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Update on Trigeminal Neuralgia

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Abstract

Purpose of review To review current treatments for trigeminal neuralgia, with an emphasis on determining which patients may benefit from neurosurgical procedures.
Recent findings A detailed history is the most helpful tool for diagnosing trigeminal neuralgia (TN) and predicting response to neurosurgical treatments. Patients with classic trigeminal neuralgia will describe severe, unilateral, intermittent facial pain that is triggered by innocuous sensory stimuli. In most cases, pain is caused by compression of the trigeminal nerve by a blood vessel near the brainstem. Magnetic resonance imaging is necessary to rule out TN secondary to multiple sclerosis or tumor. Modern high-resolution T2 images may demonstrate neurovascular contact, particularly when analyzed by a neurosurgeon with expertise in TN. Initial management involves a trial of medication, usually carbamazepine or oxcarbazepine. Microvascular decompression (MVD) is safe and effective surgery, for patients with classic TN related to neurovascular compression. For patients with TN secondary to multiple sclerosis, and for patients who are otherwise poor candidates for MVD, neurosurgical options include percutaneous trigeminal rhizotomy and radiosurgery. Neurosurgical procedures are less effective in relieving atypical facial pain.
Summary In the clinical evaluation of a patient with facial pain, it is important to distinguish classic trigeminal neuralgia from atypical facial pain. A patient with classic trigeminal neuralgia would benefit from neurosurgical consultation. The advent of high-resolution MRI and MRA sequences now allows a neurosurgeon to detect when neurovascular compression is likely, and select the optimal procedure for treatment.

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Introduction

John Fothergill first described the clinical syndrome of trigeminal neuralgia (TN) in 14 patients at a meeting of the Medical Society of London in 1773 [1]. Described as a painful affliction of the face, it also came to be known as tic douloureux in French (translated to "painful tic" in English) and later as the "suicide disease" given its severity and morbidity [2]. Since that time, management of this disease has evolved, and outcomes have improved. Currently, its estimated incidence ranges from 12 to 29 cases per 100,000 a year [3]. Its treatments have also broadened ranging from medical therapy to surgery to radiosurgery.

The International Headache Society diagnostic criteria for classic TN include (1) pain involving one or more divisions of the trigeminal nerve with no radiation beyond the trigeminal distribution and (2) pain with at least 3 of the following 4 characteristics: (a) paroxysmal attacks lasting from seconds to minutes, (b) severe intensity, (c) electric, shock-like, shooting, stabbing, and sharp quality, or (d) precipitated by innocuous stimuli [4••, 5]. TN typically results from neurovascular compression of the trigeminal nerve that leads to morphological changes. This compression is most often from the superior cerebellar artery (SCA), but can also be due to a vein or the anterior inferior cerebellar artery (AICA). TN symptoms can also occur secondary to multiple sclerosis or a cerebellopontine angle (CPA) tumor.

Despite the disease being well described clinically, the pathophysiology of classic TN remains elusive. Basic tenets posit that neurovascular compression at the trigeminal nerve root entry zone near the brainstem leads to demyelination and subsequent remyelination [6•]. The nerve root entry zone, also known as the Obersteiner-Redlich zone, is approximately 1–3 mm distally along the nerve from the brainstem. This demyelination and remyelination lead to ephaptic cross-talk between sensory A-beta fibers aberrantly activating nociceptive A-delta fibers. Other theories include the bioresonance hypothesis which theorizes that vibration around the trigeminal nerve and not simply direct compression leads to damage of the sensory fibers and abnormal impulse transmission [7]. The ignition hypothesis is yet another theory that suggests compression leads to axotomized somata which become hyperexcitable leading to paroxysmal nociceptive transmission [8]. Lastly, another phenomenon that has still yet to be determined is how the classic spontaneous and intermittent trigeminal pain transforms into a duller and more continuous pattern [9]. This is believed to be due to sensitization of neurons located in Rexed lamina V of the dorsal horns and trigeminal nerve nuclei due to prolonged signal transmission from the compressed trigeminal nerve. This sensitization is subsequently believed to result in cross-talk within these nuclei between neurons receiving afferent activity from A-beta and A-delta fibers.

