Connection between traumatic frontal intracerebral hemorrhage and lower urinary tract symptoms

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Abstract. – **OBJECTIVE:** There have been no previous studies of urinary symptoms in patients with traumatic frontal intracerebral hemorrhage. The purpose of this work was to provide first insights into the potential role of traumatic frontal intracerebral hemorrhage in the development of urinary symptoms. This condition is known to cause compression in and around the prefrontal cortex, and we wanted to examine its effect on the micturition center.

PATIENTS AND METHODS: Patients with voiding dysfunction (n = 176) were assessed for lower urinary tract symptoms using the International Prostate Symptom Score (IPSS). Out of 176 patients, 52 symptomatic patients with voiding difficulties underwent urodynamic testing. All patients with traumatic frontal intracerebral hemorrhage were treated at the University Medical Center Tuebingen, Germany, and the Azad University of Medical Sciences in Tehran, Iran, between 2017 and 2020. Lower urinary tract symptoms (LUTS) were documented in patients with compression of the frontal lobe due to local hemorrhage. All patients routinely performed Brain CT scans. Brain magnetic resonance (MRI) images of the patients with suspicion of diffuse axonal injuries were additionally performed. Out of 176 treated patients (median age of 49 years), 52 patients with voiding difficulties were evaluated.

RESULTS: Urodynamic testing of 52 symptomatic patients revealed detrusor overactivity in 25 (48%), low-compliance bladder in 4 (7.7%), detrusor-sphincter dyssynergia in 20 (38%), and uninhibited sphincter relaxation in 11 patients (21%). There was no significant correlation between the volume of hemorrhage and urinary symptoms (p=0.203, Spearman q=0.726). Frontal intracerebral hemorrhage compressing the pre-frontal cortex influences the micturition center and is responsible for lower urinary tract symptoms.

CONCLUSIONS: Hemorrhage of the right or left frontal lobe does have a direct relationship with incontinence which completely disappeared in 85% of the patients within 9 months.

Key Words:
Lower urinary tract symptoms, Prefrontal cortex, Intracerebral hemorrhage, Traumatic frontal intracerebral hemorrhage.

Introduction

Lower urinary tract symptoms (LUTS) are a series of subjective symptoms such as: urgency and frequency of voiding, nocturia, and urinary incontinence (UI)[1]. Although lower urinary tract problems and dysfunction are highly associated with pelvic structures and a healthy spinal cord, they might be correlated with the central and peripheral nervous systems, or the neural integrity between these two systems[2-4]. In this regard, previous reports have shown that 94% of patients with stroke or other brain lesions have experienced at least one of these components of LUTS[5].

Most of the patients diagnosed with new-onset of stroke typically experience stress incontinence and bladder hyperactivity during the period of areflexia, and urinary incontinence has been reported between one to two-thirds of these patients[6]. Well-known risk factors, which have been reported for urinary incontinence in patients with stroke include: age (>65 years), gender (female), lesion scale (large), depression, any comorbidity including diabetes mellitus, and activity limitations[7]. LUTS is typically triggered by tumors in the paraventricular, anteromedial frontal lobe, putamen, and white matter of the brain. In addition, urinary retention is considered highly prevalent in patients diagnosed with stroke, diabetes, aphasia, and other neurological disabilities[1].

To understand the relation between LUTS and neurological events, it is important to understand the bladder's neurophysiology.

The brain and the bladder must communicate to make sure that urination occurs only at an appropriate time. Brain areas that influence the micturition reflex have been found in cats through electrical stimulation. These include the cerebellum, periaqueductal gray, substantia nigra, red nucleus, thalamus, hypothalamus, amygdaloid body, and median or ventral aspects of the frontal lobe[8]. These excitatory and inhibitory areas for micturition are often located side by side, and many of these areas

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project to the pontine micturition center (PMC), pontine urine storage center (PUSC), or rostral pontine reticular formation (RPRF)[9,10] (Figure 1).

In this regard, during the voiding phase, both the right and left inferior frontal gyrus is significantly activated[11]. However, this process is not present in the withholding phase[11]. Thus, this region of the cortex is involved in the performance of intended actions about which a planned decision has been made. Neuronal projections are also important structures to consider in the neural mediation of micturition. Excitatory glutamatergic neurons, inhibitory glycinergic neurons, and some GABAergic neurons play an important role in the micturition reflex pathway[12-14]. Glutamatergic projections to the lumbosacral cord promote the micturition reflex, and glycinergic/GABAergic projections to the lumbosacral cord inhibit the micturition reflex and also inhibit glutamatergic neurons[14] (Figure 2).

