The connection between frontal lobe brain tumors and lower urinary tract symptoms – Series of 347 patients

R. AKHAVAN-SIGARI[1], P. MORTZAVI-ZADEH[1], L. TRAKOLIS[1], H. KEYHAN[2], B. AMEND[3], S. HERLAN[1]

[1]Department of Neurosurgery, University Medical Center, Tuebingen, Germany
[2]Department of Urology, Azad University of Medical Sciences, Tehran, Iran
[3]Department of Urology, University Medical Center, Tuebingen, Germany

Abstract. – OBJECTIVE: The present study aimed to provide an early insight into the effect of intra-axial frontal lobe tumors on the micturition center and its potential role in producing compression in and around the prefrontal cortex.

PATIENTS AND METHODS: A total of 149 symptomatic patients were selected for urodynamic testing. The study sample included all patients with intra-axial frontal lobe tumors treated at two locations: the University Medical Center Tuebingen (Germany), and Azad University of Medical Sciences (Iran) between 2017 and 2020. Lower urinary tract symptoms (LUTS) were recorded in patients with frontal lobe compression due to local tumor growth. The symptomatic patients had brain magnetic resonance (MRI) images taken to examine for possible lesions.

RESULTS: The treated patients (149 patients with a median age of 55 years) were evaluated using computer urodynamic investigation and voiding diaries. The results of urodynamic testing of 149 symptomatic patients showed detrusor over-activity in 82 (55%) patients, dyssynergia of detrusor-sphincter in 67 (45%) patients, uninhibited sphincter relaxation in 40 (27%) patients, and low-compliance bladder in 21 (14%) patients. There was no significant correlation found between tumor size and urinary symptoms ($p = 0.103$, Spearman q = 0.826).

CONCLUSIONS: Frontal intra-axial tumors compressing and infiltrating the prefrontal cortex influence the micturition center and produce lower urinary tract symptoms. The tumors of the right frontal lobe were directly associated with incontinence, which was completely disappeared in 70% of the patients within 2 years.

Key Words:
Brain Tumors, Lower urinary tract, Urodynamic testing, Micturition.

Introduction

Several factors are responsible for voiding dysfunction associated with stroke[1], Alzheimer's disease, traumatic brain lesion, normal pressure hydrocephalus, multiple sclerosis, multiple system atrophy, Parkinson's disease, brain tumors, and other cerebral disorders[2,3]. The occurrence of such perturbations has not been wholly assessed and may be underestimated.

Intraaxial tumors, such as Glioblastoma multiforme with expansion to the prefrontal cortex, right insula (RI), and to the dorsal anterior cingulate cortex (ACC) are probably the cause of some critical conditions and diseases, such as convulsions, ataxia, and convulsions disturbances. Damage to this region of the brain may also lead to urinary dysfunction. The role of the prefrontal cortex in controlling the bladder was first recognized in a study by Ueki[4] and was later confirmed by Andrew and Nathan[5] in 1964. There is clinical evidence that lesions with long-term impact on bladder activity are located in white matter tracts within the medial frontal area. Blok et al[6] conducted original positron emission tomography (PET) experiments and found that the medial prefrontal area was activated in patients with successful voiding. This region was hypothesized to be "involved in decision-making on micturition". Subsequent trials have shown the role of lateral prefrontal regions in urine withholding or full bladder[7].

Understanding urinary complications with a neurological origin requires some understanding of the neurophysiological control of the bladder. In the cerebral cortex, significant activities in the right inferior frontal and anterior cingulate gyrus

Corresponding Author: Reza Akhavan-Sigari, MD; e-mail: reza.akhavan-sigari@med.uni-tuebingen.de

have been noticed during voiding, while such activity was absent during the withholding phase. It has been hypothesized that this region of the cortex is involved in intended decision-making on whether a planned decision has to be made[8]. Peripheral innervation, arising from the caudal parts of the sacral spinal cord, as well as connections between the sacral spinal cord and the pons, must be intact to affect voiding and storage. Hence, physiological control of the bladder requires extensive innervation with suprapontine inputs, intact peripheral nerves, and intact spinal connections between the sacral cord and the pons. The severity of urinary continence testing of neurological integrity is a well-known fact since neurology texts have been written[9].