In the absence of multiple sclerosis or a tumor, classic trigeminal neuralgia is most likely caused by neurovascular compression. The development of a procedure to treat this compression has revolutionized the outlook of patients with this disease.

Diagnostic evaluation

Clinical evaluation

A detailed history and focused physical exam are the keys to diagnosing TN and selecting the appropriate treatment. In classic TN, pain is unilateral and occurs in the distribution of one, two, or three divisions of the trigeminal nerve. The V2 and V3 distributions are most commonly affected. Pain exclusively in the V1 distribution occurs in less than 5% of cases [10]. Classic TN pain is episodic in nature, lasting seconds to minutes; electric or lancinating; and associated with triggers such as touching the face, talking or chewing, wind blowing on the face, or brushing teeth. TN typically presents in middle-aged patients. Onset is usually after 40 years of age, with a peak between 50 to 60 years of age. Onset may be related to the increased tortuosity of intracranial arteries that occurs with aging. A younger presentation is more typical of patients with secondary TN,

though the average age of onset in these patients is only a few years earlier than those with classic TN. Dull, continuous pain raises suspicion of an alternative diagnosis, under the collective label of atypical facial pain. The presence of bilateral pain may occur in multiple sclerosis [4••, 10, 11]. The differential diagnosis of atypical facial pain includes post-herpetic neuralgia, Tolosa–Hunt syndrome (i.e., orbital pseudotumor), dental abnormalities, temporomandibular joint syndrome, and benign cephalgias such as cluster headaches.

The Burchiel classification is a frequently cited and clinically useful guide. It emphasizes characteristics of the trigeminal pain more so than the etiology or imaging characteristics [12]. In this classification scheme, type 1 patients experience symptoms of classic TN most of the time: electric, lancinating, stabbing pain that lasts several seconds to minutes with pain-free intervals between attacks. Type 2 patients experience symptoms of atypical facial pain most of the time: aching, throbbing, burning, or continuous pain. Type 1 patients are more likely to benefit from neurosurgical procedures.

In our practice, the initial evaluation focuses on whether a patient has classic trigeminal neuralgia or atypical facial pain (Table 1). Those with classic TN may benefit from neurosurgical intervention. Other than the symptoms described above, patients with classic TN often identify a specific area of the face which, when lightly touched, will trigger sudden severe pain. Patients may report pain-free intervals of weeks or months, with subsequent recurrence of pain. Pain typically does not wake a patient from sleep. Carbamazepine or oxcarbazepine can provide initial relief, although escalating doses are often required over time, and side effects are common.

Imaging

The clinical evaluation of a patient suspected to have trigeminal neuralgia is central to making the correct diagnosis and treatment plan. However, imaging remains an important tool in the diagnostic evaluation. Magnetic resonance imaging (MRI) has the highest sensitivity (75–95%) and specificity (26–86%) of all imaging modalities [11, 13].

MRI is necessary for the diagnostic evaluation of all patients with suspected TN. In up to 15% of patients, there is an identifiable structural lesion (e.g., CPA tumor, demyelinating plaque) [11]. Additionally, MRI can demonstrate neurovascular contact (NVC), and in some cases, it may demonstrate

Table 1. Characteristics of classic trigeminal neuralgia and atypical facial pain

Classic trigeminal neuralgia	Atypical facial pain
* Unilateral pain in a trigeminal distribution	* Dull, constant pain
* Paroxysmal pain lasting seconds to minutes	* Bilateral pain
* Electric shock-like, sharp, or stabbing pain	* Pain caused by trauma
* Pain triggered by touch, wind, washing the face, talking, brushing teeth, or chewing	* Pain caused by a dental or surgical procedure
* Specific trigger area on the face, for light cutaneous stimuli	* Known extracranial cause of pain
* Episodes of exacerbation and remission	
* Initial response to carbamazepine	
* Absence during sleep	

deformation of the trigeminal nerve. However, this finding alone does not supersede clinical evaluation. In 17% of the general population, there is evidence of NVC on MR imaging making approximately 99.94% of NVC found on MR imaging asymptomatic. Furthermore, 28% of patients with classical TN do not have NVC on imaging. These patients tend to be younger and female [14]. NVC with morphological changes to the trigeminal nerve, on the other hand, has been much more closely associated with classical TN though this too has been reported in asymptomatic patients [4••]. Thus, while MR imaging can aid in the diagnosis of TN, clinical evaluation remains a central tenet to making the diagnosis.

