CLINICAL POLYMORPHISM OF FUNCTIONAL URINATION IN PATIENTS WITH NEURODEGENERATIVE DISEASES: MULTIPLE SYSTEM ATROPHY

P.G. Schwartz, S.L. Timerbaeva, M.Yu. Krasnov, E.N. Yudina

Research Center of Neurology, Moscow

Introduction. O'Sullivan S.S. et al. (2008) convincingly demonstrated in a large sample of patients with multiple system atrophy (MSA) the leading role of early autonomic nervous system disorders in the prognosis for MSA [8]. Koellensperger M. et al. (2010) analyzed 437 cases of MSA and revealed autonomic nervous system dysfunction in 99% of patients. Urination disorders manifested in 83%, erectile function disorders in 84%, orthostatic hypotension in 75%, chronic constipation in 33% of patients [7].

Kirchhof K. et al. (2003) points out that the emergence of lower urinary tract symptoms (LUTS) precede the development of orthostatic hypotension in 76% of patients with the Shy-Drager syndrome. The authors reveal sphincter disorders according electroneuromyographic pelvic floor in 91% [6].

Benarroch E.E. et al. (2001, 2010) showed that in the early stages of MSA a degeneration of Barrington's nucleus cells occurs. Barrington's nucleus is located in the rostral pons in the brainstem and is sensitive to corticotropin releasing factor hormone. Corticoliberin is produced in the hypothalamus paraventricular nucleus and is the major mediator of the pontine micturition center. Next to Barrington's nucleus the degeneration begins in the periaqueductal gray matter which perfors the role of "manager" of descending impulses from the cortex and subcortical structures to the nuclei in the brainstem. Subsequent pathogenic mechanisms lead to desynchronization of spinal and peripheral autonomic ganglia with subcortical structures [1, 3, 4].

Sakakibara R. et al. (2000) described in detail the phenomenology and the percentage of neurogenic voiding dysfunction in Shy-Drager syndrome. MSA symptoms according to the authors are presented by urinary difficulty (79%), frequent nocturnal urination (74%), micturition urgency episodes (63%), daily pollakiuria (45%), enuresis (19 %) and chronic urinary incontinence (8%). This paper presents only the summary data of all patients without regard to individual symptoms occurring combinations [10]. In our opinion, every clinical manifestation can be individualy

convincingly explained the defeat of the specific nuclei of the brainstem and basal ganglia responsible for the implementation of the normal urination. Formation stages of various lower urinary tract symptoms (LUTS) are also not shown.
Such approach would indirectly recreate the sequence of targets involvement in the neurodegenerative process [2]. Especially because according to Sakakibara R. et al. (2000) 100% of patients wits MSA suffer from LUTS [10].

Urodynamic study methods allowed Wheeler J.S. Jr. et al. (1985), Salinas J.M. et al. (1986), Kirby R. et al. (1986) independently of each other to objectify patients complaints and describe the three forms of disturbance in micturition in MSA A [3, 11, 13]. The first form - dehiscence of the bladder neck because of the weakness of the urethral sphincter contractile activity (smooth and striated muscle). The reason for this disturbance is secondary degeneration of Onuf's nucleus that occurs in 90% of patients with MSA. (Salinas J.M. et al. 1986, Kirby R. et al. 1986; Pramstaller P.P. et al. (1995) [5, 9, 11]. The second form is detrusor areflexia - occurs in 2/3 of patients. The cause of this disorder is a degeneration of the Barrington's nucleus and nuclei in the medulla oblongata, parasympathetic neurons in the sacral center of urination and a significant reduction in neuronal density, containing acetylcholinesterase (Salinas J.M. et al., 1986). [11]. The third form is detrusor overactivity - occurs in one third of patients. The mechanism of this form is presumably associated with the loss of inhibitory effects from corpus striatum substantia nigra on the bladder (Salinas J.M. et al., 1986) [11].

Objective: To extract groups of urinary disorders symptoms which are specific to various clinical forms of MSA (Shy-Drager syndrome – MSA A, olivopontocerebellar atrophy – MSA C, striatonigral degeneration – MSA P), to analyze the dynamics of the degeneration of the nuclei in the pons, cerebellum and basal ganglia based on the dynamics of LUTS development.

Methods

The study involved 38 patients with an established diagnosis of MSA (MSA A – 13; MSA C – 8; MSA P – 17 patients) with severe LUTS (27 women, 11 men, mean age - 54,5 ± 14 years). Research Center for Neurology questionnaire was used for symptoms detection. Diseases of the genitourinary system were excluded using ultrasound and microbiological methods.

Results and discussion

85% of patients with MSA A had imperative urinary incontinence (IUI), by 43% of them this symptoms were a preliminary to neurological symptoms and appeared in an average of 6 ± 1.5 months before the development of orthostatic hypotension. In 64% of patients with MCA C were diagnosed disturbances in pelvic floor muscles

control (initiating micturition disorders) and positional disorders most pronounced in men (inability to urinate standing). In 87% of patients these symptoms were combined with cerebellar *symptoms* and developed simultaneously. In 76% of patients with MSA P was noted *nocturia* which was combined with *parkinsonism* in 100% of cases. Symptoms developed after an average of 6 months after the development of other neurological symptoms.

