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Neuropathic Pain: Mechanism, Representation, Management and Treatment

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Abstract

Despite the development of screening tests and diagnostic tools, neuropathic pain is still identified as an underdiagnosed condition lacking proper epidemiological studies. It is difficult to estimate its incidence and prevalence the population. The objective of this narrative review is to summarize current knowledge concerning complications. The underlying mechanisms have also been reviewed in the development of diagnostic or treatment strategies in patients with neuropathic pain to investigate its unique symptoms. The main focus is concentrated on expansion of possible therapeutic options for neuropathic pain treatment. Many therapies are not effective and this often leads to a significant deterioration in the patients' quality of life. So, the crucial and strategic role of therapeutics in guiding patients in the right direction should not be overlooked. The existing knowledge is so limited and has safety risks. It is truly important to provide alternative treatment strategies in selected patients with refractory neuropathic pain. Interventional therapies include different types of effective treatments for reducing neuropathic pain. Giving insight into recent findings on mechanisms of neuropathic pain may help understand and further develop strategies for correct diagnosis and successful treatment.

Keywords: Neuropathic pain; Pain management; Therapeutic strategy; Anesthetic drugs; Interventional therapies; Hyperalgesia; Allodynia

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Introduction

Neuropathic pain is a kind of persistent or chronic pain that affects approximately 100 million adults in the United States and costs exceed 500 billion annually according to a report in 2017. The number of people with neuropathic pain is increasing worldwide imposing an unpreventable burden on health care resources.[1]

Because of the lack of agreement on the definition of neuropathic pain and also the lack of proper epidemiologic studies, it is vividly hard to estimate its incidence and prevalence worldwide. Based on a systematic review on the epidemiology of chronic pain, the prevalence is reported to be 3%-17% whereas distinct incidence rates were announced for different conditions including post-herpetic neuralgia (3.9–42/100 000 person-years), trigeminal neuralgia (12.6–28.9/100 000 person-years), painful diabetic peripheral neuropathy (15.3–72.3/100 000 person-years), and glossopharyngeal neuralgia (0.2–0.4/100 000 person-years). Moreover, neuropathic pain was more common among women (approximately 60.5% of patients) and peaked at 50–64 years of age, and was more prevalent in manual workers and people from rural areas.[2] Also, about 150 billion dollars was spent in the US healthcare system for nerve injuries. The common causes of traumatic peripheral nerve injury include penetrating injury, crush, traction, ischemia, and mechanisms such as thermal, electric shock, radiation, percussion, and vibration have a lower incidence.[3]

Neuropathic pain is a clinical diagnosis and requires a systematic approach to assessment.[4] It can certainly be considered an integral part of a variety of neurodegenerative, metabolic, and autoimmune diseases. There is a significant point at which neuropathic pain is less responsive to treatments and is associated with worse health outcomes. Frequently, susceptibility to pain and experiencing drastic pain with two prominent symptoms termed "hyperalgesia" and "allodynia" is prevalent in patients with chronic neuropathic pain.[5] Altogether, Neuropathic pain can also be described as a dynamic multi-dimensional experience, since it incorporates perception, cognition, and higher-order brain center processing besides just having a sensory component.[6]

Despite the development of screening tests and diagnostic tools, neuropathic pain is still identified as an underdiagnosed condition or it is better to say that we face complexity in its management; thus, explicit and extensive classification of recent findings as a comprehensive review would be strongly instructive and applicable.[7]

It is important to note that long-lasting pain in addition to sensory deficits is a consequence of attacks to the somatosensory nervous system by diseases.[8] Pain is caused by any damage to the central nervous system, whether to the brain or the spinal cord or by any lesion or injury as a result of a disease affecting the somatosensory system. Primary pain divides into two distinct categories neuropathic and spastic with their specific characteristics.

An interesting description as stated by an article about neuropathic pain is "maladaptive plasticity caused by a lesion or disease affecting the somatosensory system alters nociceptive signal processing so that pain is felt in the absence of a stimulus, and responses to innocuous and noxious stimuli are enhanced."[8] Although there are some clinical signs and symptoms for the distinction of neuropathic pain from nociceptive pain, a wide range of heterogeneous conditions are involved in this type of pain and different pathophysiological causes may be recognizable, and separate clinical signs and symptoms can be observed.