Currently, there are multiple MR sequences that can demonstrate the relationships between the trigeminal nerve and potential sites of vascular contact/compression in the CPA. These include the T2-weighted fast imaging employing steady-state acquisition (FIESTA) and constructive interference in steady-state sequences (CISS) [10, 11]. These sequences contrast the T2-weighting so that the morphology of structures coursing through the CPA is clear. Other sequences that may be helpful are the T1-weighted gadolinium contrasted sequence which can demonstrate venous structures and the time of flight (TOF) MR angiogram (MRA) sequences which can demonstrate arterial compression [10, 11]. We have found that a combination of gadolinium-enhanced MRI, axial and coronal CISS, or FIESTA sequences, and MRA is helpful in the evaluation of patients with classic TN.

Additional diagnostic testing

Neurophysiologic testing of trigeminal reflexes or evaluation of trigeminal sensory evoked potentials is neither sufficient nor necessary to make the diagnosis of TN. These diagnostic tests usually are only employed in cases in which the clinician aims to differentiate classic from secondary TN. In secondary TN, increased latencies are more common due to damage to the sensory pathway itself. However, abnormal neurophysiologic testing has been found in patients with classic TN as well [4••]. Evoked potentials have a reported sensitivity of 84% and specificity of 52% in detecting in differentiating the two TN types [4••]. Testing of trigeminal reflexes, which include blink, masseter, mental, and lingual, have a reported sensitivity between 60 and 10% and specificity between 93 and 100% in differentiating primary from secondary TN [4••]. Given that the use of these tests in the diagnostic evaluation of TN is only truly useful for differentiating classical from secondary TN, which also can be done via other diagnostic modalities (e.g., MRI, clinical history), they are not routinely used.

Current treatments

Medical therapy

Current first-line therapy for TN is medication. Of all the agents utilized, carbamazepine at 200–1200 mg a day in two doses has been shown to be the most effective with a 60–100% response rate [4••]. However, many patients cannot tolerate the medication's side effects which can include drowsiness, cognitive impairment, dizziness, ataxia, and rash. Serial labs tests are required,

to assess for leukopenia, liver injury, and hematologic toxicity as well as testing for HLA-B*1502 in patients of Asian descent since it significantly increases the risk of Steven-Johnson syndrome in these patients. It also has numerous drug interactions being a potent inducer of multiple cytochrome P-450 hepatic oxidases including CYP3A4, CYP1A2, and CYP2C9. Lastly, contraindications to carbamazepine include tricyclic antidepressant hypersensitivity and concurrent monoamine oxidase inhibitor therapy as the structure of the molecule is very similar to tricyclic antidepressants. The quoted number needed to treat is 2 with the number needed to harm for minor side effects is 3 and for severe side effects 24 [11]. For these reasons, carbamazepine has an approximately 50% failure rate over 10 years [4•].

A better-tolerated agent is oxcarbazepine. Patients can develop symptomatic hyponatremia on this medication. While other side effects, interactions, and contraindications of this agent are similar to carbamazepine; the frequency of them is lower. It is generally considered not as effective as carbamazepine, although it may have up to an 88% response rate [15]. Other medications that have been reported to have a response rate above placebo are lamotrigine and gabapentin. Baclofen, botulinum toxin, pregabalin, levetiracetam, valproate, and clonazepam also have been used as adjunctive agents to treat TN in patients whose symptoms are not controlled on traditional medical therapy [4•]. These therapies are summarized in Table 2.

