

CASE REPORT

Levetiracetam improves symptoms of multiple chemical sensitivity : Case report

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Abstract : Multiple chemical sensitivity (MCS) is a disorder of unknown etiology with no effective treatment. Many clinicians accept that a diagnosis of somatic symptoms disorder (SSD) is an appropriate diagnostic category for MCS. We found that administration of levetiracetam improved recurrent symptoms of MCS in a patient. A 23-year-old female presented with recurrent multiple symptoms of musculoskeletal, airway or mucous membrane, heart/chest-related, gastrointestinal, cognitive, affective, neuromuscular, head-related, and skin-related induced by exposure to diesel or gas engine exhaust, tobacco smoke, insecticide, gasoline, paint or paint thinner, cleaning products, fragrances, tar or asphalt, nail polish or hairspray, and new furnishings. Gastrointestinal, cognitive, and skin-related symptoms were precipitated by some food additives. She suffered partial seizures from the age of 17 years, and was diagnosed with right parietal lobe epilepsy. Administration of levetiracetam (250 mg/day) eliminated her MCS symptoms. Levetiracetam reduces the release of presynaptic neurotransmitter including glutamate by binding to presynaptic vesicle protein. A recent study established the presence of glutamatergic overactivation in somatization disorder, a form of SSD. Our case may indicate that a subset of patients with SSD have glutamatergic overactivation, which levetiracetam can normalize. *J. Med. Invest.* 64 : 296-298, August, 2017

Keywords : multiple chemical sensitivity, N-methyl-D-aspartate sensitization, somatic symptoms disorder, levetiracetam, glutamate

INTRODUCTION

Multiple chemical sensitivity (MCS) is defined as “an acquired disorder characterized by recurrent symptoms, referable to multiple organ systems, occurring in response to demonstrable exposure to many chemically unrelated compounds at doses below those established in the general population to cause harmful effects” (1). The definition differentiates MCS from allergic or toxicologic diseases, which were previously candidates as the cause of MCS. To screen and study the complicated profile of MCS patients, a questionnaire was established, called the Quick Environment Exposure Sensitivity Inventory (QEESI), which remains the gold standard for MCS diagnosis (2). Currently, MCS symptoms cannot be explained fully based on the general medical condition or the direct effect of a substance (3, 4). Many clinicians accept that a diagnosis of somatic symptoms disorder (SSD) is an appropriate diagnostic category for MCS (3). A pathophysiological hypothesis has been proposed for MCS. Exogenous toxic exposures cause toxicant-induced loss of tolerance with dysregulation of immune state (5), which may involve N-methyl-D-aspartate (NMDA) sensitization with increased level of nitric oxide (NO) and peroxynitrite (5). No medication has been found to be effective for the treatment of MCS (3).

Levetiracetam is an antiepileptic agent which reduces the release of presynaptic neurotransmitter, including glutamate, by binding to a presynaptic vesicle protein (6). The mechanisms are paradoxical ; the amplitudes of the late postsynaptic field potentials

are decreased for hyperactive synapses, with minimal effect on normal synaptic transmission (7). Recent studies also showed that levetiracetam has antioxidant property (8, 9), and inhibits NO level (10).

We treated a patient with MCS with levetiracetam administration based on a diagnosis of epilepsy. We found that levetiracetam medication eliminated multiple symptoms induced by exposure to chemicals. This preliminary report of this curious phenomenon proposes further investigation.

CASE REPORT

A 23-year-old female with uneventful birth and normal development. Ever since she was old enough to talk, she had complained of multiple symptoms induced by several causative agents as shown in Table 1, based on the QEESI (2), which was retrospectively confirmed at age of 20. Symptoms of musculoskeletal, airway or mucous membrane, heart/chest-related, gastrointestinal, cognitive, affective, neuromuscular, head-related, and skin-related were triggered by exposure to diesel or gas engine exhaust, tobacco smoke, insecticide, gasoline, paint or paint thinner, cleaning products, fragrances, tar or asphalt, nailpolish or hairspray, and new furnishings. Additionally, the patient also reported either increase or decrease of body temperature with exposure to paint or paint thinner, cleaning products, fragrances, tar or asphalt, nail polish or hairspray, and new furnishings. Gastrointestinal, cognitive, and skin-related symptoms could be precipitated by food intake. The patient and her parents speculated these symptoms were probably due to inclusion of agricultural chemicals and/or chemical seasonings. Retrospectively, her mother thought that the patient's MCS had started at the age of 1 year as gastrointestinal symptoms and/or change in body temperature induced by the smell or ingestion of

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causative chemicals. Her symptoms fulfilled the diagnostic criteria of MCS (1). She started to suffer partial seizures from the age of 17 years. The seizures started with unpleasant feeling followed by visual illusions with rare secondary generalization. Physical examination found no abnormalities. Ictal electroencephalography clarified that the seizures originated from the right parietal region. Magnetic resonance (MR) imaging detected no abnormalities. Levetiracetam (250 mg/day) administration was started under a diagnosis of right parietal lobe epilepsy. Her multiple MCS symptoms disappeared completely within 2 days of starting levetiracetam medication despite continuous exposure to the sensitizers. Three months later, transient cessation of levetiracetam administration

resulted in recurrence of abdominal pain and headache. Resumption of levetiracetam medication resulted in freedom from MCS symptoms, which has continued for over 3 years with residual epileptic seizures. The clinical course of the case is shown in Fig. 1.

