NEUROGENIC BLADDER: TYPES, ETIOLOGY, SYMPTOMS, DIAGNOSIS AND TREATMENT METHODS, OUR EXPERIENCE TO DATE.

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ABSTRACT

Neurogenic lower urinary tract dysfunction is a dysfunction of the bladder, bladder neck, or sphincters associated with some type of neurological disorder. Neurogenic bladder can manifest as three basic clinical conditions: overactive bladder, atonic (flexible) bladder, or urinary incontinence. Treatment depends on the type of neurogenic dysfunction.

At the Urology Department of the City General Hospital "8 September", Skopje, Republic of Macedonia, 12 patients with different clinical presentations and etiology of neurogenic bladder dysfunction have been diagnosed and treated in the last four years.

Objectives of the study are determination of the etiology and pathophysiological changes of patients with neurogenic lower urinary tract dysfunction in the study group, analysis of the differences between the symptoms and signs of various types of neurogenic bladder in the treated patients, analysis of the diagnostic results of various types of neurogenic lower urinary tract dysfunction in the study group and comparative analysis of the types and efficacy of conservative and surgical treatment in current practice, published in recent studies, compared with our experience to date.

Out of a total of 12 patients, 7 patients or 58.3% were diagnosed with the so-called flaccid or atonic bladder, accompanied by urinary retention, with hydronephrosis on both sides, between the second and fourth stages, continuous presence of mixed uroinfections and the need for catheterization or self-catheterization. 3 patients or 25% were diagnosed with the so-called hyperactive bladder with urinary incontinence, and 2 patients or 16.7% were diagnosed with complete dysfunction of the detrusor, internal and external sphincter, with alternating retention, incontinence and pronounced dysuric complaints.

Neurogenic lower urinary tract dysfunction is a constant challenge in urology and it greatly impairs the quality of life of these patients. The fact that the causes of its occurrence, as well as the clinical picture, differ in each patient, treatment should be based on the principle of an individual approach and it most often requires multimodal and multidisciplinary treatment. Our practice so far has shown the best results, regardless of the type of neurogenic lower urinary tract dysfunction, the combination of mini-invasive surgical treatment with long-term conservative treatment, gives a higher percentage of satisfactory results, and in some cases a definitive resolution of this type of condition.

KEYWORDS:

neurogenic bladder, neurogenic lower urinary tract dysfunction, atonic bladder, urinary incontinence, overactive bladder, autoimmune diseases.

INTRODUCTION

Neurogenic lower urinary tract dysfunction is a dysfunction of the bladder, bladder neck, or sphincters associated with some type of neurological disorder. It is a serious impairment of the quality of life of patients. The type of neurogenic lower urinary tract dysfunction depends on the localization of the damage to the nervous system, generally divided into three levels: lesions above the pons, lesions below the pons (spinal) and lesions at the level of sacral nerve fibers.

Neurogenic bladder can manifest as three basic clinical conditions: overactive bladder, atonic (flexible) bladder, or urinary incontinence. Sometimes, certain lesions can cause all three conditions to occur simultaneously or a combination of two of them.

According to etiology, in previous studies, neurogenic bladder occurs in approximately: 38 to 71% in Parkinson.s disease, 32 to 96% in patients with multiple sclerosis, spinal cord injuries in 70 to 84%, and in children with spina bifida it occurs in more than 90% of cases. (1)

Treatment depends on the type of neurogenic dysfunction. The very fact that it is often a combination of drug therapy, minimally invasive or invasive surgical intervention, neuromodulation, electrical nerve stimulation, physical therapy, and neurological and psychiatric therapy indicates the complexity of the clinical picture, which is why attempts and research are constantly being made to find new and more effective methods of treatment.

MATERIAL AND METHODS:

At the Urology Department of the City General Hospital "8 September", Skopje, Republic of Macedonia, 12 patients with different clinical presentations and etiology of neurogenic bladder dysfunction have been diagnosed and treated in the last four years.

The treated patients were analyzed according to etiology, symptoms and treatment methods, and the data were processed and statistically presented through percentage representation, tabular, diagrammatic presentation and descriptive analysis.