For acute exacerbations of trigeminal pain, intravenous (IV) medical therapy has been utilized. Though there is not a plethora of data supporting IV fosphenytoin or lidocaine for acute exacerbations, they have been effective in reducing symptoms so that oral medications can begin to work (16–18). For fosphenytoin, the medication is administered as a 15–20 mg/kg IV bolus at a rate no greater than 2 mg/kg/min or 150 mg/min [17]. Given that a single IV bolus is all that is necessary, fosphenytoin does not have many drug interactions since prolonged therapy is required to induce cytochrome P-450 hepatic enzymes. Side effects of an IV bolus are cardiac conduction blocks, hypersensitivity, rash, headache, nystagmus, drowsiness, and fatigue. For lidocaine, a

Table 2. Medical therapies for trigeminal neuralgia

First line therapies	Second line/adjunctive therapies	Acute exacerbation therapy
Carbamazepine 200–1200 mg/day Oxcarbazepine 600–1800 mg/day	*Lamotrigine 100–400 mg/day *Gabapentin 300–1800 mg/day Baclofen 60–80 mg/day Pregabalin 150–600 md/day Levetiracetam 1000–4000 mg/day Botulinum toxin *Second line therapy	Intravenous fosphenytoin 15–20 mg/kg bolus Intravenous lidocaine 5 mg/kg bolus

5 mg/kg continuous infusion over an hour has been reported to be effective [16, 18]. Side effects from an intravenous infusion include cardiac depression, hypotension, and arrhythmias. Thus, continuous cardiac monitoring is necessary, and history of ventricular arrhythmias is a contraindication. In addition to fosphenytoin and lidocaine, during acute exacerbations supportive medical care such as intravenous hydration can be critical as patients often will not be able to take enough fluids per orum. Opioids, interestingly enough, have been shown to be relatively ineffective [4•].

Medication is initially effective in the majority of TN patients. In a study of 200 patients, a minority of patients who initially responded to medical therapy–developed treatment resistance and worsening symptoms while on their medical regimen [19]. Patients often seek neurosurgical intervention when medical treatment fails, or when side effects of medication become significant.

Microvascular decompression surgery

In 1965, Peter Jannetta pioneered the most successful operation in the treatment of TN, microvascular decompression (MVD) [20••]. An MVD involves a small retrosigmoid craniectomy which provides a corridor to the cerebellopontine angle. Release of cerebrospinal fluid from the CPA allows for cerebellar relaxation, allowing the surgeon to gain an unobstructed view of the trigeminal nerve. After the trigeminal nerve and compression site is clearly identified, the offending artery is dissected free from the nerve, transposed and usually held away from the nerve with a polytetrafluoroethylene (Teflon) pledget (Fig. 1). Slings to the tentorium that cradle the artery have also been described [21]. In cases where no neurovascular compression is identified during surgery, some surgeons perform a retrogasserian rhizotomy by sectioning or briefly compressing the nerve. Currently, MVD remains the most successful treatment modality with pain relief in 90% of patients, maintained in 68–88% after 5 years and in 61–88% after 10 years [22, 23]. In cases of recurrence, the surgery can be repeated with good results. Risks include cerebrospinal fluid leak and ipsilateral hearing loss. These risks can be minimized with specific surgical techniques [11, 21]. Unlike destructive procedures (percutaneous trigeminal rhizotomy or radiosurgery), MVD surgery preserves the function of the trigeminal nerve.

In a recent retrospective clinical series, a novel scoring system was developed to predict response to MVD for trigeminal neuralgia [24••]. Presence of arterial compression on imaging and classic trigeminal neuralgia symptoms correlated with favorable and durable response to MVD. Other studies support these findings, and they have also demonstrated that response to medical therapy correlates with a positive response to MVD as well [25–27]. While pain relief after MVD has been reported in patients with atypical facial pain, response rates are much lower than in classic TN [28].

In our practice, we offer MVD surgery to patients with classic TN, if our analysis of the high-resolution MRI and MRA suggests the presence of neurovascular compression. We perform a 3-cm retrosigmoid craniectomy. We avoid the use of brain retractors, to preserve hearing. A neurologist monitors auditory brainstem responses during the surgery. Under the operating

