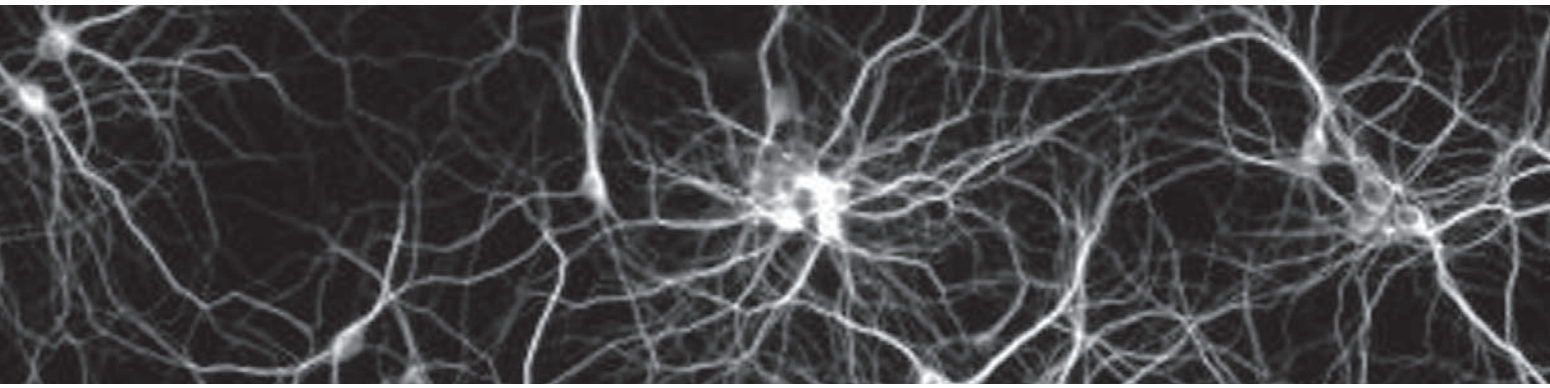

Neurotoxin-induced fibromyalgia or fibromyalgia after ciguatera (tilapia fish) poisoning?

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ABSTRACT – **Background:** Global climate change and the consequent increase in seawater temperatures have not spared the Adriatic Sea, leaving trace on its flora and fauna. Due to rises in seawater temperatures over the last few years, the dinoflagellatae algae that contain a potent neurotoxin, ciguatera, can now be found in the Adriatic Sea. The chronic form of ciguatera poisoning is characterized by chronic fatigue, chronic pain and diffuse sensory disturbances. Diagnosis of fibromyalgia is based on clinical signs and diagnostic criteria, with pain in the characteristic trigger points being the leading symptom. The clinical presentations of fibromyalgia and the chronic form of ciguatera poisoning largely overlap, and it is known that fibromyalgia may develop after infections with neurotrophic viruses or bacteria, as well as after certain poisonings. **Case reports:** This paper presents two patients with ciguatera poisoning that developed the chronic pain syndrome, the characteristics of which meet the criteria for the diagnosis of fibromyalgia. In both patients, excellent results were achieved using antidepressants in the treatment of their pain. **Conclusions:** Clinical studies are needed to assess the efficacy of antidepressants in pain treatment in the chronic form of ciguatera poisoning. Since ciguatera neurotoxin is currently present in plants found in the Adriatic Sea, we believe that this paper may help in the understanding and differential diagnosis of acute and chronic neurological syndromes that develop after the ingestion of fish from the Adriatic Sea.

Key words: fibromyalgia, ciguatera poisoning, global warming, antidepressants

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INTRODUCTION

Ciguatera toxin poisoning (CP) is the most commonly reported disease caused by a toxin of marine origin and caused by the ingestion of contaminated coral fish (1,2). Interest in CP in Europe has risen in the last few years because of climate change and increase in seawater temperatures as well as the growth of dinoflagellates in the Adriatic Sea. The dinoflagellatae algae contain a potent ciguatera toxin (CTX) that causes acute and chronic neurological symptoms. It activates voltage-gated Na^+ channels (VGSC) increasing the permeability to Na^+ ions and depolarizing neurons (3-5). It is assumed that this depolarization of neurons causes the neurological signs associated with acute CP. Neurological symptoms in CP include paresthesia, numbness and itching, myalgia, arthralgia and fatigue (1,6). Fibromyalgia is a condition of prolonged, extended, chronic pain that changes in location and strength, and may be associated with disorders of sleep and mood. The pain in fibromyalgia is frequently associated with symptoms such as chronic fatigue, irritable bowel, interstitial cystitis, temporomandibular pain, depression, cognitive dysfunction and insomnia, and it is often more convenient to refer to it as fibromyalgia syndrome (FMS) (2). Environmental factors that contribute to the development of fibromyalgia are emotional stress, physical trauma and infections with neurotropic viruses and bacteria (7). Dual antidepressants prevent the reuptake of norepinephrine and serotonin, thereby reducing pain in syndromes of central neuropathic pain, as well as regulating sleep and reducing the anxious-depressive component of the clinical picture in chronic pain syndromes (8,9). Pregabalin is the first US Food and Drug Administration approved drug for the treatment of fibromyalgia; it has also been proposed as a possible treatment for pain in acute and chronic forms of CP. The pain in the chronic form of CP (CCP) has some characteristics of central neuropathic pain, is not dependent on movement or load, is associated with sleep disorders, and can be controlled with the use of antidepressants and pregabalin, highly resembling the pain of FMS.