The changes of glycine in the lumbosacral cord after spinal cord injury are reflected by the serum glycine level with a delay of 1-2 weeks[15]. On the other hand, cerebral infarction in patients with cerebrovascular disease induces urinary frequency and urgency[16]. Therefore, the overall effect of the brain is to inhibit the micturition reflex. There are both excitatory and inhibitory bladder-to-bladder, bladder-to-urethra, urethra-to bladder, or urethra-to-urethra reflexes[17]. When urine is being stored, these reflexes are set to promote storage. Some of the main switches for these reflexes are in the pons, and some are in the spinal cord. The cerebral cortex exerts voluntary control and turns these switches on or off as needed (Figure 3).

The interconnected electrical impulses between the pons, the sacral spinal cord, and the peripheral innervation from the caudal sections of the sacral cord are essential for the storage and voiding of urine. Therefore, any complication such as hemorrhage or tumors in this pathway might result in LUTS. Since there have been no previous urodynamic reports of urinary symptoms in patients with traumatic frontal intracerebral hemorrhage, this study aimed to provide first insights into the potential role of traumatic frontal intracerebral hemorrhage, which causes compression in and around the prefrontal cortex and its effect on the micturition center.

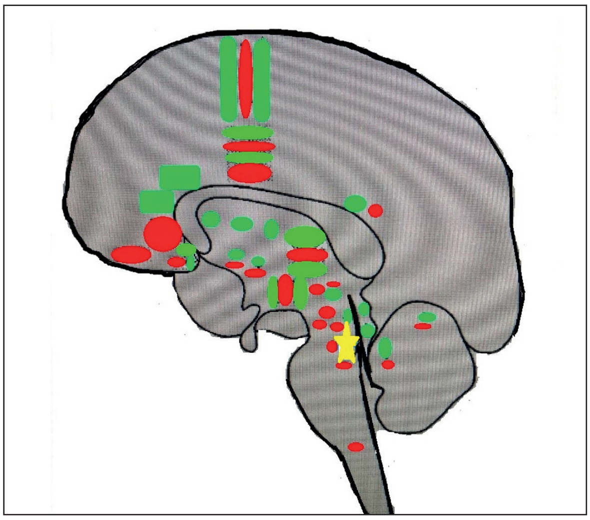

Figure 1. Excitatory (green) and inhibitory (red) areas for micturition in the brain. There are many excitatory and inhibitory areas in the median, lateral, and ventral aspects of the frontal lobe. These excitatory and inhibitory areas are often located side by side. An *asterisk* (yellow) show the pontine micturition center.

Patients and Methods

Patient Demographic Details

There were 176 consecutive patients with traumatic frontal intracerebral hemorrhage, who treated at the University Medical Center Tuebingen, Germany, and Azad University of Medical Sciences in Tehran/Iran between 2017 and 2020. Brain CT Scan confirmed traumatic frontal intracerebral

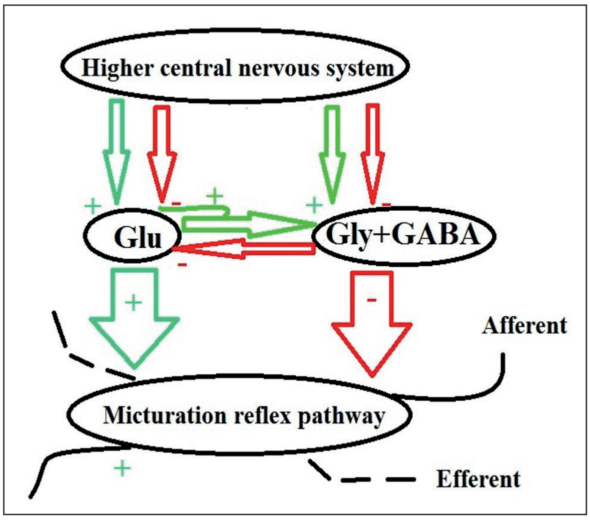

Figure 2. Micturation reflex pathway in the lumbosacral cord and the role of glutamatergic and glycinergic/GABAergic neurons. Glutamatergic neurons (Glu) stimulate the afferent and efferent limbs of the micturition reflex, while glycinergic/GABAergic neurons (Gly GABA) inhibit them. They inhibit glutamatergic neurons as well. These glutamatergic and glycinergic/GABAergic neurons receive inputs from the higher central nervous system and also from peripheral afferent neurons.