OBJECTIVES OF THE STUDY

- -Determination of the etiology and pathophysiological changes of patients with neurogenic lower urinary tract dysfunction in the study group.
- -Analysis of the differences between the symptoms and signs of various types of neurogenic bladder in the treated patients.
- -Analysis of the diagnostic results of various types of neurogenic lower urinary tract dysfunction in the study group.
- -Comparative analysis of the types and efficacy of conservative and surgical treatment in current practice, published in recent studies,

compared with our experience to date.

RESULTS

In the last 2.5 years, the urology department at the "8th September" General Hospital has treated 12 patients with neurodysfunction of the lower urinary tract caused by various etiological factors, as follows: 5 patients or 41.7% as a complication of autoimmune disease (3 patients with multiple sclerosis, one patient with Myasthenia Gravis and one patient with Wolfram.s Syndrome), 2 patients or 16.7% as a consequence of spinal cord injury (in one of them in combination with untreated posterior urethral valve), 3 patients or 25% with neurogenic bladder due to Spina bifida, one patient (8.3%) after a previous meningoencephalitis and one patient (8.3%) with neurogenic bladder of unclear etiology (with diagnosed initial disc herniation and depressive syndrome) (Table 1).

Table 1. Etiology of lower urinary tract neurodysfunction in patients treated at the General City Hospital "8th of September", Skopje.

Etiology of lower urinary tract neurodysfunction in the study group	Number of patients	Percentage representation	
Autoimmune diseases:			
-Myasthenia Gravis (1)			
-Sclerosis Multiplex (3)	5	41,7%	
-Wolfram Syndrom (1)			
Spina Bifida	3	25%	
Spinal cord injury	2	16,7%	
Meningoencephalitis	1	8,3%	
Disc hernia and posterior urethral valve	1	8,3%	
Total	12	100%	

Types of treated neurodysfunctions of the lower urinary tract in the study group.

Out of a total of 12 patients, 7 patients or 58.3% were diagnosed with the so-called flaccid or atonic bladder, accompanied by urinary retention, with hydronephrosis on both sides, between the second and fourth stages, continuous presence of mixed uroinfections and the need for catheterization or self-catheterization. 3 patients or 25% were diagnosed with the so-called hyperactive bladder with urinary incontinence, and 2 patients or 16.7% were diagnosed with complete dysfunction of the detrusor, internal and external sphincter, with alternating retention, incontinence and pronounced dysuric complaints (Table no. 2).

Types of lower urinary tract neurodysfunction	Symptoms	Number of patients	
Atonic (flaccid) bladder	-Urinary retention		
	-hydronephrosis		
	-urinary tract infection	7 (58,3%)	
	-catheterization or self- catheterization		
Overactive bladder with urinary incontinence	-Severe dysuric complaints		
	-urinary incontinence		
	-urgent micturition		
	-nocturia	3(25%)	
	-stress incontinence		
Mixed neurodysfunction of the lower urinary tract	-uncontrolled and intermittent urinary retention with dysuria,	2(16,7%)	
	incontinence and nocturnal enuresis		

Table 2. Types and symptoms of treated neurodysfunction of the lower urinary tract in the study group.

Diagnosis of patients with lower urinary tract neurodysfunction

In the patients from the study group, the diagnosis was made based on the use of diagnostic procedures related to the underlying disease or injury that led to the occurrence of neurodysfunction of the lower urinary tract and with standard urological examinations to determine the type and degree of damage and impaired function of the detrusor, internal and external sphincter. In addition, autoimmune diseases such as Multiple Sclerosis, Myasthenia Gravis and Wolfram syndrome were confirmed by neurological examination, computed tomography and magnetic resonance imaging of the brain, muscle biopsy, laboratory and immunological examinations for autoimmune diseases, pelvic floor electromyography, and in several patients, due to impaired mental state caused by the condition, a psychiatric examination was performed and psychiatric therapy was given. The degree and type of neurodysfunction of the bladder and urinary sphincters is determined by standard urological diagnostic examinations such as: ultrasound examination, computed tomography urography, magnetic resonance urography, urethrocystography, urethrocystoscopy, culture and urodynamic examinations: cystometry and uroflowmetry.

The diagnosis of patients with atonic bladder in the study group included the following findings:

 Ultrasound: finding of a markedly dilated bladder, with residual urine between 240 and 450 ml and hydronephrosis on both sides from the second to the fourth degree (Figures 1 and 2).