Several million people all over the world suffer from this form of pain and according to a report, the approximate morbidity rate due to neuropathic pain is estimated to be 1%-7% in developed countries. However, many therapies have not been effective often leading to psychiatric symptoms such as depression, lowering the patients' quality of life. More effective therapeutic options for neuropathic pain treatment should be developed.[9]

Since the physical disability resulting from these traumatic injuries largely influences young adults of the working-age, it is crucial to control neuropathic pain, despite observing spontaneous recovery in some cases. Surgery is the only way to improve neurological deficits in many individuals.[3]

In General, unknown underlying pathophysiology in neuropathic pain exclusive of several proposed theories concerning its mechanism including central and peripheral nervous system sensitization, neurogenic inflammation, and the wind-up theory, has led to ineffective management and control of this critical situation.[4] And the more pathophysiology sheds light on this mysterious condition, the more optimistic viewpoint and the higher growth in the development of new diagnostic procedures.[10]

Interesting ideas about the mechanisms of injury leading to neuropathic pain have been proposed in various studies on whether peripheral nerve injury and microglia-driven disinhibition in the dorsal horn can lead to the transformation of lamina I output neurons in this region from silent and strictly responsive to noxious stimuli and through this transformation, spontaneous activity will be granted to these neurons and will be able to drive them by innocuous peripheral stimulation. The results of one study clearly demonstrate the amplification of responses to noxious and innocuous stimulation after nerve injury, it can be said that the sensory specificity of lamina I neurons has been changed under influence of this nerve injury which is totally consistent with hyperalgesia and allodynia.[11]

Nature of Pain

Over the centuries, various theories have been predicated on the mechanisms underlying pain perception. Centuries of ideas and work on the concept of pain have led to the definition organized by the International Association for the Study of Pain in 1986 defining pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of tissue damage, or both."[12]

In fact, pain is interpreted as an unpleasant and transient sensation which often arouses by noxious stimuli and is eliminated by diminishing them. But in many medical conditions it was observed that patients experience pain for a long time, months or even years and in some cases despite the healing of the initial injury.[13]

While each organ of sense is designed with receiving a certain capacity of changes but each of them is completely impotent of receiving the perceptions destined for another organ of sensation. An impression made on two different nerves of sense, though with the same instrument, will produce two distinct sensations; and the ideas resulting will only have relation to the organ affected.[12]

Pain Origin, Distinction and Manifestations

Pain originating from damaged or abnormal nerves and often accompanied shooting or burning sensation is known as neuropathic pain. This kind of pain especially its chronic form is very troublesome and has a negative effect on the patients' well-being, activities of daily living activities as well as their social relationships and work productivity.[14] Neuropathic pain can complicate stroke, chronic inflammation, and also cancer, but sometimes a physical pressure on a nerve by a tumor and chemotherapy can cause this neuropathic pain.

Pain can be classified by its underlying mechanism,[13] therefore two main categories of this persistent pain are neuropathic pain which is the pain that arises from the nervous system as a result of damage to the peripheral nerves or to the spinal cord or the brain. Nociceptive pain is more than muscle pain, skeletal pain under the influence of a noxious stimulus as a result of injury to body tissue and not directly related to nerve damage. Of course, there is another category of pain called inflammatory pain which arises in response to the release of inflammatory mediators from injured tissue.[4]

The first stage would certainly be recognition of this type of pain, it can be said that it is disproportionate to tissue injury and it tends to persist for a long time and it can be constant or paroxysmal. They are mostly expressed with words such as burning, stabbing, shooting, and

lancinating, there may often be numbness as well, tingling, and electrical sensations; all indicators that the pain could be neuropathic.

The characteristic symptoms related to neuropathic pain are termed "hyperalgesia," which is defined as increased sensitivity to pain, and "allodynia," a condition wherein typically nonpainful stimuli lead to pain-sensation.[6] Hyperalgesia is enhanced pain perception to noxious stimuli and Allodynia is designated pain experienced in response to an innocuous stimulus or it is described as pain after a small stimulus that normally would not cause pain. Paresthesia also can be enumerated among the other signs of neuropathic pain that can be defined as a situation that dictates the perception of inconsistent sensations proportional to needle bites, tingling and itching, and reduced, or even loss of sensitivity.

