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PAIN MANAGEMENT OF SENSORIMOTOR POLYNEUROPATHY IN COVID-19 INFECTIONS

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A 73-year-old man has tested positive for SARS-CoV-2. On the tenth day of the disease, a symmetrical distribution of spontaneous pain and dysesthesia occurs in both feet. Initial pain management, ordered by general practitioner was not effective, so he was referred to the pain specialist. The new therapy included combination of anticonvulsants, antidepressants and adjuvant therapy with partial, but satisfactory reduction in pain. Education/reeducation of general practitioners would accelerate the detection and symptomatic treatment in the early stages of COVID-19. An even better suggestion would be to refer these patients to pain medicine specialists. Acta Medica Medianae 2023;62(3):70-74.

***Key words**: peripheral neuropathy, COVID-19, chronic pain, pain management, treatment outcome*

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Introduction

Since December 2019, an unknown, fast spreading cause of viral pneumonia, called Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV-2), has spread from China to the rest of the world. Initially, it was assumed that respiratory symptoms predominate, but, over time, a significant clinical spectrum of complaints appeared (1). Depending on the severity of the clinical picture, neurological manifestations were recorded in 36.4% to 45.5% of patients infected with SARS-CoV-2. The most common manifestations of the central nervous system (CNS) were headache, cerebrovascular disease and epileptic seizures, while damage to the peripheral nervous system (PNS) was manifested by ageusia, anosmia, polyneuropathy (2, 3). Although their pathogenesis has yet to be fully elucidated, neurological symptoms have been attributed to the neuroinvasive potential and neurotropic characteristics of SARS-CoV-2 during and after infection (3, 4). We focused on the therapeutic approach to neuropathic pain in the patient with COVID polyneuropathy, examined and treated as ar outpatient.

Case report

In October 2020, a 73-year-old man has tested positive for SARS-Cov-2, with a mild clinical picture: fever (up to 38.4ºC), cough, headache, without myalgia, pneumonia or unpleasant smell and taste. On the 10th day of the disease, a symmetric distribution of spontaneous pain and dysesthesia(tingling, burning) occurred in both feet. The intensity of the pain gradually increased tomaximum rated 8/10 on the Numerical Pain Rating Scale (NPRS). The complaints were especially expressed at night, accompanied by sleep disturbances and anxiety. After COVID infection sanation, the pain (6/10 on NPRS) persisted for the next few months, despite analgesic therapy (paracetamol, ibuprofen and thioctic acid with topical application of capsaicin cream). This therapy was prescribed by a general practitioner. The patient'spersonal medical record stored data ofmedically regulated hypertension, prostatic hyperplasia,a non-smokingas well asnoalcohol consumption status. After 6 months, during his first neurological examination, the following evoked positive symptoms were

revealed: bilateral distal hyperalgesia, mechanical and thermal allodynia as a result of a pathological increase in nerve excitability. Dysesthesia and paroxysmal pain in the affected region indicated the presence of spontaneous positive symptoms. All upper extremity reflexes were intact; however, patellar and Achilles reflexes were absent. His physical examination was unremarkable. Pain DETECT questionnaire (PD-Q) score was 31/38, DN4-questionnaire 6/10. Electromyoneurography (EMNG) examination showed distal sensorimotor, dominantly sensory polyneuropathy (PN). In addition to the possible association of COVIDinfection with the clinical picture, we also searched for all common causes of PN: inflammatory, endocrinological, toxic, nutritional deficiencies, tumors, neurodegenerative causes. Oncomarkers: total prostate-specific antigen (tPSA), carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA 19-9), Beta-2-microglobulin; immunological tests: IgG, IgA, IgM, complement components C3 and C4, rheumatoid factor (RF), antineutrophil cytoplasmic antibodies (ANCA), antinuclear antibodies (ANA), anti-cyclic citrullinated peptide antibodies (antiCCP) and thyroid status—all were normal. Viral panel (HIV 1 and 2 antibodies, p24 antigen, HBs antigen,

Borrelia burgdorferi antibodies), serum micronutrient levels (folic acid, vitamin B12) and serum protein electrophoresis were also normal. Lumbar MRI, performed without contrast, did not reveal any compression of the nerve root and spinal cord. Nerve biopsy and lumbar puncture were not performed.His physical exam was unremarkable.