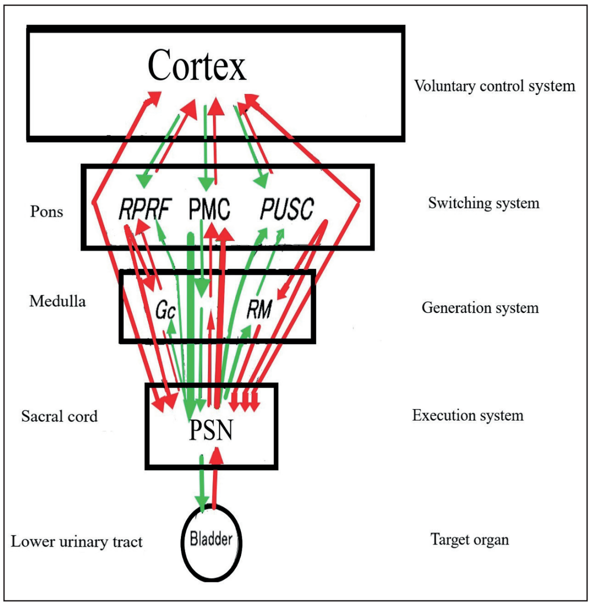

Figure 3. The pathway of micturition. The micturition and urine storage switching systems (PMC, PUSC, and RPRF) is located in the pons and the power generation systems (Gc, and RM) is located in the medulla. There are few connections between the PMC, PUSC, and RPRF, or between the Gc and RM. The cerebral cortex exerts voluntary control and turns the switches on or off as needed. Gc, nucleus reticularis gigantocellularis; PMC, pontine micturition center; PSN, parasympathetic nucleus (pelvic nerve nucleus); PUSC, pontine urine storage center; RM, nucleus raphe magnus; RPRF, rostral pontine reticular formation.

hemorrhage. Of these patients, 80 cases were female, and 96 cases were male with the mean age of 49±15 ranged from 19 to 88 years).

Patients' Selection

Across the enrolled patient cohort (n = 176), we observed lower urinary tract symptoms (LUTS) with compression of the frontal lobe due to local hemorrhage in 52 patients. Brain CT scans were routinely given to patients with brain trauma upon admission. In addition, brain magnetic resonance (MRI) images of patients with suspicion of diffuse axonal injuries were additionally performed. Those patients with diffuse axonal injuries were excluded from this study.

Lower Urinary Tract Symptoms Assessment

The International Prostate Symptom Score (IPSS) was used to evaluate the lower urinary tract symptoms in enrolled patients with symptoms of voiding dysfunction. We observed that 52 of the 176 patients experienced voiding difficulties and were furthered assessed with the IPSS questionnaire. These patients underwent urodynamic testing from day 1 (at the admission to the hospital) after diagnosis, up to a maximum of one year after the operation of the frontal lobe bleeding tumor (Table I). Urodynamics consisted of measuring residual urine, urethral pressure profilometry, and water cystometry, as described previously[18]. The sites of lesions are also shown (Figure 4). Patients with neurological deficits such as a low level of consciousness, dizziness, and gait disturbance had fixed indwelling urinary catheters placed during the first week of hospitalization.

The study protocol was approved by the local Ethics Committee.

Statistical Analysis

The correlation of marker expression was evaluated using the Spearman rank correlation test. All calculations and analyses were performed with SPSS 18.0. Sample size and power of each analysis were evaluated by SPSS (IBM Corp., Armonk, NY, USA) sample power and G*Power, respectively [we set α error at 0.05 and power (1-β) at 0.8]. The statistical significance level was considered to be p-value less than 0.05.

Results

General Patients' Information

In this study, 176 patients were enrolled in, and 52 cases of them showed lower urinary tract symptoms (LUTS) with compression of the frontal lobe due to local hemorrhage. The mean age of the 176 patients was 49±15, and the studied population consisted of 80 females (45.4%) and 96 males (54.6%). The mean age of patients with LUTS was 48.2±21.8 (Table II). Our results showed failed to show any significant difference between the age and gender of patients with LUTS and without LUTS (p>0.05).

Initial Assessment of LUTS

Patients were followed up in periods ranging from 3 months to 1 year with a mean follow-up time of 9 months. According to IPSS questionnaires, our results showed that the most frequent voiding complaints included incomplete emptying (17.3%), urgency (13.0%), frequency (19.0%), intermittency (19.2%), staining (11.5%) and nocturia (25.0%). Furthermore, the meantime for presenting urinary symptoms after the onset of neurological symptoms, namely the signs of raised intracranial pressure (e.g., deterioration in the level of consciousness, headache, pupillary

Table I. Urodynamic testing was performed by 52 patients. Here are some examples of results of urodynamic study in 31 patients.