And a distinctive feature of neuropathic pain is that perceived pain is routinely spontaneous and apparent without needing any stimulus. The quality of life of patients is terribly influenced by this pathological condition and their mental state is severely endangered.[2]

Mechanisms of Neuropathic Pain Development

In one study, distinguishing different physiological and behavioral responses incited by some noxious stimuli from those induced by the conduction of a standardized innocuous stimulus introduced it as an evaluator for recognizing the unpleasant responses associated with injury diagnosis.[15]

Moreover, from the neuroanatomical aspect, lamina I neurons which are located on the superficial of the dorsal horn, normally encode and transmit noxious or thermal information and do not generally respond to innocuous mechanical inputs that are required for the tactile allodynia. Also, lamina I neurons have little or no spontaneous activity required for the spontaneous response of neuropathic pain. Over cutaneous stimulation, ongoing activity of lamina I neurons has been looked over for spontaneous pain and despite little difference, some peaks in the firing pattern of this spontaneous activity have been detected. Since comparisons have been made in both the absence and presence of the peripheral stimuli and the difference was negligible, it can be concluded that spontaneous activity is independent of peripheral stimuli and ongoing activity is consistent with spontaneous pain in neuropathic conditions. Furthermore, after local spinal administration of ATP-stimulated microglia, it was observed that there are a number of potent spikes in response to noxious and innocuous stimulation and the burst of spontaneous activity in a group of neurons which is consistent with spontaneous pain in neuropathic conditions.[11]

Another noticeable consideration can be after applying DIOA as a blocker of cation-chloride co-transporters in neurons and witnessing the very higher responses of lamina I neurons after this disruption of chloride homeostasis. Although significant attenuation of GABAA/glycine receptor-mediated inhibition by impairing chloride homeostasis was reflected in previous studies and now by applying Bicuculline as a blocker of GABAA receptors, response to noxious stimuli and the burst of spontaneous activities was inquired as well. This shows constancy to spontaneous pain in neuropathic states.[11]

It is so interesting to know it has different manifestations including "hyperalgesia" which delineates as a greater generated action potential output through nociceptive relay neurons by a quantitative change in response properties of them, "allodynia" is hinted as a qualitative change and interpreted as a miscoding of information such that innocuous inputs are converted into a nociceptive message, allodynia is known as an indication of neuropathic pain even is experienced when the pain stimulation is very low contrary to what happens in normal pain and there is no pain perception in low-level intensities. And spontaneous pain explicates what spontaneous bursts of spikes appear in lamina I output neurons after nerve injury. In all experimental groups of research performed by Keller and colleagues[11] including peripheral nerve injury, ATP-stimulated microglia, or disruption of chloride homeostasis, all three mentioned manifestations have been perceived. Also, a central mechanism that was affected in their experimental conditions was proposed and it was a disruption of anion homeostasis effectively weakening inhibition, and as a loss of KCC2, which normally extrudes Cl- from the cells, appears to be the underlying mechanism.

As it was understandably mentioned, there were reasonable causes in their study that the latter mechanism is unlikely to contribute to the effects observed. One was in the first experimental group that peripheral nerve injury was associated with a loss of KCC2 expression, the other was in the second experimental group, ATP-stimulated microglia gives rise to tactile allodynia via the release of brain derived neurotrophic factor (BDNF) which is an important brain-derived neurotrophic factor for the regulation of synaptic activity, and then BDNF-trkB signaling whose pathway mediates a wide variety of functions in CNS throughout life, such as cell survival, migration, the outgrowth of axons and dendrites, synaptogenesis, synaptic transmission, and remodeling of synapses is linked to downregulation of KCC2. Additionally, the blocker of cation-chloride co-transport, DIOA, discriminatively inhibits KCC2 and not NKCC1. Interestingly, it can be concluded based on these findings that selective impairment of postsynaptic Cl- homeostasis in the spinal dorsal horn is sufficient to reveal the relay of innocuous input through normally nociceptive specific pathways. Unmasking polysynaptic connections in the superficial dorsal horn functionally linking low threshold

afferents and nociceptive lamina I projection neurons can create the improper relay of innocuous input.[11]