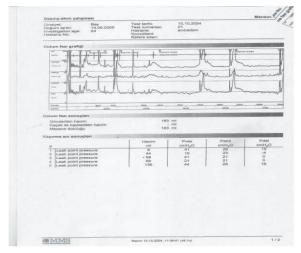
Figure 1. Ultrasound findings of the bladder in a 27-year-old patient with atonic bladder following spinal cord injury





Figure 2. Ultrasound finding in the same patient of both kidneys - hydronephrosis grade 2-3

- -CT urography: finding of an atonic bladder, markedly slow elimination of contrast with hydronephrosis of varying degrees,
- -Uretrocystoscopy: finding of a hypertrophied, fibrously altered high bladder neck (in one patient also finding of a posterior urethral valve).
- -Urine culture: constant presence of gramnegative aerobic bacteria (Escherichia Coli, Enterococcus, Klebsiela).
- -Cystometry: finding of markedly reduced detrusor contractility, with completely impaired compliance (diagram 1 cystogram in one of the patients compared to a normal diagram, diagram 2 cystogram in a patient with completely discordanced compliance between the detrusor and both sphincters).



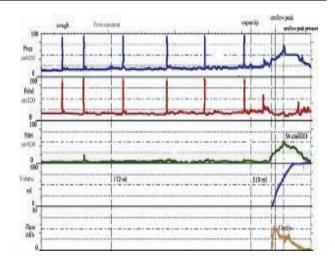


Diagram 1. Cystogram in a 27-year-old patient with atonic bladder following spinal cord injury, compared to a normal cystogram.

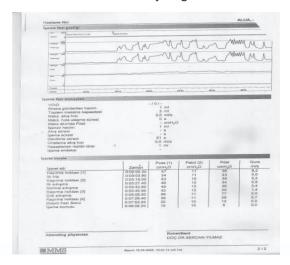


Diagram No. 2. Cystometrogram in a 28-year-old patient with completely impaired compliance after a previous case of meningoencephalitis.

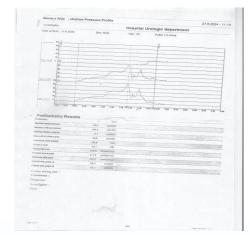


Diagram No. 3. Urethral pressure profile in the same patient.

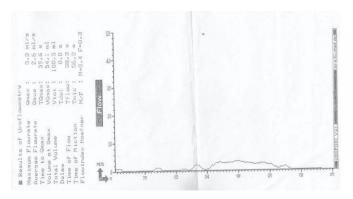


Diagram No. 4. Uroflowmetry in a 28-year-old patient with bladder atony and posterior urethral valve.

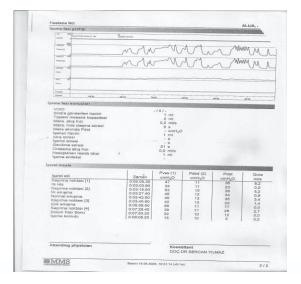


Diagram No. 5. EMG findings in a 27-year-old patient with completely impaired compliance between the detrusor and both urinary sphincters, after a history of meningoencephalitis.

Treatment of patients with lower urinary tract neurodysfunction in the study group

The treatment of patients with atonic bladder due to different etiologies consisted of

combined (multimodal) dual or triple therapy, as follows:

- 1. Treatment of the underlying disease from which the neurodysfunction of the lower urinary tract arose as a complication (immunological-biological and oncological therapy of autoimmune diseases: Miasthenia Gravis, Sclerosis Multiplex and Wolfram.s Syndrome),
- 2. Transurethral incision and resection of the bladder neck with transurethral inoculation of Mitomycin C of 20 mgr, during the intervention and installation of a 20Fr silicone catheter and
- 3. Postoperative treatment with Distigmine Bromide 5 mgr tab. for one to two months, depending on the case.

With this multimodal treatment, significant improvement was achieved in ten patients without further need for catheterization or self-catheterization, as follows:

- in the patient with Miasthenia Gravis,
- in one patient with Multiple Sclerosis,
- in two patients with spinal cord injury (in one in combination with posterior urethral valve)
- in a patient with unclear etiology most likely related to lumbar disc herniation as the cause and
- in two patients with Spina Bifida

In the remaining two patients with Multiple Sclerosis, there was a reduction in painful sensations in the suprapubic region and a decrease in the number of self-catheterizations, while in the patient with Wolfram syndrome no improvement was observed and he was left with a permanent urinary catheter (Table 3).