CASE REPORTS

CASE 1

A 47-year-old female was admitted to the Department of Neurology due to chronic fatigue syndrome, diffuse paresthesias, ataxia, myalgia and arthralgia, which had developed after short-term gastrointestinal symptoms of nausea and abdominal pain. Paresthesia was described as a "feeling of cold and warm water flowing down the limbs" or as a "splash of cold water". She complained of perceiving a cold sensation on the soles of her feet as hot. Upon clinical neurological examination, a disturbance in temperature sensation was recorded (i.e. temperature sensation reversal), as well as a mildly attenuated triceps reflex, excessive sweating of the face, and mild fatigability and pelvic muscle pain on repeated squatting. An underlying cause was not found after an extensive diagnostic workup. Lumbar puncture was normal, and there were no signs of a recent neurotrophic viral or bacterial infection. Electromyoneurographic (EMNG) findings suggested a mild polytopic radiculopathy. The repetitive nerve stimulation test was normal. Antibodies to muscle specific kinase (MuSK) and nicotinic acetylcholine receptor (NAChR) were negative. Pyridostigmine bromide (2x60 mg) therapy was initiated with a modest therapeutic effect. History data indicated that clinical manifestations had developed after the ingestion of fish during the patient's stay in Maldives (Republic of Maldives, Indian Ocean). Altogether, her clinical symptoms and medical history pointed to CP. The diagnosis of CCP was made based on her clinical presentation, medical history and the results of the laboratory, neuroradiological, immunological and electrophysiological workup.

The patient was monitored over a period of two years, and gradual improvement of the neurological symptoms was noted. In the meantime, the patient developed an allergy to milk, wheat, eggs, chicken and propolis. Antidepressant therapy (duloxetine 60 mg daily) has been introduced with significant pain reduction and regulation of sleep disturbances, but allergies to the mentioned antigens have persisted.

CASE 2

A 54-year-old female was referred to the Center for Neuromuscular Diseases due to paresthesias in the extremities, pain in the muscles, joints and extremities, sleep disturbances and depression, as well as chronic fatigue syndrome that remained after an acute episode of fever, sore throat and abdominal pain. The first symptoms appeared during a trip to Texas, six months prior to the checkup, and after the ingestion of a raw tropical fish, tilapia, caught on the northern coast of the Gulf of Mexico. During the patient's first neurological examination, a

disturbance in temperature sensation in the feet, muscle weakness, and pain in the shoulder and pelvic area were noted, as well as painful acroparesthesia. Myotatic reflexes were normal, and mild radiculopathy of L5-S1 was detected in her EMNG findings. No other cause of the syndrome was found upon diagnostic workup. A diagnosis of CCP was made based on her medical history and clinical presentation. Given the associated chronic fatigue syndrome, depression, sleep disturbances and pain in the characteristic points, fibromyalgia syndrome was also diagnosed. Duloxetine (60 mg daily) was introduced and resulted in excellent clinical response.