Considering the severity of the reported pain, a new analgesic therapy was introduced, which included a combination of analgesic (anticonvulsant-pregabalin in a dose of 300–600 mg daily, and antidepressant-duloxetine 60 mg/day), neuroregenerative agents (nucleotides and B vitamins, once a day). In the meantime, physical treatment (kinesitherapy and magnetotherapy) was started. After 4 months, partial but still satisfactory pain remission was reported, NPS 4/10 with significant improvement in sleep and quality of life.

It is interesting that the patient overcame a second infection with COVID-19 a year and a half after the first infection, and after a full vaccination with the Sinopharm COVID-19 vaccine. There was no worsening of neurological complaints.

Discussion

Distinguishing features of the COVID-19 infection are the genetic diversity and rapid evolution of the virus. Although the precise pathophysiological mechanism of both central and peripheral neurological lesions has not been established yet, the characteristic "cytokine storm" is considered the main mediator of this viral infection (5). In a study of 35 autopsies performed on patients with COVID-19 infection, no signs of direct viral invasion of muscle and nerve fibers were detected. PN is considered to be a consequence of inflammatory and immune damage associated with cytokine release (6).

To our knowledge, the literature reports a small prevalence of peripheral sensorimotor PN associated with COVID-19. In a recent study conducted on 1760 patients with neurological symptoms of COVID-19, Rifino et al. (7) identified 31 (22.6%) patients with clinically evident involvement of the PNS: 17 patients with Guillain-Barré syndrome, 9 myopathy and critical illness neuropathy (CRitical Illness MYopathy and/or Neuropathy-CRIMYNE), 2 brachial plexopathy and 3 peripheral polyneuropathy cases. Some cases of hospital-treated motor PN as a complication of COVID-19 have also been recorded (8, 9).

Neuropathic pain is difficult to treat effectively. The initial pain therapy for our patient had no literature confirmation. Paracetamol is not recommended in the treatment of chronic nociceptive and neuropathic pain neither as monotherapy nor as polytherapy. On the other hand, it is believed that approximately 40% of patients with neuropathic pain take NSAIDs (nonsteroidal anti-inflammatory drugs), although there is insufficient data on their effectiveness for this purpose. Commonly used ibuprofen is a non-selective inhibitor of cyclooxygenase (COX-1) that inhibits the production of proinflammatory prostaglandins (PG) and thus exerts an analgesic and anti-inflammatory effect in acute inflammatory nociceptive pain or during exacerbation. Although there is a hypothesis about the immunological pathogenesis of neuropathic pain in Covid-19 PN followed by increased PG production, where NSAIDs might find their place, their use is still not recommended in chronic neuropathic pain (10).

Alpha lipoic acid (ALA), also known as thioctic acid, is a powerful endogenous and exogenous antioxidant. In addition to the known effect on increasing the level of endogenous antioxidants (glutathione and coenzyme Q10), it reduces the production of proinflammatory cytokines (interleukin, chemokines, tumor necrosis factor-α-TNF-α). The hypothesis that the entry of SARS-CoV-2 into the cell could be slowed down or prevented if ALA is used at the same time, could contribute to the therapeutic potential of this agent in Covid PN (11).

Capsaicin is a selective, potent, high-affinity agonist for the transient receptor potential vanilloid type 1 (TRPV1) ion channel complex. Since it has not shown interactions with other commonly used analgesics, it can be combined with them. According to the Special Interest Group on Neuropathic Pain of the International Association for the Study of Pain, capsaicin is recommended as a second-line drug for the treatment of peripheral neuropathic pain (12). The guidelines of the German Society of Neurology (German Society of Neurology) advise the 8% capsaicin dermal patch as a first-line option for

localized neuropathic pain and as a second-line option for neuropathic pain of any cause (13).