Table 3. Results of treatment methods for patients with atonic bladder of different etiologies in the study group

Etiology of atonic bladder	TUR incision and resection of the bladder neck + Amp. Mitomycin C 20mgr i.v.	Immunological and oncological therapy	Distigmine bromide a 5 mgr	Significant improvement in symptoms	Partial improvement of symptoms	No improvement
Sclerosis Multiplex		3	3	1	2	
Miasthenia Gravis		1	1	1		
Spina Bifida	2		3	3		
Wolfram Syndrome		1	1			1
Повреда на рбетен столб	2		2	2		
Meningoencephalitis	1		1	1		
Lumbar disc herniation	1		1	1		
Total				9	2	1

Treatment of patients with overactive bladder and urinary incontinence

Out of a total of 12 treated patients, two were treated for intermittent - mixed neurodysfunction of the lower urinary tract, with completely impaired compliance, namely: one patient with intermittent atony with periods of overactive bladder accompanied by incontinence and urgency, and one patient with atony and occasional nocturnal and stress incontinence.

-In the first patient with completely impaired compliance after a previous meningoencephalitis with reversible paraplegia, after two unsuccessful attempts to resolve the alternating symptoms of atony with retention and hyperactive detrusor accompanied by a very frequent urge to urinate, urgent urination, nocturnal and stress incontinence, with intravesical inoculation of Botulinum Toxin Type A and Sacral neuromodulation stimulation (implantation of the InterStim® device in the sacral nerves), the treatment of the patient in our department consisted of combined surgical and conservative therapy: transurethral incision and resection of the bladder neck with intravesical inoculation of Mitomycin C 20 mg and postoperative stimulation of the detrusor with a tablet of Distigmine Bromide 5 mg. Moreover, two weeks after therapy, post-void residual urine decreased from 450ml to 90ml, without further need for catheterization or self-catheterization.

-In the second patient with symptoms of very frequent urination, nocturnal and stress incontinence, a herniated disc at the level of L1-L2, depressive syndrome, cystoscopically high and fibrously altered bladder neck with consecutive grade 2 hydronephrosis on both sides was diagnosed. The multimodal treatment consisted of: transurethral resection of the bladder neck with inoculation of Mitomycin C 20 mgr intraoperatively, tab. Distigmine Bromide 5 mgr and tab. Duloxetine 1x30 mgr in the evening prescribed by a psychiatrist. After one month, the patient.s urination completely normalized and night incontinence disappeared.

DISCUSSION

Lower urinary tract neurodysfunction (neurogenic bladder) is a condition of impaired function and dyscoordination of the contraction of the bladder muscles (detrusor), internal and external urinary sphincters. It occurs as a result of damaged innervation, which leads to impaired

communication between the brain, spinal cord and lower urinary tract.

Types. Neurogenic bladder, depending on the type and degree of neurogenic damage, can occur in several types of impaired bladder function and symptoms, including:

- Atonic (flaccid) bladder accompanied by urinary retention and subsequent hydronephrosis,
- Overactive bladder, accompanied by very frequent urination in combination with or without some form of urinary incontinence and
- Urinary incontinence.

Etiology: The most common causes that lead to disruption of nervous regulation and the appearance of neurogenic bladder are:

- Brain damage due to various autoimmune degenerative diseases such as: Multiple sclerosis, Parkinson.s disease, Myasthenia Gravis, Wolfram syndrome, Alzheimer.s disease, etc.,
- Spinal cord injuries,
- Spina bifida,
- Metabolic diseases that damage the nervous system such as Diabetes Mellitus,
- Damage to the central or autonomic nervous system due to brain or spinal cord tumors or acute inflammatory processes such as encephalitis and meningoencephalitis.

Pathophysiology of neurogenic lower urinary tract dysfunction.