Given the fact that cerebral blood flow in voiding is higher than that of the resting state, it was thought that small regions in the mid pons extending into the midbrain, bilateral supplementary motor, the right lateral frontal cortex, and the left sensorimotor cortex are activated during bladder emptying[10]. The clinical feature of frontal lobe incontinency has been described previously in some case reports. For example, a patient with severe urgency, micturition frequency, and urge incontinency but without dementia, who is socially aware and embarrassed by his/her incontinence. Patients with brain lesions have also been reported to have urinary retention in some cases.

As far as we know, there has been no previous urodynamic study investigating urinary symptoms in patients with frontal intra-axial tumors. While reporting the results of micturition histories and urodynamic studies in patients with intra-axial frontal brain tumors, this study tries to determine any potential connections (if any) between urinary disturbances and right insula (RI), the dorsal anterior cingulate cortex (ACC) and intraaxial frontal brain tumors with prefrontal cortex.

Patients and Methods

Patients Data and Study Design

In total, this study obtained participants from a pool of 347 patients (148 women and 199 men). These patients were treated at one of two institutions: the University Medical Center of Tübingen in Germany, or the Neurosurgical Departments of the Azad University of Medical Sciences in Tehran from 2017 to 2020. The median age of patients was 55 years, ranging from 18 to 86 years. Brain MRI was conducted for all the patients. Patients with status lacunaris were excluded from the study. Status lacunaris is a condition where numerous small areas of degeneration occur in the cerebral arteriosclerosis and are known as a cause of micturition disturbance[11]. Thus, 238 out of 347 patients treated for frontal lobe tumors were included in the study and adequate documentation was obtained from them. Patients with voiding dysfunction were assessed for lower urinary tract symptoms using the International Prostate Symptom Score (IPSS). Out of 238 patients, 49 were recognized with voiding difficulties and were selected to fill in the IPSS questionnaires. Urodynamic testing of these patients was conducted from 1 day after diagnosis (as soon as possible, preoperatively), up to 2 years after the frontal lobe tumor operation (Table I). Urodynamic testing includes the measurement of residual urine, water cystometry, and urethral pressure profilometry, as described previously[12]. The sites of lesions are displayed in Figure 1A-C.

Statistical Analysis

Spearman rank correlation test was used to evaluate the correlation between tumor size and urinary symptoms. Data analyses and calculations were performed using SPSS v18.0 software (SPSS Inc. PASW Statistics for Windows, Chicago, IL, USA). A *p*-value lower than 5% ($p < 0.05$) was considered to be statistically significant.

Results

During the first week of hospitalization, 96 patients needed indwelling urinary catheters because of neurological deficits such as dizziness, low level of consciousness, and gait disturbance. The patients were observed for 3 months to 1 year periods. Voiding complaints by the patients included: incomplete emptying, intermittency, urgency, incomplete emptying, nocturia, and staining. The symptoms of urinary dysfunction occurred within 90 days after the beginning of the neurological symptoms, i.e., the signs of increased intracranial pressure including pupillary dysfunction, deterioration in the level of consciousness, possible papilledema, headache, vomiting, etc.). Cerebral edema associated with a brain tumor was the main cause of raised intracranial pressure. Urinary complaints were observed in 149 patients (63%) (Table II). Nocturia was the most common symptom (observed in 40