Age	Sex	Diagnosis	Latency*	Urinary symptoms at urodynamic testing	Residual urine (ml)	UP_{max} (cmH_2O)	FDV (ml)	MDV (ml)	Detrusor hyper-reflexia	DSD	USR	Low compliance
19	m	frontal intracerebral hemorrhage left	5 days	Incomplete emptying, urgency	160	81	32	421	–	–	+	–
31	w	frontal intracerebral hemorrhage right	12 days	Incomplete emptying, urgency	253	69	58	602	–	–	–	–
65	w	frontal intracerebral hemorrhage right	1 month	Nocturia, incontinence, frequency, intermittency	405	np	329	357	+	+	+	+
46	m	frontal intracerebral hemorrhage left	14 days	Pollakiuria, nocturia	0	39	115	271	+	+	–	–
78	m	frontal intracerebral hemorrhage right	7 days	Frequency, intermittency	112	22	68	266	+	+	+	–
81	w	frontal intracerebral hemorrhage left	18 days	Nocturia, urgency.	85	57	31	63	+	+	+	–
26	w	frontal intracerebral hemorrhage right	3 days	Nocturia, frequency, intermittency	np	25	221	384	–	+	–	–
59	m	frontal intracerebral hemorrhage right	4 days	Frequency, intermittency	99	51	165	263	–	–	+	+
38	m	frontal intracerebral hemorrhage left	1 month	Frequency, intermittency	45	76	72	436	+	–	–	–
28	w	frontal intracerebral hemorrhage right	2 day	Incomplete emptying, urgency	0	48	322	589	–	–	–	–
22	m	frontal intracerebral hemorrhage left	4 days	Frequency, intermittency	np	65	225	248	+	+	+	–
27	w	frontal intracerebral hemorrhage right	11 days	Retention	np	26	96	225	–	–	+	–
52	m	frontal intracerebral hemorrhage right	23 days	Urgency, nocturia	205	27	35	217	+	+	–	–
73	w	frontal intracerebral hemorrhage left	6 days	Frequency, intermittency	0	29	47	391	+	–	+	–
44	m	frontal intracerebral hemorrhage right	6 days	Pollakiuria	np	97	35	481	+	–	+	–

Continued

Table I (continued). Urodynamic testing was performed by 52 patients. Here are some examples of results of urodynamic study in 31 patients.

Age	Sex	Diagnosis	Latency*	Urinary symptoms at urodynamic testing	Residual urine (ml)	UP_{max} (cmH_2O)	FDV (ml)	MDV (ml)	Detrusor hyper-reflexia	DSD	USR	Low compliance
88	w	frontal intracerebral hemorrhage right	3 months	Retention	30	58	113	224	–	–	–	–
75		frontal intracerebral hemorrhage left	9 days	Retention	138	66	78	336	–	–	+	–
41		frontal intracerebral hemorrhageright	12 days	Incomplete emptying, urgency	214	53	312	579	+	+	–	–
24		frontal intracerebral hemorrhage left	1 month	Nocturia, incontinence, frequency, intermittency	56	61	215	228	+	–	+	–
67	m	frontal intracerebral hemorrhage left	7 days	Pollakiuria, nocturia	234	27	97	215	–	+	–	–
83	w	frontal intracerebral hemorrhage right	9 days	Incomplete emptying, urgency	58	28	39	227	–	–	+	+
48	w	frontal intracerebral hemorrhage right	15 days	Frequency, intermittency	82	32	41	394	–	–	+	+
42	m	frontal intracerebral hemorrhage right	9 days	Retention	49	91	32	488	+	+	+	+
62	m	frontal intracerebral hemorrhage right	8 days	Urgency, nocturia	66	52	163	220	+	+	–	–
21	m	frontal intracerebral hemorrhage left	4 days	Frequency, intermittency	89	73	62	406	–	–	+	–
83	w	frontal intracerebral hemorrhage left	6 days	Nocturia, pollakiuria	75	44	170	337	+	+	–	–
26	m	frontal intracerebral hemorrhage right	9 day	Nocturia, urgency	76	88	215	526	–	+	+	–
25	w	frontal intracerebral hemorrhage left	12 days	Incomplete emptying, urgency	202	28	166	462	–	+	–	+
34	m	frontal intracerebral hemorrhage right	7 days	Retention	110	19	158	228	+	+	–	–
39	m	frontal intracerebral hemorrhage left	1 months	Retention	71	37	223	521	–	–	+	–
47	w	frontal intracerebral hemorrhage right	2 months	Retention	60	49	56	225	+	+	–	–

*latency of urodynamic study after the occurrence of the neurological deficits. Np: Not performed, UPmax: Maximum urethral closure pressure, FDV: First desire to void, MDV: Maximum desire to void, DSD: Detruor sphincter dyssynergia, USR: Uninhibited sphincter relaxation.