The smooth muscle (detrusor) of the bladder, the internal sphincter, and the external sphincter are innervated by the autonomic (involuntary) and central (voluntary) nervous systems. The internal urethral sphincter controls the involuntary flow of urine from the bladder to the urethra, and the external urethral sphincter controls the voluntary flow of urine. The sympathetic nervous system innervates from T10—L2 by the hypogastric nerve, which mediates bladder filling by activating 61 adrenergic receptors on the bladder neck and 83 adrenergic receptors on the dome of the detrusor, causing relaxation of the detrusor, or bladder. (1,2) The parasympathetic nervous system acts on the bladder via the pelvic splanchnic nerves that arise from the S2—S4 spinal segments, causing bladder emptying through its effect on the M3 cholinergic receptors of the detrusor. (3,4,5)

The pudendal nerve, which also arises from the S2—S4 segment, innervates the external urethral sphincter and the muscles of the pelvic diaphragm under voluntary, somatic control (Figure 3).

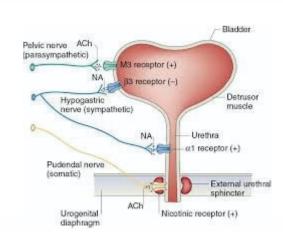


Figure 3 Innervation of the lower urinary tract (https://commonfund.nih.gov/sites/default/files/SPARCdeGroat-UPitt-Sess1.pdf)

Damage at any level of any of these nerve centers for controlling the function of the smooth muscles of the bladder and both sphincters can lead to neurogenic dysfunction of the lower urinary tract. In this case:

- damage to the parasympathetic innervation leads to the occurrence of the so-called atonic or flaccid bladder accompanied by atony, urinary retention and consecutive hydronephrosis with gradual impairment of renal function,
- damage to the sympathetic innervation leads to the so-called hyperactive bladder accompanied by very frequent contractions and incontinence,
- -damage to brain activity leads to impaired voluntary control of urination accompanied by incontinence and
- -damage to two or more nerve centers leads to impaired compliance with a mixed form of neurogenic dysfunction of the lower urinary tract.

In the patients from the studied group, all types of neurodysfunction of the lower urinary tract were diagnosed.

Treatment of various types of neurogenic dysfunction of the lower urinary tract

The treatment of atonic bladder, in recent published studies, varies depending on the etiology and clinical picture of the patient, with attempts to strengthen the contractile ability of the detrusor described using: surgical treatment from incision of the bladder neck to sphincterectomy (which has not yet proven effective), conservative

treatment with tab. Distigmine bromide to mini-invasive treatment with implantation of an electroinhibitor (electromodulator) of the sympathetic nerves and stimulation of parasympathetic innervation. (6,7,8) In extreme cases, cystectomies with orthotopic urinary diversion have been described. (9) Experience to date shows that none of these methods alone provides satisfactory results, so a multimodal and multidisciplinary approach to treatment is recommended.

The multimodal and multi-disciplinary approach has been used in our patients, with satisfactory improvement observed in about 80% of patients. In addition, our practice to date has shown that significant improvement in symptoms and quality of life in patients with atonic bladder was achieved by applying combined surgical and conservative therapy consisting of:

-Transurethral incision or resection of the bladder neck with intraoperative inoculation of Amp Mitomycin C from 20 to 40 mgr, at the site of the incision and

-postoperative treatment with tabl. Distigmine bromide from 5 mgr for the next at least two months.

Treatment of overactive bladder accompanied by incontinence

CONSERVATIVE TREATMENT

In most published studies, the current practice of conservative treatment of overactive bladder, which occurs as a result of damage to sympathetic innervation, consists of using:

- -Antimuscarinic drugs, i.e. anticholinergics, which, through inhibition of acetylcholine, block the contraction of the detrusor and lead to its relaxation, thereby reducing the symptoms of incontinence, urgency and frequent urination. The most commonly used today are oxybutynin, propantheline, tolterodine and solifenacin. Side effects of these drugs include dry mouth and eyes, constipation, tachycardia and headache.
- 61 Adrenergic antagonists (61 blockers), such as tamsulosin and terazosin, which relax the bladder neck and thus reduce incontinence, increase bladder capacity and facilitate emptying. Negative effects of these drugs are hypotension and erectile dysfunction and
- Beta 3 Adrenergic agonists such as Mirabegron, which give quite good effects in the treatment of overactive bladder. In

this case, the activation of 63 adrenergic receptors causes relaxation of the detrusor, thereby reducing symptoms of urgency and incontinence, especially in patients with spina bifida. (10)