Treatment Strategies

Neuropathic pain is known as a type of chronic pain and one of the most debilitating medical conditions worldwide our existing knowledge about treatment options is very limited and we're observing modest success, limited acceptability, and considerable safety risks in existing treatments.[16] Currently, there is no consensus concerning the optimal therapeutic strategy for neuropathic pain and its comorbid conditions. Since there is no systematic or mechanistic approach to neuropathic pain management, treatment strategies are generally based on anecdotal evidence and data from a few clinical trials.[1]

Inhibitory control in dorsal horn neurons can be compromised by altered chloride homeostasis and thereby finding therapeutic approaches to compensate for this form of disinhibition is crucial. Meanwhile, drugs may be ineffective in reversing nerve injury-induced allodynia by enhancing GABAA/glycine receptor-mediated inhibition. Therefore, before making any inference three elements must be considered in designing a new treatment. First, intracellular [Cl-] estimation is known as an important factor in suppressing the component of inhibition caused by hyperpolarizing the neuron or guiding treatments based on GABA-modulating agents, next to normal anion homeostasis reinstatement along with targeting excitatory transmission can contribute to building on successful therapeutic strategies.[11]

Differentiating between physiological and behavioral responses to various noxious stimuli to those of an innocuous stimulus is of special importance.[15] To guard against tissue injury, it is imperative that the body is aware of potentially damaging stimuli. This awareness is achieved by a noxious stimulus-detecting sensory system.[8]

Recently, the relationships between noxious stimuli, pain perception, and behavioral responses have been quantitatively investigated through a simple paradigm where by applying painful and non-painful stimuli and analyzing relationships between intensity ratings and reaction times in response to the applied stimuli, moderated multi-level mediation analyses have been performed.[17]

Undoubtedly, it is very important to distinguish between nociceptive and neuropathic pain because the nociceptive typical anesthetic drugs or anesthetic analgesic drugs usually do not work for neuropathic pain and we do need separate treatments. But next level after realizing the causes and features of neuropathic pain we should be able to properly manage it.

Neuropathic Pain Management

In spite of repeated expression of pain as a perceptual phenomenon, the protective function of pain should be fundamentally related to appropriate motor responses to potentially harmful stimuli. Nevertheless, the association between motor responses and pain perception is imprecise and the study performed by Heitmann and colleagues authenticates the remarkable involvement of motor responses to noxious stimuli in shaping pain perception in healthy human participants. In practice, this leads to a better comprehension of the role of behavioral therapies and motor-related stimulation techniques in redrawing pain perception in patients with chronic pain. The appropriate behavioral responses are far more implicated in the basic protective function of acute pain compared with perception. Correspondingly more and more would be acknowledged motivational and motor processes as important constituents of pain.[17]

Chronic pain does not appear to be associated with consistently marked alterations in the brain's response to noxious stimuli and functional neuroimaging is a valuable tool for understanding how patients with chronic pain respond to painful stimuli.[16]

Medicament treatment including the use of antidepressants, antiepileptics, topical anesthetics, and opioids have been the first line of treatment for a long time but nonpharmacological treatments have been outstandingly raised as well.[4] Cognitive-behavioral therapy (CBT) which identifies maladaptive thoughts and behaviors and challenges them, trying to develop different ways of thinking and acting to improve the psychological and physical outcomes for patients is one way to deal with this challenge in the management of neuropathic pain.

In Table S1, a summary of drugs with their efficacy on the treatment of neuropathic pain is shown.

Notably, interventional therapies include different types of effective treatments, each of which in its position has been able to have a high effectiveness in reducing neuropathic pain, which has been proven in some cases and in others is under further investigation.