The winning therapeutic combination for Covid PN in our case was the following: anticonvulsants, antidepressants and nutritional agents. Although there are no clinical trials studying the use of antiepileptics pregabalin (PGB) or gabapentin (GBP) for neuropathic pain associated with SARS-CoV-2, they are still traditionally used. Anticonvulsants bind with high affinity to the α2-δ-subunit of neuronal calcium channels in peripheral and central nociceptive neurons, thereby reducing the influx of calcium ions. According to the recommendations, they are used as first-line therapy: GBP in a daily dose of 1200−3600 mg, divided into three doses, and PGB, in a daily dose of 300−600 mg, divided into two doses. Gabapentin is approved for the treatment of peripheral neuropathic pain and pregabalin for peripheral and central neuropathic pain (14).

Combination of anticonvulsants with tricyclic antidepressants (amitriptyline) and serotonin and noradrenaline reuptake inhibitors-SNRI (venlafaxine and duloxetine) are the first-line treatment of peripheral neuropathic pain.

Duloxetine is a balanced neuromodulator of pain. Its analgesic effect results from potentiation of descending nociceptive inhibitory pathways by inhibition of presynaptic reuptake of serotonin and norepinephrine, two monoaminergic neurotransmitters. Common side effects (nausea, headache, dry mouth, insomnia, constipation) are classified as mild to moderate and are less common than tricyclic antidepressants, making them more acceptable. The initial dose is 30 mg daily, with an increase in the dose over a period of 7 to 14 days. The target dose to be achieved initially should be 60 mg, and the maximum dose is 120 mg once daily in the morning (13, 15).

In our case, as in many other cases of COVID infection, the administration of group B vitamins had adjuvant support. Vitamins B1, B6 and B12 contribute to analgesia in different ways: they regulate nerve conduction/excitation and selectively inhibit conduction in sensory nerves. Prolonged inhibition of pain is caused by the interaction of vitamins with intraspinal and supraspinal receptors in various systems, releasing endogenous opioids or inhibiting non-opioid neurotransmitters (γ-aminobutyric acid). On the other hand, data of their antiviral effect on the replication of the Sars-CoV-2 virus contribute to the positive effect of B group vitamins (16, 17).

Conclusion

Although a clear mechanism of neurological manifestations of SARS-CoV-2 has not yet been established, our example confirms the effect of a standard pharmacological approach to neuropathies: anticonvulsants and antidepressants, topical analgesics and nutritional agents. In patients recovering from COVID-19 infection, persistent neuropathic pain has a negative effect on their quality of life, physical functioning, and emotional status. Our experiences suggest that neuropathic pain is underdiagnosed in primary health care, therapy is usually carried out with inadequate drugs, and when specific drug therapy is included, it is often underdosed. Therefore, the education/reeducation of general practitioners considering pain therapy would accelerate the detection and symptomatic treatment in the early stages of COVID-19. An even better proposal would involve referring these patients to pain medicine specialists, which would enable a multidisciplinary approach and thus provide a chance for a better outcome in all aspects as well as prevent the emergence of SARS-Cov-2 post-viral burden.

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TERAPIJA BOLA SENZOMOTORNE POLINEUROPATIJE U INFEKCIJI IZAZVANOJ COVID-19 VIRUSOM

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Sedamdesettrogodišnji muškarac oboleo je od SARS-CoV-2 sa blagom kliničkom slikom. Desetog dana bolesti javljaju se simetrična distribucija spontanog bola i dizestezija u oba stopala. Inicijalna terapija bola, ordinirana od strane primarne zdravstvene zaštite, nije dala zadovoljavajući efekat. Nova terapija, ordinirana od strane specijaliste medicine bola, podrazumevala je kombinaciju antikonvulziva, antidepresiva i adjuvantne terapije. Time je izvršena delimična, ali ipak zadovoljavajuća redukcija bola. Edukacija/reedukacija službe primarne zdravstvene zaštite u pravcu terapije bola ubrzala bi detekciju i simptomatsko lečenje u ranim fazama infekcije izazvane COVID-19 virusom. Još bolji predlog podrazumevao bi upućivanje ovih bolesnika specijalistima terapije bola. Acta Medica Medianae 2023;62(3):70-74.

***Ključne reči**: periferna neuropatija, COVID-19, hronični bol, terapija bola, ishod*