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CASE REPORT

Exacerbation of refractory chronic oral pain due to mild consciousness disorder associated with valproate-induced hyperammonemia: A case report

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ABSTRACT

We describe a 48-year-old man with history of chronic pain radiating from the right oral cavity to the occipital region with comorbid depression. He received anti-depressant drugs such as sodium valproate and maprotiline for comorbid depression, but these had little effect. His decreased concentration and motivation became protracted, leaving him unable to work. Electroencephalographic findings suggested a mild consciousness disorder. Blood tests indicated that his serum ammonia levels were abnormally elevated. After valproate administration was gradually tapered off, the symptoms of decreased motivation and cognitive inhibition rapidly improved and he became more active. Although his moderate pain persisted, he no longer complained of pain. Finally, he succeeded in returning to work. The central nervous system depression due to valproate and hyperammonemia may have decreased his activity levels and exacerbated his pain. The objective of chronic pain therapy should be to help improve the patient's quality of life, and attention must be paid to the possibility that the adverse drug effects may exacerbate pain due to a consciousness disorder and one's decreased activity levels. This case report is valuable because there are few reports regarding a relationship between chronic pain and disorders of consciousness.

Key words: Pain; Chronic oral pain; Consciousness disorder; Valproate; Hyperammonemia

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INTRODUCTION

Chronic pain is often unrelated to tissue damage, and pain resulting from a combination of biological and psychosocial factors can become refractory to treatment. As a result, psychological complications such as somatoform disorders, mood disorders and anxiety disorders are common and it has been reported that 41%–99% patients with chronic low-back pain have some type of psychiatric disease as a comorbidity.[1]

Valproate is widely utilized in daily medical care as an antiepileptic drug, mood stabilizer, and migraine headache drug. Its adverse effects include drowsiness, depression, headache, vomiting, liver disorder, cytopenia, acute pancreatitis, toxic epidermal necrolysis, dementia-like symptoms, Parkinson's disease-like symptoms, and syndrome of inappropriate antidiuretic hormone secretion. Consciousness disorder associated with valproate-induced hyperammonemia also occurs and can lead to coma or death in severe cases[2], but there has been no published report about relationship between chronic pain and consciousness disorder associated with valproate-induced hyperammonemia.

In this case, a patient with refractory chronic oral pain was receiving long-term therapy with valproate for a comorbid mood disorder. The patient experienced exacerbated oral pain, decreased concentration and decreased motivation. Examination findings indicated mild consciousness disorder with hyperammonemia. A gradual reduction and discontinuation of valproate led to an improvement in the consciousness disorder, which in turn eliminated the negative effects of pain on the patient's daily life. This could be a valuable case report to show adverse effects of consciousness disorder on chronic pain due to psychotropic involved valproate.

Written consent was obtained from the patient.

CASE PEPORT

A 48-year-old man reported to our medical department with the chief complaint of continuous pain that radiated from right oral cavity to his occipital region. His medical history included depression for 5 years, which led to a 1-year leave of absence from work. His pain first occurred 2 years ago, and although he underwent detailed examinations at otorhinolaryngology, orthopedic surgery, neurosurgery as well as internal medicine departments, no abnormal findings were detected. Pharmacotherapy and nerve-block therapy were tried at department of psychosomatic medicine and a pain clinic, but had little effect. One year back he suffered from fever of unknown origin and pantalgia, that was treated with steroid pulse therapy. This resulted in a recurrence of depression and he once again took a leave of absence from work. As he was unable to return to work due to persistent pain, decreased concentration, and a tendency to stay in bed at home, he was referred to our medical department.