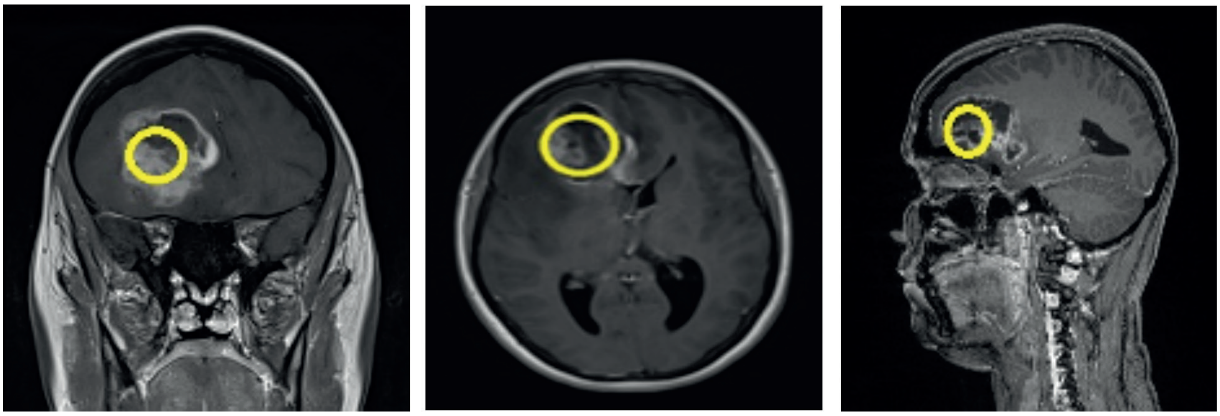

Figure 1. (A-C). MRI studies of lesion sites that cause incontinence and voiding difficulties in the patients studied. The yellow ellipse indicates locations where white-matter lesions have led to lasting urinary tract disorder. Here is an example of a patient with glioblastoma multiforme frontal right.

(27%) of patients), followed by frequency and intermittency (observed in 28 (19%) of patients). All patients experienced urinary retention and tumor recurrence could not urinate for 6 months from the onset. It seemed that all patients with frontal lobe tumors experienced voiding problems, especially nocturia, frequency, and intermittency.

Findings of Urodynamic Studies

There were various urinary issues that the 149 patients described as having voiding problems (by the IPSS) had at the time of urodynamic testing. These included: frequency and intermittency (47 patients), incontinence (6 patients), urgency (9 patients), pollakiuria (21 patients), urinary retention (33 patients), and nocturia (43 patients) (Table I). These symptoms were associated with the occurrence of neurological symptoms. Residual urine was measured in 102 patients, 89 (87%) of which had residual urine from 41 to 523 ml, with an average of 189 ml. Water cytometry was also conducted in all patients. The results showed that the bladder volume desire to void at first, (maximum desire to void) was increased in 48 (32%) patients and decreased in 115 (77%) patients. Detrusor overactivity was observed in 82 (55%) patients, detrusor-sphincter dyssynergia in 67 (45%), uninhibited sphincter relaxation in 40 (27%), and low-compliance bladder in 21 (14%).

Discussion

Lesions close or adjacent to the micturition area in the dorsal anterior cingulate cortex (ACC) and the prefrontal cortex can cause lower urinary tract symptoms (LUTS) which may be associated with multiple neurological signs. There are many possible causes of LUTS, such as inflammatory, neurologic and infectious etiologies, among others. Although infrequent, the role of intracranial mass lesions in LUTS has been well-established. However, this has received less attention because frontal brain tumors may cause a serious neurological state specified by disrupted consciousness.

The results of the present study showed that 149 of 238 patients (63%) with an intra-axial tumor in or around the prefrontal cortex and the dorsal anterior cingulate cortex (ACC) had urinary problems. The major symptoms were intermittency and frequency in 47 (31%) patients, nocturia in 43 (29%), and urinary retention in 33 (22%). The occurrence of urinary problems in the patients seems to be more associated with a frontal mass tumor around the prefrontal cortex. Andrew and Nathan[5] also reported voiding difficulty in a patient with frontal mass lesion, including the syndrome of urinary urgency, frequency, and urinary incontinence. In a subsequent case study, Maurice-Williams[13] reported LUTS in 7 out of 50 consecutive patients having frontal lobe tumors.