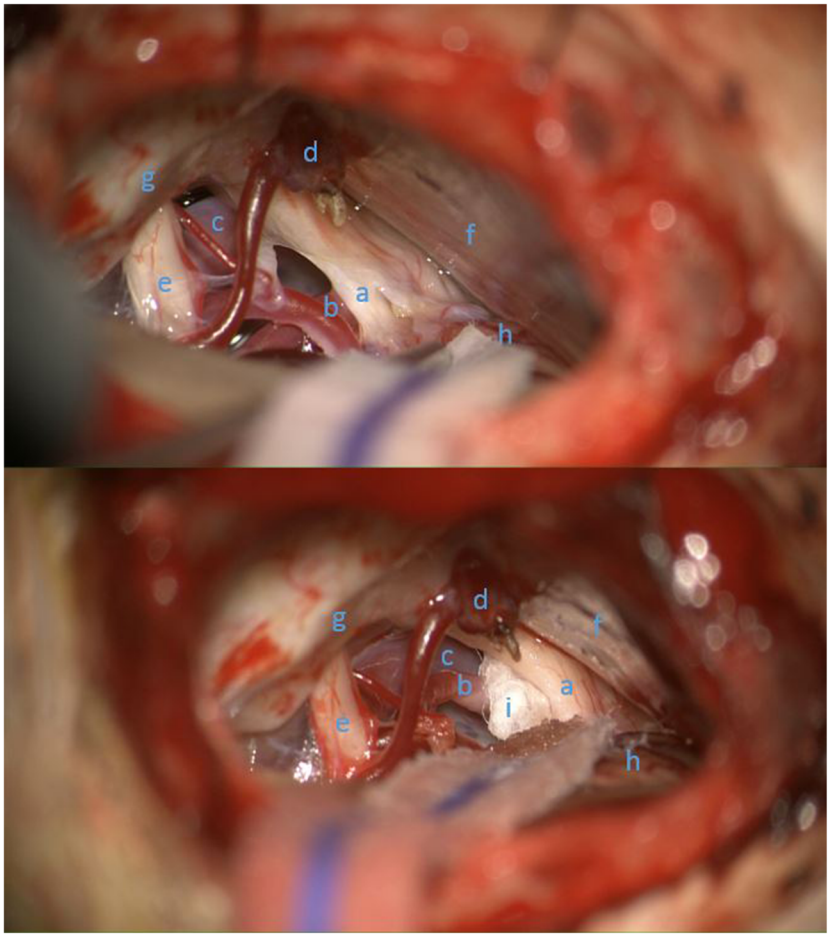

Fig. 1. Microvascular decompression for left trigeminal neuralgia. A 68-year-old woman with pain in a left V2 distribution, and MRI evidence of neurovascular compression by an AICA-PICA variant artery and the vertebral artery. Top**,** view through operating microscope after a left retrosigmoid craniectomy and opening of the dura. Bottom, the left trigeminal nerve has been decompressed by the placement of a Teflon felt pledget. **a** Trigeminal nerve, **b** AICA-PICA variant artery, **c** vertebral artery, **d** petrosal vein (divided), **e** facial-vestibulocochlear nerve complex, **f** tentorium, **g** posterior petrosal dura, **h** cerebellar hemisphere (covered with cotton paddy), **i** Teflon felt pledget.

microscope, we inspect all aspects of the trigeminal nerve, from the brainstem to the entrance into Meckel's cave, to identify all possible sites of neurovascular compression. Most commonly, the superior cerebellar artery causes rostroventral compression of the trigeminal nerve at the root entry zone. With microsurgical techniques, we mobilize the artery to the dorsal side of the nerve, redirecting its vector of flow to prevent recurrent compression. We then place Teflon felt pledgets, typically between the brainstem and the artery, to maintain the artery in its new position. In cases of venous compression, we divide the vein to decompress the nerve.

Percutaneous trigeminal rhizotomy

Certain patients with classic TN are poor candidates for MVD surgery: patients with multiple sclerosis, patients who cannot tolerate cranial surgery because of

advanced age or comorbidities, and patients whose high-resolution imaging demonstrates a clear absence of neurovascular contact. For these patients, percutaneous trigeminal rhizotomy (PTR) is an attractive option. This procedure involves percutaneously inserting a needle into Meckel's cave through foramen ovale and partially ablating the trigeminal nerve. Approximately 70–85% of patients report an initial response to these procedures with the response rate at 5 years around 55–65% [4•, 10, 11]. While patients with classic symptoms tend to have a higher response, PTR can offer some relief in patients who have failed MVD or have atypical symptoms [4•]. Additionally, it can be repeated as needed to treat recurrences of pain. Complications include dysesthesias, anesthesia dolorosa, intraoperative arrhythmias from trigeminal stimulation, and aseptic meningitis. Sensory loss occurs in about half of patients. Facial numbness is a positive predictor of response to PTR. If sensory loss occurs in the first division of the trigeminal nerve, keratitis can develop.