At the time of examination he was on a course of maprotiline hydrochloride 75 mg/d, sodium valproate 600 mg/d sustained release tablets, flunitrazepam 1 mg/d, and lorazepam 2 mg/d, prescribed by a psychiatry department of another hospital. A medical examination of the patient did not indicate any neurological abnormality. There were no trigger points within his oral cavity, but the range of neck motion was limited (particularly left lateral flexion). Because of an intramuscular induration that caused pain predominantly in his right cervical region (e.g. temporalis, masseter, splenius and scalene), he was diagnosed with myofascial pain syndrome. In addition, he had a comorbidity of severe depression with marked decrease in motivation and interest. His medical questionnaire form on initial examination indicated that his Brief Pain Inventory (BPI) scores had been a maximum of 8, a minimum of 5, an average of 7, and was currently 5, Pain Disability Assessment Scale (PDAS) score was 18, Pain Catastrophizing Scale (PCS) score was 36, Hospital Anxiety and Depression Scale-Anxiety Subscale (HADS-A) score was 13, Depression Subscale (HADS-D) score was 15, Pain Self-Efficacy Questionnaire (PSEQ) score was 9, and Athens Insomnia Scale (AIS) score was 14. He was provided with chronic pain education and stretching guidance, and acupuncture sessions provided by an acupuncturist, as well as autogenic training provided by a clinical psychologist. Approximately 5 months after his initial examination, his pain improved slightly. However, he had a blank look on his face, he wanted to return to work but felt no motivation and was engaged in escapism because of the pain. He also stated that he had decreased concentration and had mental lethargy, saying, "before I am able to answer a question, I forget what it was that I wanted to say." Electroencephalography (EEG) showed a basic rhythm of approximately 8.5 Hz indicating a mild slowing of wave rhythm, which indicated mild consciousness disorder. Blood tests showed no abnormalities in the complete blood count or serum valproate level of 60 μg/mL (normal range 50–100 μg/mL). His liver and kidney function tests were normal. However, the serum ammonia level was 103 μg/dL (normal range 30–86 μg/dL), indicating hyperammonemia. On the basis of the above findings, we diagnosed the patient as having consciousness disorder associated with valproate-induced hyperammonemia. Therefore, the valproate was gradually tapered off (at a rate of 200 mg/week) under hospitalization and close cooperation with hospital psychiatrists. This resulted in a complete discontinuation of valproate 2 weeks later. After discontinuation, the patient complained that the pain intensified in the first week but he had become more active. He stopped spending the entire day in bed and went for walks within the hospital ward of his own motivation. One month after discontinuing valproate, his serum ammonia level fell to 59 μg/dL (within the normal range) and his brain wave basic rhythm improved to around 10 Hz (Figure 1).

In addition, a medical questionnaire completed 2 months after discontinuing valproate showed that the BPI maximum was 6, the minimum was 2, the average was 4, and the current score was 5, PDAS was 2, PCS was 10, HADS-A was 7, HADS-D was 6, PSEQ was 45, and AIS was 9, indicating that the pain intensity had improved to "mild", and other variables also showed marked improvement (Figure 2), as did