DISCUSSION

The symptoms of CCP largely overlap with the clinical picture of FMS. In this paper, we present two patients with CCP that developed a chronic pain syndrome, with the characteristics meeting the criteria for FMS and showing significant pain reduction after duloxetine administration. It is well known that infections with neurotropic viruses and bacteria can lead to FMS, and it is possible that the chronic pain found in CCP is neurotoxin-induced fibromyalgia (7). The mechanism of action of ciguatoxin is fairly well understood. However, CCP is substantially more complex and goes beyond the initial toxic damage to peripheral nerves. Many similarities between FMS and CCP have been noted as a result of studies on chronic inflammatory response syndrome (10,11). Some less frequent laboratory abnormalities found in CCP have helped identify a complex syndrome characterized by the host response to inflammation, autoimmune disease, and coagulopathy. HLA-DR haplotype is predictive of other chronic diseases sharing similar characteristics with CCP (12). Abnormalities in the following parameters have been noted in CCP: visual contrast sensitivity (VCS) deficits, HLA-DR, melanocyte stimulating hormone abnormalities (MSH), vasoactive intestinal peptide (VIP), C4A, TGFβ1, matrix-metalloproteinase-9 (MMP9), ACTH/cortisol and ADH/osmolality. Ciguatoxins are extremely potent activators of VGSC, which exhibit their effects predominantly in the peripheral nervous system. VGSC have now been found in various types of non-excitable cells and these channels contribute to the activation of inflammatory pathways in many immune cells (3). The first patient presented developed an allergic response to multiple allergens during the sub-chronic stage of the disease. A deficit of VIP and MSH, two neuropeptide regulators of the inflammatory response, has been observed in patients with CP indicating a lack of inflammatory regulation in those suffering from CCP (13). Increased activity of MMP9 is characteristic of several inflammatory and autoimmune conditions. TGFβ1, an anti-inflammatory cytokine, up-regulates MMP9, which can promote the progression of CCP (3,12). The differentiation between acute illness and the development of chronic disease can be made according to HLA genotype, dysfunction of antigen presentation or regulation of auto-reactive T cells. Inflammation is an important step in the development of various forms of neuropathic pain, both central and peripheral. There is convincing evidence that proinflammatory cytokines present in chronic inflammation promote the development of neuropathic low back pain, complex regional pain syndrome and fibromyalgia (14-16). Other than a constitutional predisposition to the development of disease, abnormal regulation of neuropeptides and immune response, CCP and FMS share several clinical features: chronic fatigue, chronic pain, depression, and sleep disturbances. A positive therapeutic response to pregabalin in the treatment of chronic pain in both conditions is another common feature (17). In this paper, we have presented two patients with CCP whose symptoms fulfilled the diagnostic criteria for FMS, and who showed an excellent response to duloxetine in the treatment of their pain (18). The overlap of neurological symptoms present in these two syndromes may indicate the possibility of common pathophysiological mechanisms and suggests that ciguatera toxin may be a possible environmental cause of FMS. It is possible that changes in the host immune response occur in genetically predisposed individuals, as well as a wide range of changes to immunoregulatory molecules and neuropeptides, setting the basis for the development of fibromyalgia. The chronic pain syndrome in CCP is likely triggered by initial nociceptive damage to peripheral nerves, although in constitutionally predisposed individuals chronic neuropathic pain, as seen in fibromyalgia, can also develop. Although the patients have exhibited an excellent response to duloxetine in the treatment of chronic pain in CCP, a substantially larger sample group is needed to evaluate the efficacy of duloxetine in the treatment of CCP. Future research on the association between chronic inflammation and stress as the underlying basis for the development of CCP and FMS may provide new therapeutic options in the treatment of FMS, as well as other chronic pain syndromes such as CCP.

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Fibromialgija nakon otrovanja ciguaterom ili neurotoksinom izazvana fibromialgija?

SAŽETAK - **Podloga:** Globalne klimatske promjene s posljedičnim porastom temperature mora utjecale su na floru i faunu Jadrana. Zbog porasta temperature mora u posljednjih nekoliko godina alge dinoflagelata koje sadrže snažan neurotoksin ciguateru sada se mogu naći i u Jadranskom moru. Kronični oblik otrovanja ciguaterom obilježava kronični umor, kronični bolovi i difuzni poremećaj osjeta. Klinička dijagnoza fibromialgije temelji se na bolovima u karakterističnim točkama-okidačima kao vodećem simptomu. Klinička slika fibromialgije i kroničnog oblika otrovanja ciguaterom je vrlo slična. Također je poznato da se fibromialgija može razviti nakon infekcije neurotropnim virusima i bakterijama, kao i nakon određenih vrsta otrovanja. **Prikazi slučajeva:** U ovom radu prikazujemo dvije bolesnice kod kojih se nakon otrovanja ciguaterom razvio kronični bolni sindrom sa značajkama fibromialgije. U obje bolesnice izvrstan analgetski učinak postignut je upotrebom antidepresiva. **Zaključak:** Za procjenu učinka antidepresiva u liječenju boli u bolesnika s kroničnim oblikom otrovanja ciguaterom neophodna su daljnja klinička istraživanja. S obzirom na to da je ciguatera neurotoksin trenutno prisutan i u flori Jadranskoga mora vjerujemo da će ovaj rad pomoći u razumijevanju i diferencijalnoj dijagnostici akutnih i kroničnih neuroloških poremećaja nastalih nakon konzumacije ribe iz Jadranskog mora.

Ključne riječi: fibromialgija, otrovanje ciguaterom, globalno zatopljenje, antidepresivi