Only a few isolated case reports on this syndrome can be found in the literature[14]. There are many components to understanding the pathology. The study of LUTS requires a relevant medical history, physical examination including urinalysis, frequency-volume charts, symptom scoring using relevant tools like IPSS, and PSA tests in men more than 40 years old[15]. Standard, uncomplicated treatments for LUTS include changes in lifestyle, behavior modification, bladder training, and medicinal management. Cytology with

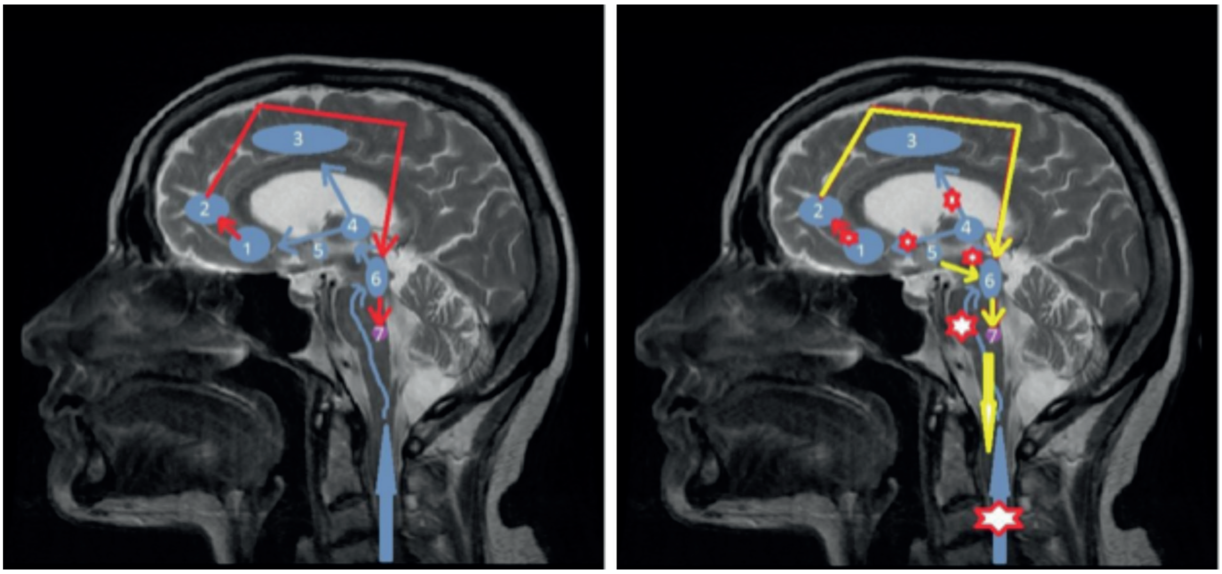

Figure 2 (A and B). Simple major central pathways of micturition by higher brain centers. A long-loop spinobulbospinal voiding reflex with a rostral terminus in the brainstem mediates the switch of LUT function between voiding and storage. During storage with a full bladder, afferent signals (blue) interconnect on the midbrain periaqueductal gray (PAG), and their strength increases until they overpass a specified threshold in the brainstem. This may cause the Pontine Micturation Center (PMC) to be triggered and the bladder to be contracted without interference from higher centers of the brain. This may be the main cause of incontinence in infancy or the frequency of micturition in rats. Through the thalamus (TH) and hypothalamus (H), the PAG is related to the lateral prefrontal cortex (LPFC), right insula (RI), and the dorsal anterior cingulate cortex (ACC). During the storage phase, they are passed to the medial prefrontal cortex (MPFC, *red arrows*) which is responsible for decision-making about whether or not voiding should occur. The bladder or the spinal cord does not send signals directly to the thalamus. The decision in the storage phase (Figure 2A) is not to void, thus the PAG is chronically inhibited through a long pathway (*red arrows*) from the MPFC to maintain this situation. This leads to suppression of the pontine micturition center (PMC, *red arrows*) and voiding is inhibited. When a voiding decision is made (Figure 2B), the MPFC releases the PAG (*arrows in yellow*), and a signal is also provided by the hypothalamus (H). As a result, the PMC is triggered, which in turn, transmits descending motor output (*arrows in yellow*) to the sacral spinal cord, causing relaxation of the urethral sphincter, contraction of the detrusor, and finally, the occurrence of voiding. Urine storage recommences whenever the bladder is empty. During urine storage, the PMC is inactive but the PAG is activated by the bladder's afferent input. (1) The lateral prefrontal cortex (LPFC) and right insula (RI). (2) The medial prefrontal cortex (MPFC). (3) Anterior cingulate cortex (ACC). (4) Thalamus. (5) Hypothalamus. (6) Pontine micturition center (PMC). (7) Periaqueductal gray (PAG). *Asterisk:* Inhibition of signal.

or without urethrocystoscopy is also suggested in LUTS patients with neurogenic symptoms to detect possible factors that can imitate neurogenic LUTS, such as stones, urethral strictures, and bladder tumors. Routine spinal or brain imaging has not been indicated in these patients but in those with new-onset of vomiting, headache, and increased urinary symptoms.