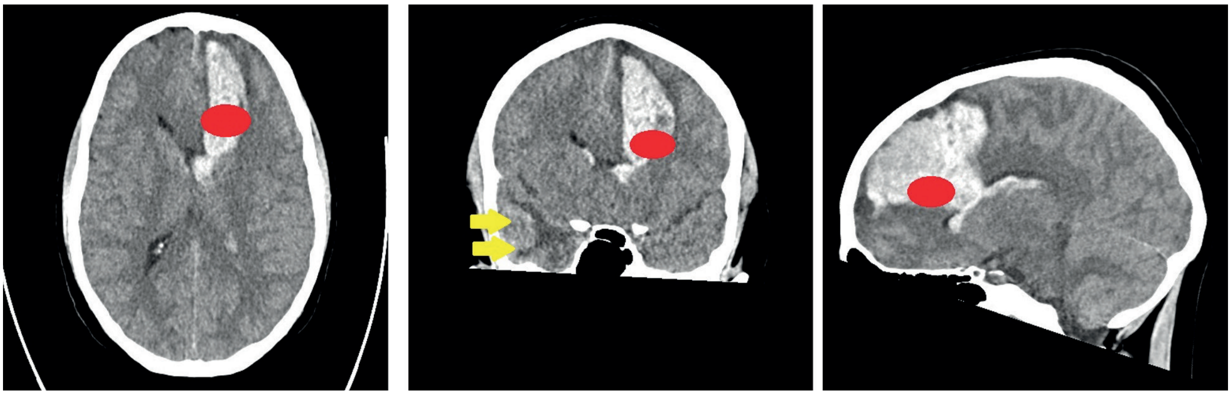

Figure 4. Location of lesions causing incontinence (or occasionally retention) in the group of patients studied by us. The red ellipse shows where white-matter lesions caused lasting urinary tract dysfunction. The *yellow arrows* show the location of contusion on the temporal lobe with brain edema.

dysfunction, vomiting, and possible papilledema) was 3 weeks ± 4 days).

Increased intracranial pressure was mainly due to the cerebral edema associated with brain hemorrhage. As mentioned earlier, of total 176 cases, 52 patients (29.5%) had urinary complaints (Table II). All patients with traumatic frontal intracerebral hemorrhage and urinary retention became unable to urinate 6 months from the onset. Voiding problems, especially nocturia, frequency, and intermittency, seemed to be present in all patients with traumatic frontal intracerebral hemorrhage.

Findings of Urodynamic Studies

The IPSS questionnaire indicated that all 52 patients had urinary problems at the time of urodynamic testing. These included frequency (n = 10, 19.2%), intermittency (n = 10, 19.2%), nocturia (n = 13, 25.0%), urinary retention (n = 7, 13.5%), urgency (n = 10, 19.2%), and pollakiuria (n = 4, 7.7%) (Table I). These symptoms continued together with the occurrence of the neurological symptoms. Measurement of residual urine was also performed on the patients, which showed that 45 (86.5%) had 71-523 ml of residual urine, with an average of 128 ml. Water cystometry showed that the bladder volume at first desire to void and/or maximum desire to void was decreased in 37 (71.1%) and increased in 17 (33%) patients. Detrusor overactivity was noted in 16 patients (31%). In addition, low-compliance bladder was found in six patients (11.5%), detrusor-sphincter dyssynergia in 24 patients (46.1%), and uninhibited sphincter relaxation in 12 patients (23.0%).

Discussion

In the current study, we observed that 52 patients from 176 showed voiding difficulties following frontal intracerebral hemorrhage. Urodynamic

Table II. Patients with micturitional disturbances.