Currently, there are three different methods to perform a PTR: mechanical balloon compression, glycerol injection, or radiofrequency ablation. All procedures have demonstrated efficacy, but generally glycerol injection is thought to have a lower durability and initial response rate [4•]. Mechanical compression also has the risk of causing temporary masticatory problems via injury to the third division of the trigeminal nerve and requires general anesthesia. Repeat PTR after failure or recurrence of symptoms is often considered and performed with favorable success rates [4•, 10, 11]. A relative contraindication to any method of percutaneous rhizotomy is a significant cardiac history since the procedure may trigger severe bradycardic from a trigeminal cardiac reflex.

A question that remains unanswered is whether surgery should be considered early after the diagnosis of TN. Though a patient's symptoms rarely change significantly over the course of the disease, there is a suspicion that pathological changes intrinsic to the trigeminal nerve may occur over time. This process is theorized to account for treatment resistance and recurrence [8, 9]. Thus, earlier surgical intervention may be beneficial.

Radiosurgery

For patients who are not surgical candidates and fail medical therapy, stereotactic radiosurgery (SRS) remains a viable option. For decades, Gamma Knife and more recently other linear accelerator-based modalities have been available. The dorsal nerve root entry zone is targeted with a single dose of 70–90 Gy, limiting the brainstem exposure to less than 10 Gy. There is a latency period of 3 months to pain improvement, and an initial response rate of 70%, which decreases to 50% at 3 years [29–32]. It is common for patients to continue to require medication after radiosurgery. Similar to percutaneous rhizotomy, radiosurgery is a destructive procedure that causes facial numbness. Repeat treatment with SRS has been reported, with lower doses of 50–70 Gy [33, 34]. Complications from radiosurgery include facial paresthesias and V1 numbness, radiation injury to the brainstem, and anesthesia dolorosa. Classic TN symptoms, response to medications, and response to prior procedures predict a favorable response to SRS [29–32]. Additionally, postoperative facial numbness has been reported by several studies to predict treatment

response [29, 30]. Many series have reported lower response rates in patients with atypical symptoms or those with secondary TN [31, 32, 35].

Emerging strategies to treat TN with radiation therapy include fractionation of the radiation dose and targeting parts of the trigeminal nerve outside the root entry zone [36, 37]. Fractionation is commonly utilized to treat tumors such as acoustic neuromas in order to limit radiation dose to surrounding neural tissue. This may be a good strategy to limit radiation dose to the brainstem [36]. More anterior targeting of the trigeminal nerve has also been proposed and performed with promising results [37].

Conclusions

To determine which patients with facial pain will benefit from neurosurgical intervention, a detailed history is essential. Patients with classic trigeminal neuralgia can benefit from neurosurgical procedures, whereas those with atypical facial pain may benefit most from medical management. For a patient with classic trigeminal neuralgia, high-resolution imaging should be reviewed by a neurosurgeon with expertise in this condition, to evaluate for neurovascular compression. In many patients who have had high-resolution T2 imaging, we have detected neurovascular compression on MRI that was not noted in the radiology report, and these patients have benefited from MVD surgery.

Microvascular decompression surgery is usually the best option, if neurovascular compression is suspected. Unlike other procedures that treat trigeminal neuralgia, MVD surgery preserves trigeminal nerve function, and it is associated with the highest rates of pain relief and lowest rates of recurrence. For most patients with classic trigeminal neuralgia and neurovascular compression, MVD surgery should be offered early: this operation is well-tolerated and will likely cure these patients. Early surgical treatment allows patients to avoid the side effects that occur with long-term medication use.

For patients with classic trigeminal neuralgia secondary to multiple sclerosis, for those unable to tolerate MVD surgery, and for those without neurovascular compression, percutaneous trigeminal rhizotomy can be effective. Radiosurgery remains an option for patients who are poor candidates for other procedures. Because both percutaneous trigeminal rhizotomy and radiosurgery are destructive procedures, they should be reserved for patients who fail medical management.

Compliance with Ethical Standards

Conflict of Interest
Alexander X. Tai and Vikram V. Nayar each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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