It is truly important to providing alternative treatment strategies in selected patients with refractory neuropathic pain, therefore for this purpose, treatments such as nerve blocks, surgical procedures for drug distribution to targeted areas, or modulation of specific neural structures have been designed. Although generally safe, there is a potential that spinal cord stimulation and peripheral nerve stimulation have been associated with biological complications such as infections or will probably lead to treatment-related adverse effects including painful paresthesia.[10]

Neural Blockade and Steroid Injections

In order to alleviate the pain, several distinct neural blockade and steroid injections have been designated. These techniques include perineural injection of steroids which provide temporary relief (1 to 3 months) for trauma-linked and compression-linked peripheral nerve pain,

and epidural steroid injections which have been indicated to a prompt moderate diminution in pain and function of fewer than 3 months duration for the treatment of cervical and lumbar radiculopathies and other methods of working such as epidural local anesthetic and steroid nerve blocks by weak recommendation have been recruited in lumbar radiculopathy and acute zoster-associated neuropathic pain treatments. Employment of sympathetic ganglion blocks has been reported to treat pain in some patients with complex regional pain syndromes as well.[10]

Also, to improve the management of neuropathic pain, special attention has been paid to stimulation in different parts of the peripheral and central nervous system which is rapidly developing. Based on the results of various clinical experiences, stimulation can be named as the main contributing factor in switching the patient from pathetic mode to a painless state.

Spinal Cord Stimulation

One of the conventional and the well-studied neuromodulation strategies to modulate pain signals conveyed by the unmyelinated C fibers would be spinal cord stimulation which was initiated through Low-intensity electrical stimulation of large myelinated Aβ fibers. Eminently, paresthesia-free stimulation or better pain relief in contrast to monophasic square-wave pulse (frequency range 30–100 Hz) has been provided through recent stimulation parameters such as burst (40 Hz burst with five spikes at 500 Hz per burst) and high-frequency (which differentiates by 10 kHz with sinusoidal waveforms) spinal cord stimulation. Basically, there are some dominant issues including comparative safety, cost-efficiently in prolonged use and reversibility have been raised for spinal cord stimulation and considerably have made it in combination with medical treatment as an attractive strategy for managing patients with refractory chronic neuropathic pain.[10] Remarkably in patients with severe phantom pain if there is still resistance to treatment, Surgical treatments and stimulation of the spinal cord including Implantation of electrodes on dorsal columns or stimulating the deep parts of the brain especially the sensory thalamus, spinothalamic tract which is set of fibers for pain transmission will be working solution. Although according to current European guidelines, spinal cord stimulation even in combination with medical treatment weakly recommended in situations such as diabetic neuropathic pain. The success of spinal cord stimulation mostly depends on the appropriate choice of patients in terms of psychological characteristics, sensory phenotype, strengthen central sensitization, and reduced conditioned pain modulation.

Dorsal Root Ganglion, Peripheral Nerve, and Peripheral Nerve Field Stimulation

In a wide range of severe chronic neuropathic pain conditions such as occipital neuralgia and postherpetic neuralgia, stimulation of nerve fibers located outside the spinal cord that conduct impulses toward it including dorsal root ganglion, peripheral nerve, and also peripheral nerve field stimulation has particular significance. A multicenter prospective cohort study reported a decline of about 50% in pain (about 56% pain reduction with a 60% responder rate). However, these precursory studies are under further investigation. Meanwhile, other types of neurostimulation have been proposed in specific brain areas including the Epidural motor cortex and pre-central motor cortex at levels below the motor threshold. These stimulations have been known under headings of epidural motor cortex stimulation (ECMS), repetitive transcranial magnetic stimulation (rTMS), and transcranial direct current stimulation (tDCS) as therapeutic alternatives for patients with persistent chronic neuropathic pain. In cortical neurostimulations such as EMCS which is a neurosurgical procedure for flawless consequences implemented by precise intra-operative emplacement of the stimulating electrode over the motor cortex region corresponding to the excruciating part of pain and as it has been mentioned in meta-analyses, the pain diminishes rate would be greater than 40% and in a range 60%–65% through this approach. In contrast, there are other less invasive therapies such as rTMS and tDCS and there is evidence of their effectiveness in neuropathic pain that is not resistant to treatment. In these methods, stimulation of neuronal regions of interest is done by magnetic coils or electrodes on the scalp. In the opinion of clinical reports, these therapies were mainly recommended in situations where we are facing a combination of central, peripheral, and facial neuropathic pain. At present according to European guidelines, The EMCS and rTMS are weakly approved in refractory chronic neuropathic pain and it would be desirable if tDCS applies only for peripheral neuropathic pain. The existence of any history of medical conditions such as epilepsy and the presence of aneurysm clips, deep brain electrodes, cardiac pacemakers, and cochlear implants are some of the circumstances in which the use of rTMS is prohibited.[10]