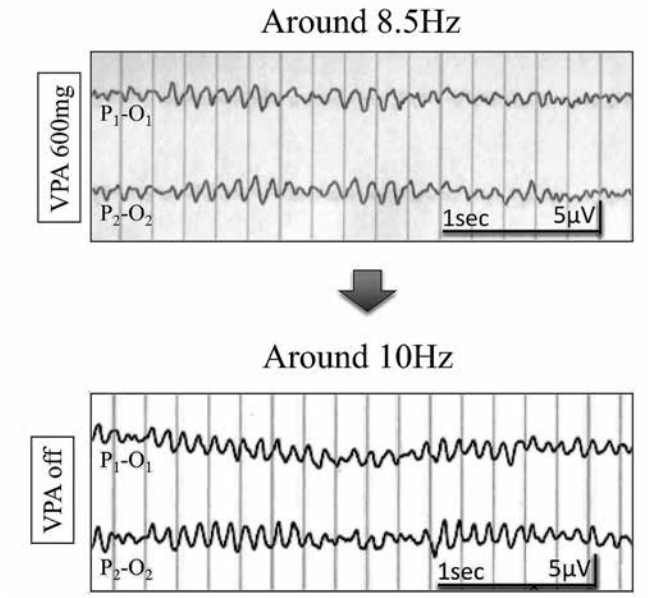

Figure 1: Improvement in brain wave basic rhythm after cessation of valproate

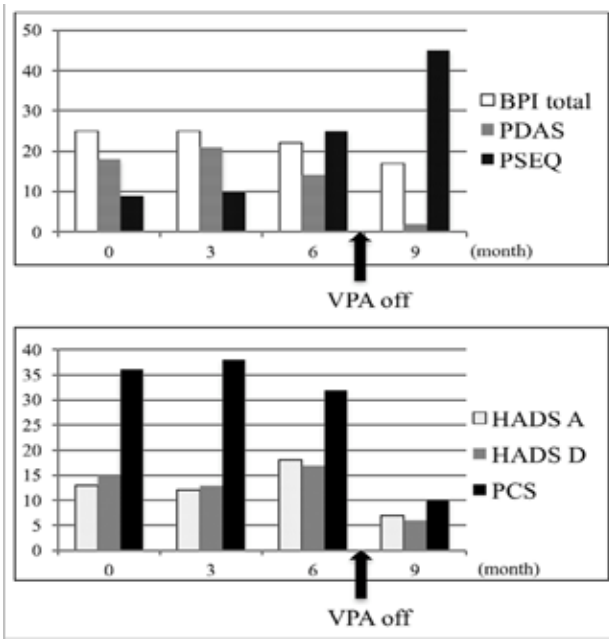

Figure 2: Clinical pain assessment scores before and after cessation of valproate

Legend: BPI- Brief Pain Inventory; PDAS-Pain Disability Assessment Scale; PCS-Pain Catastrophizing Scale; HADS-A-Hospital Anxiety and Depression Scale-Anxiety Subscale; HADS-D-Depression Subscale; PSEQ-Pain Self-Efficacy Questionnaire; AIS-Athens Insomnia Scale

DISCUSSION

Hyperammonemia is a frequent side-effect of valproate therapy, which points to an imbalance between ammoniagenesis and ammonia disposal via the urea cycle. The impairment of this liver-specific metabolic pathway induced either by primary genetic defects or by secondary causes, namely associated with drugs administration, may result in accumulation of ammonia.[3] Exposure of astrocytes in the brain to high levels of ammonia results in both cell swelling (acute exposure) and Alzheimer Type II astrocytosis (chronic exposure),[4] which causes consciousness disorder.

In this case, we observed a consciousness disorder that was difficult to recognize by a superficial examination. It was caused by hyperammonemia following the long-term administration of valproate, a drug commonly used for migraine prophylactic medicine in pain clinics, and the additional presentation of depression eventually led to the patient taking a leave of absence from work. A discontinuation of valproate led to an improvement in his consciousness disorder and depression along with improvements in concentration and motivation, allowing the patient to return to work after a long-term leave of absence. The patient reported that "although moderate or worse pain remains, it is no longer difficult to bear." The patient no longer complained of pain during subsequent medical examinations and instead talked about work and family. Therefore, we hypothesize that the pain was exacerbated by the consciousness disorder, which intensified catastrophic ideas regarding the pain, thereby decreasing the patient's quality of life (QOL). Consciousness disorder is a condition of decreased function in the brainstem and reticular regulatory system or the cerebral cortex in which there is dysfunction in the frontal lobe's ability to regulate the stress of pain and other stimuli. As a result, the patient becomes unable to endure stress such as pain and complaints of pain become more pronounced. If it's true, it is important to ascertain whether mild consciousness disorder is present or not in chronic pain patient. For example, organic changes in the brain associated with aging or sedative drug administration can cause a mild consciousness disorder, even if during a superficial examination the patient seems to be able to maintain a good communication. Consider that while the present case had symptoms that caused us to be suspicious of consciousness disorder, such as decreased concentration, mental lethargy, and decreased

motivation and activity due to psychotropic drug administration, it was the EEG that indicated a slowing of brain wave rhythms which led to the diagnosis. However, the symptoms of consciousness disorder are very similar to those of depression presented by chronic pain patients. This indicated that it was necessary to identify the specific cause.

CONCLUSIONS

We believe that the long-term administration of valproate can cause the consciousness disorder. However, the combined use of multiple drugs with a sedative effect, such as antiepileptics, antidepressants, sleeping pills, anti-anxiety drugs, and analgesics can also cause a consciousness disorder. Thus, physicians must be fully aware of the possibility that an iatrogenic decline in quality of life of chronic pain patients can be caused by the administration of drugs frequently used in pain clinics.

Conflict of interest: Nil declared by the authors

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Authors' contribution:

TH: manuscript writing

MH & YH: supervised to shape this manuscript

MK: revision of the manuscript

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