Micturitional symptoms According to IPSS questionnaires	Age ≥50-≤70 (N=84) ≤ 50 (N=92)	Gender Male (N=96) Female (N=80)	52/176	29.5%
Urinary retention/Incomplete emptying	29 39	58 22	9	17%
Weak stream/straining	22 45	41 28	6	11%
Nocturnal urinary frequency	39 74	92 27	13	25%
Frequency/intermittency	62 55	86 27	10	19%
Urinary urgency	62 31	43 35	7	13%

testing of 52 symptomatic patients revealed detrusor overactivity in 25 (48%) low-compliance bladders in 4 (7.7%) detrusor-sphincter dyssynergia in 20 (38%) and uninhibited sphincter relaxation in 11 patients (21%). Our findings also demonstrated that there was no significant correlation between the volume of hemorrhage and urinary symptoms.

It has been shown that 47% of acute-phase patients and in 19% of six-month follow-up patients with stroke had urinary incontinence. Lower urinary tract symptoms (LUTS) can be linked with numerous neurological manifestations that might be specifically related to lesions near the prefrontal cortex and the dorsal anterior cingulate cortex (ACC)[19]. LUTS factors include etiologies of many types (e.g., physiological, inflammatory, and idiopathic). Intracranial mass lesions are uncommon, but are a well-established source of LUTS[20]. However, little attention has been given to this, as traumatic frontal brain hemorrhage might be a significant trigger of severe neurological disorder marked by disturbed consciousness and LUTS[21].

One study has reported that urinary storage and emptying disorder were linked with hemorrhagic and ischemic strokes[22]. The study showed that there was 73.3% in the hemorrhagic diseases in comparison to 63.6% in the ischemic diseases[22]. Pre-clinical studies have demonstrated that induction of ICH by direct injection of collagenase to the brain hippocampal CA1 region can improve the role of the bladder and neuronal voiding centers[23,24]. The results of animal studies have shown that the bladder contraction in ICH-induced rats was found to be considerably higher compared to normal rats, while voiding pressure and times were substantially decreased by ICH induction[24]. This has suggested that ICH contributed to bladder function degradation and subsequently to induction of overactive bladder[24]. Although many clinical studies have been conducted to evaluate the association of brain lesions and LUTS, their scope has been limited to solid brain lesions, not hemorrhagic. The current study evaluated the correlation between intracerebral hemorrhagic brain lesions and assessed the specific traumatic frontal hemorrhagic lesion (not all types of ICH). In our opinion, this clearly demonstrates the relation of hemorrhagic incidents in specific regions of the brain to the prevalence of LUTS.

The acute presentation of ICH can be difficult to distinguish from ischemic stroke. Symptoms may include headache, nausea, seizures, and focal or generalized neurologic symptoms. Findings such as coma, headache, vomiting, seizures, neck stiffness, and raised diastolic blood pressure increase the likelihood of ICH compared to ischemic stroke, but only neuroimaging can provide a definitive diagnosis[25].

Tibaek et al[1] showed that the prevalence of at least one symptom of LUTS was 94% in patients diagnosed with stroke and symptoms (listed in terms of their frequency) were as follows: nocturia (76%), urgency (70%, the most severe), and frequency (59%). Among respondents who had at least one symptom, the prevalence of bother was 78%. It could be concluded that LUTS are highly prevalent in post-stroke settings, which can highly impact on patients' quality of life.

On the other hand, Burney et al[26] evaluated the relation of the brain injuries' sites with urodynamic findings in 60 patients. Their results demonstrated the association of cerebellar and hemorrhagic infarctions with detrusor areflexia. They showed that the majority of cortical and internal capsule lesions resulted in detrusor hyperreflexia. They reported that 47% had urinary retention, mainly due to detrusor areflexia (75%). Out of 20 patients with hemorrhagic infarcts, 17 (85%) had areflexia, compared to only 4 of 40 (10%) with ischemic infarcts. In addition, they observed that all six cases with cerebellar infarction had detrusor areflexia. The current study results showed that 52 of the total 176 patients have shown voiding difficulties following traumatic frontal intracerebral hemorrhage (prevalence = 29.5%), which is significantly lower than brain lesion based on previous studies (prevalence = 45%-95%). These results have demonstrated that hemorrhagic lesions might be the smaller contributors to LUTS following brain lesions in comparison to solid lesions.

Conclusions

Multiple areas of the brain are involved in micturition. The forebrain influences the voluntary control of the human micturition switch and the maintenance of continence. Frontal intracerebral hemorrhage compressing the prefrontal cortex influence the micturition center and is responsible for lower urinary tract symptoms. Hemorrhage of the right frontal lobe does have a direct relationship with incontinence which was completely disappeared in 85% of the patients within 9 months.

Conflict of Interests

The Authors declare that they have no conflict of interests.

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