):577-580.
doi: 10.1016/s0022-5347(01)63987-9
38. Yokoyama O, Yoshiyama M, Namiki M, De Groat WC. Glutamatergic and dopaminergic contributions to rat bladder hyperactivity after cerebral artery occlusion. *Am J Physiol*. 1999;276(4):R935-R942.
doi: 10.1152/ajpregu.1999.276.4.R935
39. Andersson KE, Pehrson R. CNS involvement in overactive bladder: Pathophysiology and opportunities for pharmacological intervention. *Drugs*. 2003;63(23):2595-2611.
doi: 10.2165/00003495-200363230-00003
40. Nagasaka Y, Yokoyama O, Komatsu K, Ishiura Y, Nakamura Y, Namiki M. Effects of opioid subtypes on detrusor overactivity in rats with cerebral infarction. *Int J Urol*. 2007;14(3):226-231, discussion 232.
doi: 10.1111/j.1442-2042.2007.01700.x
41. Kanie S, Yokoyama O, Komatsu K, *et al*. GABAergic contribution to rat bladder hyperactivity after middle cerebral artery occlusion. *Am J Physiol Regul Integr Comp Physiol*. 2000;279(4):R1230-R1238.
doi: 10.1152/ajpregu.2000.279.4.R1230
42. Yokoyama O, Yoshiyama M, Namiki M, De Groat WC. Changes in dopaminergic and glutamatergic excitatory mechanisms of micturition reflex after middle cerebral artery occlusion in conscious rats. *Exp Neurol*. 2002;173(1):129-135.
doi: 10.1006/exnr.2001.7833
43. Yokoyama O, Mizuno H, Komatsu K, Akino H, Tanase K, Namiki M. Role of glutamate receptors in the development and maintenance of bladder overactivity after cerebral infarction in the rat. *J Urol*. 2004;171(4):1709-1714.
doi: 10.1097/01.ju.0000104861.73314.fe
44. Yokoyama O, Yoshiyama M, Namiki M, De Groat WC. Role of the forebrain in bladder overactivity following cerebral infarction in the rat. *Exp Neurol*. 2000;163(2):469-476.
doi: 10.1006/exnr.2000.7391

45. Yokoyama O, Yoshiyama M, Namiki M, De Groat WC. Interaction between D2 dopaminergic and glutamatergic excitatory influences on lower urinary tract function in normal and cerebral-infarcted rats. *Exp Neurol*. 2001;169(1): 148-155.
doi: 10.1006/exnr.2001.7639
46. Liu HT, Liu AB, Chancellor MB, Kuo HC. Urinary nerve growth factor level is correlated with the severity of neurological impairment in patients with cerebrovascular accident. *BJU Int*. 2009;104(8):1158-1162.
doi: 10.1111/j.1464-410X.2009.08533.x
47. Yokokawa R, Akino H, Ito H, Zha X, Yokoyama O. Nerve growth factor release from the urothelium increases via activation of bladder C-fiber in rats with cerebral infarction. *Neurourol Urodyn*. 2017;36(6):1448-1455.
doi: 10.1002/nau.23142
48. Ishiura Y. Experimental study of voiding dysfunction induced by cerebral infarction in rats. *Nihon Hinyokika Gakkai Zasshi*. 1996;87(11):1221-1230. [In Japanese].
doi: 10.5980/jpnjurol1989.87.1221
49. Obara K, Suzuki S, Shibata H, *et al*. Noradrenaline-induced relaxation of urinary bladder smooth muscle is primarily triggered through the β_3-adrenoceptor in rats. *Biol Pharm Bull.* 2019;42(5):736-743.
doi: 10.1248/bpb.b18-00903
50. Andersson KE. Muscarinic acetylcholine receptors in the urinary tract. *Handb Exp Pharmacol*. 2011;202:319-344.
doi: 10.1007/978-3-642-16499-6_16
51. Jeanson G, Lebreton F. Corrélats neuroanatomiques entre lésions AVC et troubles urinaires: Une revue de la littérature [Neuroanatomical correlates between stroke lesions and urinary disorders: A narrative review]. *Prog Urol*. 2019;29(4):226-234. [In French].
doi: 10.1016/j.purol.2018.10.004
52. Yokoyama O. Pharmacological and genetic analysis of mechanisms underlying detrusor overactivity in rats. *Neurourol Urodyn*. 2010;29(1):107-111.
doi: 10.1002/nau.20746
53. Andersson KE. Mechanisms of disease: Central nervous system involvement in overactive bladder syndrome. *Nat Clin Pract Urol*. 2004;1(2):103-108.
doi: 10.1038/ncpuro0021
54. Pikov V, McCreery DB. Spinal hyperexcitability and bladder hyperreflexia during reversible frontal cortical inactivation induced by low-frequency electrical stimulation in the cat. *J Neurotrauma*. 2009;26(1):109-119.
doi: 10.1089/neu.2008.0584
55. Kreydin E, Zhong H, Latack K, Ye S, Edgerton VR, Gad P. Transcutaneous electrical spinal cord neuromodulator (TESCoN) Improves symptoms of overactive bladder. *Front Syst Neurosci*. 2020;14:1.
doi: 10.3389/fnsys.2020.00001
56. Natsume O. Detrusor contractility and overactive bladder in patients with cerebrovascular accident. *Int J Urol*. 2008;15(6):505-510.
doi: 10.1111/j.1442-2042.2008.02045.x
57. Yared JE, Gormley EA. The role of urodynamics in elderly patients. *Clin Geriatr Med*. 2015;31(4):567-579.
doi: 10.1016/j.cger.2015.06.003