Phenomenology and dynamics of micturition disorders relative "neurological" MSA symptoms depending on the form of the disease is presented in **Table 1.**

MSA type	(n)	micturition disorders onset relative to neurological symptoms onset		Most typically occurring micturition disorders		degeneration zone (Accumulation of alpha synuclein)
			frequency of occurrence, %	symptoms	frequency of occurrence, %	
MSA A[1]	13	-1	43	urgency urinary incontinence	85	Barrington's nucleus (M-region); Locus coeruleus
MSA C	8	1	87	pseudodysynergia	64	vermis
MSA P	17	+3	100	*nocturia*	76	Paraventrilar nucleus of the hypothalamus

Differential diagnosis of MSA and its clinical forms is extremely complicated. The definitive diagnosis is often established only in the later stages of this rapidly progressive neurodegenerative disease. Including neurourological tests in diagnostic procedures of MSA can help provisionally diagnose in a short time MSA. It can help to rule out other well-known diseases such as Parkinson's disease (micturition disturbances 5-6 years after disease onset), stress urinary incontinence (absence of orthostatic hypotension), amyotrophic lateral sclerosis (no electroneuromyographic signs of *Onuf's nucleus* damage, no sphincter dysfunction), vascular parkinsonism (MRI), idiopathic hyperactive bladder syndrome (no neurological symptoms) [2].

There are two drug therapy components in urination disorders treatment by MSA. Competitive muscarinic receptor antagonists (tartrate tolterodine, oxybutynin hydrochloride, trospium chloride, solifenacin succinate) compensate cerebral effects on spinal micturition center (by neurogenic detrusor overactivity). Acetylcholinesterase inhibitors (pyridostigmine bromide, distigmine bromide) by detrusor hypotonia and non-selective adrenergic agonists

(midodrine), selective noradrenaline and serotonin reuptake inhibitors (duloxetine) by stress urinary incontinence directly affect the peripheral mechanisms of regulation of micturition.

Conclusions

Analysis of the results suggests the involvement in the neurodegenerative process certain regulating urination areas ("nuclei"). In the case of MSA A – Barrington's nucleus which regulates the detrusor contractility activity, in MSA C – the cerebellum vermis which determines the position during urination and indirectly, *Onuf's nucleus which is* responsible for the contractile activity of the pelvic floor. Isolated symptom of nocturia by MSA P points to hypothalamus paraventricular nucleus damage that regulates daily rhythms of urination and urine output. Analysis of symptoms allows indirectly suggest zones in the brain involved in the process of degeneration and make easier the differential diagnosis of MSA types.

References

1. Illarioshkin S.N. Glava 13. Parkinsonizm pri nasledstvennykh mul'tisistemnykh degeneratsiyakh TsNS. [Chapter 13. Parkinsonism in hereditary multisystem degenerations CNS.] / In.: V.N. Shtok, I.A. Ivanova-Smolenskaya, O.S. Levin (eds.) Ekstrapiramidnye rasstroystva. Rukovodstvo po diagnostike i lecheniyu [Extrapyramidal disorders. Diagnosis and treatment Guide] Moscow: MEDpress-inform, 2002. 608 p. (In Russ.)
2. Shvarts P.G., Yudina E.N. et al. Klinicheskiy polimorfizm narusheniy mocheispuskaniya u patsientov s mul'tisistemnoy atrofiey (MSA) [Clinical polymorphism of urination disorders in patients with multiple system atrophy (MSA)] / In: Tezisy Vserossiyskoy nauchno-prakticheskoy konferentsii «Davidenkovskie chteniya» (obshchaya nevrologiya) [Abstracts of the Russian scientific-practical conference "Davidenkovskie read" (general neurology)]. 2014. St-Petersburg. p. 300. (In Russ.).
3. Benarroch E.E., Schmeichel A.M. Depletion of corticotrophin-releasing factor neurons in the pontine micturition area in multiple system atrophy // Annals of Neurology. 2012; 50: 640-645.
4. Benarroch E.E., Schmeichel A.M., Low P.A., Parisi J.E. Differential involvement of the periaqueductal gray in multiple system atrophy. // Auton Neurosci. 2010; 158 (1-2): 111-117.
5. Kirby R.S., Bannister R. Bladder dysfunction in progressive autonomic failure // Br. Med. J. 1986; 293(6541): 223-224.
6. Kirchhof K., Mathias C.J., Fowler C.J. The relationship of urogenital dysfunction to other features of

autonomic failure in MSA // Clin. Auton. Res.1999. 9: 1–28.
7. Köllensperger M., Geser F. et al. Presentation, diagnosis, and management of multiple system atrophy in Europe: final analysis of the European multiple system atrophy registry. // Mov. Disord. 2010; 25(15): 2604-2612.
8. O'Sullivan S.S., Holton J.L., et al., Parkinson's disease with Onuf's nucleus involvement mimicking multiple system atrophy // J Neurol Neurosurg Psychiatry. 2008; 79(2): 232-234.
9. Pramstaller P.P., Wenning G.K., et al. Nerve conduction studies, skeletal muscle EMG, and sphincter EMG in multiple system atrophy. // J Neurol Neurosurg Psychiatry. 1995; 58(5): 618-621.
10. Sakakibara R., et al. Urinary dysfunction and orthostatic hypotension in multiple system atrophy: which is the more common and earlier manifestation // J. Neurol. Neurosurg. Psychiatry. 2000; 68: 65–69.
11. Salinas J.M., Berger Y., De La Rocha R.E., Blaivas J.G. Urological evaluation in the Shy Drager syndrome // J. Urol. 1986; 135(4): 741-743.
12. Seseke S. et al. Voluntary pelvic floor muscle control — An fMRI study // Nueroimage. 2006; 31: 1399–1407.
13. Wheeler J.S. Jr, Canning J.R. Voiding dysfunction in Shy-Drager syndrome // J. Urol. 1985; 134(2): 362-363.