- Bladder chemodenervation, which has been increasingly used in recent years as a method for patients who do not improve with conservative medical therapy. Botox toxin type A blocks the release of acetylcholine and thus blocks the synaptic activity of the neuromuscular junction, thereby blocking detrusor muscle contraction. However, this minimally invasive method is reversible and the effect lasts for a maximum of 9 months. In addition, common side effects have been observed, such as: autonomic dysreflexia during the procedure, urinary retention, and systemic effects of botulism, including weakness and respiratory depression. (11)

Combined treatment with antimuscarinic drugs, alpha blockers and multiple inoculations of Botox toxin type A into the detrusor did not produce any significant improvement in patients with overactive bladder in the study group. On the contrary, urinary retention occurred as a complication in both patients, which prolonged the need for self-catheterization.

SURGICAL TREATMENT

In the studies published so far (12,13,14,15,16), surgical treatment of patients with overactive neurogenic bladder, depending on the etiology and clinical picture of the patients, includes the following methods:

- External urethral sphincterectomy, in patients who agree to use a condom catheter or to have an intraurethral stent implanted to facilitate bladder emptying. However, experience to date shows that this method does not give a successful result in 78% of patients. (17,18)
- Anterior sacral root stimulation (SARS) and sacral neuromodulation.

Anterior sacral root stimulation (SARS)

As a surgical method, it is used in severe spinal cord damage due to injuries, in which the detrusor is unable to contract. In this case, stimulation of the anterior root of the sacral muscle (SARS) can be used to stimulate the emptying of the bladder. The stimulator is placed intradurally on the anterior root of the sacral muscle to stimulate

the sacral pelvic nerve and cause contraction of the detrusor. To prevent detrusor hyperreflexia, the so-called rhizotomy of the posterior root of the sacral muscle is performed in the same surgical act by removing the sensory afferent pelvic nerves.

Sacral neuromodulation is a less invasive approach than SARS, in which the electrode is placed extradurally and there is no need for a rhizotomy of the posterior root. (19,20)

In one patient from the study group, with completely impaired compliance between the detrusor and both sphincters after suffering a severe form of meningo-encephalitis accompanied by paraplegia, after two unsuccessful treatments with intravesical application of Botox toxin type A (two treatments in a private hospital in Skopje), Sacral neuromodulation stimulation was implanted (implantation of an InterStim® device in the sacral nerves in a private hospital in Turkey), but it was removed after one month, because it did not provide any improvement in terms of symptoms. In the patient, due to cystoscopic findings of a high and fibrously altered bladder neck and alternating episodes of urinary retention with urge incontinence, nocturnal enuresis and constant suprapubic pain, we decided on the following multimodal treatment: transurethral incision and resection of the bladder neck with intraoperative transurethral inoculation of Mitomycin C of 40 mgr and postoperative treatment with a tablet of Distigmine Bromide of 5 mgr and a tablet of Duloxetin of 30 mgr once a night before bedtime. After two weeks, a significant improvement was noted (reduced residual urine from 450 to 90 ml. without the need for constant self-catheterization, improvement in incontinence, loss of nocturnal enuresis and reduction in suprapubic pain).

In the second patient from the study group, with an overactive bladder resulting from a spinal cord injury during a fall, after urethrocystoscopy, where in addition to a markedly high bladder neck, a posterior urethral valve was also found, the multimodal treatment consisted of: transurethral resection of the posterior urethral valve, incision and resection of the bladder neck with intraoperative inoculation of Mitomycin C of 20 mgr and postoperative treatment with a tablet of Distigmine Bromide of 5 mgr. In this case, we obtained a significant improvement in symptoms.

 Classical surgical methods such as: bladder augmentation or cystectomy with orthotopic urinary diversion, have not been used in our practice to date.

CONCLUSION

Neurogenic lower urinary tract dysfunction is a constant challenge in urology and it greatly impairs the quality of life of these patients.

The fact that the causes of its occurrence, as well as the clinical picture, differ in each patient, treatment should be based on the principle of an individual approach and it most often requires multimodal and multidisciplinary treatment.

Our practice so far has shown the best results, regardless of the type of neurogenic lower urinary tract dysfunction, the combination of mini-invasive surgical treatment with long-term conservative treatment, gives a higher percentage of satisfactory results, and in some cases a definitive resolution of this type of condition.

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