According to the results of urodynamic tests in 149 patients, detrusor overactivity was observed in 81 patients (54%), detrusor-sphincter dyssynergia in 67 (45%), low-compliance bladder in 20 (13%), and uninhibited sphincter relaxation in 40 (26%). Out of 149 patients, detailed postoperative follow-up was performed on 115 patients. The results of repeated urodynamic studies over a follow-up period of 2 years showed that detrusor-sphincter dyssynergia and detrusor overactivity completely disappeared in 81 patients (70%). There were 38 patients (33%) suffering from urinary retention and low-compliance bladder, whom regained the ability to urinate after a 4-months follow-up period. Furthermore, 35 patients (30%) were still observed to have untreated sphincter relaxation and detrusor-sphincter dyssynergia after a 2 year follow-up period.

The study by Andrew and Nathan[5] was one of the most influential studies in which 38 patients with lesions in the anterior frontal lobe were described with micturition disorders. The authors described the usual clinical feature of frontal lobe incontinency as follows: a patient with serious urgency, micturition frequency, and urge incontinency but without dementia, who is socially aware and embarrassed by his/her incontinence. Surprisingly, removing either the causative lesion or the area it involves in the brain may alleviate this syndrome. Maurice-Williams[13] reported that

Table I. Results of urodynamic study in 22 patients. Urodynamic testing was performed by 149 patients.

Age	Sex	Diagnosis/ expansion	Latency*	Urinary symptoms at urodynamic testing	Residual urine (ml)	UP_{max} (cmH_2O)	FDV (ml)	MDV (ml)	Detrusor hyperreflexia	DSD	USR	Low compliance
32	W	GBM	1 day	Incomplete emptying, urgency	130	83	38	522	-	-	+	-
35	M	GBM	1 day	Incomplete emptying, urgency	Np	66	55	600	-	-	-	-
65	W	Anaplastic astrocytoma WHO III	3 months	Nocturia, incontinence, frequency, intermittency	Np	np	322	480	+	+	+	+
40	W	Astrocytoma WHO III	2 months	Pollakiuria, nocturia	58	39	110	276	+	+	-	-
68	M	GBM	2 days	Frequency, intermittency	0	29	66	268	+	+	+	-
69	W	GBM	1 month	Nocturia, urgency.	85	56	38	66	+	+	+	-
43	M	Diffuse astrocytoma WHO III	3 days	Noctuna, frequency, intermittency	Np	25	224	385	-	+	-	-
82	M	GBM	5 days	Frequency, intermittency	99	53	160	268	-	-	+	+
38	M	Astrocytoma WHOIII	1 month	Frequency, intermittency	45	74	78	430	+	-	-	-
31	W	GBM	2 day	Incomplete emptying, urgency	0	45	320	586	-	-	-	-
80	M	GBM	4 days	Frequency, intermittency	160	69	125	348	+	+	+	-
27	W	Astrocytoma WHO II	2 days	Retention	253	22	91	325	-	-	+	-
51	M	GBM	5 days	Urgency, nocturia	405	29	39	267	+	+	-	-
70	M	GBM	4 days	Frequency, intermittency	0	28	42	394	+	-	+	-
36	M	Astrocytoma WHO I	3 days	Pollakiuria	Np	87	25	580	+	-	+	-
72	W	GBM	2 months	Retension	30	68	103	220	_	-	-	-
65	W	GBM	6 days	Nocturia, pollakiuria,	75	49	180	387	+	+	-	-
48	M	Astrocytoma WHOIII	1 day	Nocturia, urgency.	76	89	205	536	-	+	+	-
38	W	Astrocytoma WHO II	2 days	Incomplete emptying, urgency	202	18	176	562	-	+	-	+
71	M	GBM	5 days	Retention.	110	39	158	248	+	+	-	-
52	M	GBM	3 months	Retention.	71	36	233	511	-	-	+	-
48	W	Astrocytoma WHO III	2 months	Retention.	60	69	66	325	+	+	-	-

*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; GBM: Glioblastoma multiforme.