Deep Brain Stimulation

This is usually applied to treat a number of medical conditions including Parkinson's disease and epilepsy and regulates abnormal impulses by generating electrical impulses in certain areas of the brain. It has performed by implanting electrodes that can affect particular cells and chemicals within the brain. A pacemaker-like device that is implanted under the skin in the upper chest, connects to the electrodes via a wire that travels under the skin and controls the amount of stimulation in the deep brain areas. Several brain areas including the internal capsule, various nuclei in the sensory thalamus, periaqueductal and periventricular grey, motor cortex,

septum, nucleus accumbens, posterior hypothalamus, and anterior cingulate cortex have been recognized as targeted regions for deep brain stimulation and control of pain. Although long-term intracranial stimulation in the treatment of neuropathic pain is still a controversial issue. Notable potential risks such as intra-operative seizure, lead fractures, and wound infections threaten the safety of the deep brain stimulation method, and The UK National Institute for Health and Care Excellence (NICE) guidelines are believed this procedure would be effective in patients with persistent forms of neuropathic pain.[10]

But there are several situations in that we are witnessing the refractory to conservative treatments, including psychological, physical, and pharmacological and neuromodulation therapies thus the other alternatives like Intrathecal therapies have been seriously raised.

Intrathecal Therapies

In this advanced technique which is utilized for individuals with chronic severe pain or spasticity, drugs have been delivered into targeted nerves through an implanted and refillable pump but according to a report of the Poly-analgesic Consensus Conference in 2012 this therapy has been accompanied by high risks of morbidity and mortality and only two US FDA-approved drugs (morphine and ziconotide) are applicable by this device whose efficacy have not been evaluated by any high-quality randomized trials, therefore, this therapy continues to be a subject of controversy.[10]

Physical Therapies

Without any doubt, the results indicate the usefulness of therapies including physical therapy, exercise, and movement representation techniques such as mirror therapy and motor imagery in neuropathic pain management. In these therapies, the pain has been reduced based on observation and/or imagination of normal pain-free movements. Although the quality of evidence supporting these interventions for neuropathic pain is not strong and certainly requires more consideration.

Psychological Interventions

As people with such chronic pain constantly seek pain relief, the crucial and strategic role of therapeutic help in guiding them in the right direction should not be overlooked, although evidence-based studies to identify the target community for effective psychological interventions are not in hands. Furthermore, frequently after the failure of pharmacological or physical interventions, another category of interventions play role in promoting the management of pain. Markedly, there are some psychological interventions that are invented to improve pain management and reduce its unfavorable consequences. However, it is possible to initiate them in combination or even earlier than non-psychological interventions.

One modern therapy, which can be used in a wide range of mental and physical health problems and remarkably seems to have been highlighted in recent studies, is currently known as CBT, in such therapies, it is tried talking to help the patient control the disease by relying on changing the way of thinking and behaving to overcome pain. Naturally, CBT is not a single treatment; it can be considered as a family of techniques that primarily address mood (especially in depression), function, and social engagement, as well as indirectly targeting analgesia and subsequently some secondary outcomes including therapeutic confederacy and self-efficacy in treatment management.

In Table S2, the mechanism of management methods in neuropathic pain has been shown in detail.

Conclusion

The brain has an important contribution to our understanding and the way pain is experienced, whether neuropathic or non-neuropathic pain, the role of the brain in regulating the expression of pain is very important. Thus, this issue makes some people have excellent pain tolerance, or higher than normal, while others have severe pain responses. Truly addressing the mechanisms of development of neuropathic pain after nerve injury and demonstrating what elements contribute to understanding neuropathic pathways is critical in attacking this problem.

Difficulty to treat is one of the dominant challenges we face in neuropathic pain and a multilateral approach means using the combination of several treatments is strongly recommended. It may be much more effective than monotherapy. Markedly, pharmacological treatments are known as a cornerstone of cure but now nonpharmacological treatments including interventional therapies and surgical procedures are highly raised as well.

Conflict of Interest Disclosures

The authors declare that they have no conflict of interests.

Ethical Statement

Not applicable.

Supplementary Materials

Supplementary file 1 contains Table S1.
Supplementary file 2 contains Table S2.

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