Table II. Patients with micturitional disturbances.

Micturitional symptoms According to IPSS questionnaires	Age	Gender		
	≥50-≤70 (N=94) ≤ 50 (N=55)	Male (N=82) Female (N=67)	149/238	63%
Urinary retention/incomplete emptying	36 49	62 25	19	13%
Weak stream/straining	25	42	12	8%
Nocturnal urinary frequency	49 71	95 25	40	27%
Frequency/intermittency	65 58	89 25	28	19%
Urinary urgency	61 31	47 37	16	11%

excision relieved the micturition symptoms in five cases for up to 26 months. Many cases may be overlooked, for example, tumor progression at the admittance time has led to clouded consciousness of intellectual deterioration in patients which, in turn, hides the original distress of the patient at his/her micturition symptoms. Frontal lobe syndrome of disinhibition and apathy has known to be responsible for these symptoms.

The remarkable fact is that micturition symptoms may be absent in the case of extensive and large frontal tumors. Moreover, susceptibility to these symptoms may vary from person to person, and many patients may experience an asymptomatic variation in micturition function[16]. The findings of Andrew and Nathan[5] support this possibility. In their work, post-operative cystometrography of leucotomy patients (with no complaints related to micturition symptoms) showed no changes relative to a pre-operative state. The authors, based on these results[5], deduced their most persuasive proof for localization within the frontal lobes of a particular region associated with the control of defecation and micturition. They argued that the information they obtained from the tumor cases did not let them precisely localize a tumor. Thus, the existence of mictruition syndrome seems to only permit localization of a tumor in the frontal region, not when it is within a certain region of the frontal lobes. These researchers[5] have pointed out that lesions in their postulated area would involve fibers traveling to and from the genu of the corpus callosum and hence could be placed in either hemisphere. To the best of our knowledge, this is the first study with a large number of patients with urodynamic studies and urinary symptoms associated with frontal intra-axial tumors.

The results of our study showed that LUTS is common among patients with frontal lobe tumors within and around the prefrontal cortex. This has led to the hypothesis that intra-axial tumors in this region influence the frontal micturition center. In our work, we also found no significant association between the site of lesion and urodynamic results. Although there was no preponderance of right-sided lesions, lesion size was discovered to be associated with the incidence of urinary symptoms. The results of this research revealed that damage to the patients' basal ganglia and anteromedial frontal lobe and the relevant descending pathway is the main factor of micturition disorders (Figure 2A-B).

A higher incidence of incontinence increases is when a tumor penetrates the medial surface of both frontal lobes or when it expands into the subcortical substance of the frontal lobe. Incontinence is usually transient after tumor removal or frontal lobectomy. Thus, attributing incontinency to the absence of the frontal function is difficult.

Conclusions

This study aimed to review the previous urodynamic studies and describes micturition histories in patients with frontal lobe tumors as well as to investigate lesion sites that are responsible for micturition disorders. We believe that this is the first study conducted that has shown urinary symptoms to be associated with frontal intra-axial tumors in a large patient cohort using urodynamic studies. We showed that there was a direct relationship between the intra-axial tumor of the right frontal lobe and the incontinency which completely disappeared in 70% of the patients examined within two years after surgery. There may be other reasons why incontinence arises other than direct absence of frontal function. However, this study has helped to provide some evidence in the correlation between frontal tumor and urinary dysfunction which may ultimately help clinicians to understand the complex interrelationship between neurology and urinary pathology in the case of frontal lobe brain tumors.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contributions

RAS, PMZ, LT, HK, BA, and SH conceived and designed the study, collected the data and performed the literature search and was involved in the writing of the manuscript. All authors have read and approved the final manuscript.

Ethical Approval

The entire clinical procedure was approved by the University Medical Center of Tübingen in Germany and the Neurosurgical Departments of the Azad University of Medical Sciences in Tehran Local Ethics Committee.

Informed Consent

Written informed consent for participation was obtained from patients.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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