DISCUSSION

The present case showed that levetiracetam administration can improve recurrent MCS symptoms. Our experience may indicate that MCS involves a pathophysiological abnormality which can be reduced by levetiracetam. The underlying etiology of MCS may

Table 1. Detailed relationship between the precipitating factors and presenting multiple chemical sensitivity (MCS) symptoms of Case 1

Precipitating agents (Q1 of QEESI)	Type of exposure	MCS symptoms (Q3 of QEESI) if exposed without LEV										
		1. Musculo skeletal	2. Airway or mucous membrane related	3. Heart/ chest-related	4. Gastro-intestinal	5. Cognitive	6. Affective	7. Neuro-muscular	8. Head-related	9. Skin-related	10. Genito-urinary	Miscellaneous
1. Diesel or gas engine exhaust	Olfactory	N	N	Y	Y	Y	N	N	Y	Y	N	Insomnia
2. Tobacco smoke	Olfactory	N	N	N	Y	Y	N	N	Y	N	N	Insomnia
3. Insecticide	Olfactory	N	N	N	Y	N	N	N	Y	N	N	
4. Gasoline	Olfactory	N	N	Y	Y	Y	N	N	Y	Y	N	Insomnia
5. Paint or paint thinner	Olfactory	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Increased BT
6. Cleaning products	Olfactory	Y	N	N	Y	Y	Y	Y	Y	Y	N	Decreased BT/ Insomnia
7. Fragrances	Olfactory	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Increased or decreased BT, Insomnia
8. Tar or asphalt	Olfactory	Y	Y	N	Y	Y	N	Y	Y	Y	N	Increased BT
9. Nail polish or hairspray	Olfactory	N	N	N	Y	Y	N	N	Y	Y	N	Increased or decreased BT, Insomnia
10. New furnishings	Olfactory	N	N	N	Y	Y	N	N	Y	Y	N	Increased BT

Precipitating agents for MCS symptoms are listed from Q1 of the Quick Environment Exposure Sensitivity Inventory (QEESI). Occurrence of MCS symptoms, from Q3 of QEESI, are shown with/without levetiracetam (LEV). Note that 1) various MCS symptoms appear with multiple chemical agents without LEV, and 2) all symptoms disappear with administration of LEV. BT, body temperature ; Y, yes ; N, no.

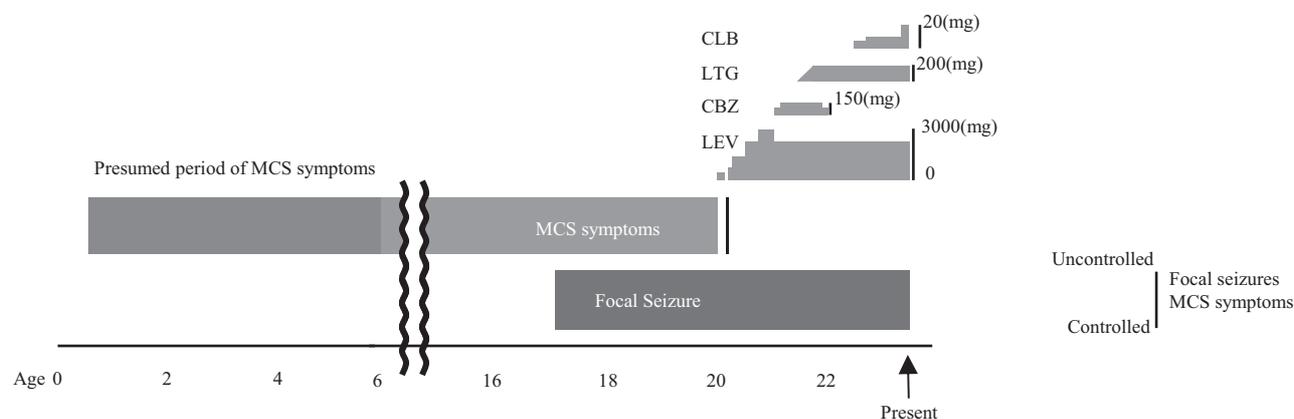


Fig. 1. Clinical course of the case. Arrow indicates the present point. Levetiracetam (LEV) administration eliminated multiple chemical sensitivity (MCS) symptoms. CBZ, carbamazepine ; CLB, clobazam ; LTG, lamotrigine.

involve NMDA sensitization as a vicious cycle of hypersensitive NMDA receptors and elevation of NO, peroxynitrite (11). Chemicals first activate the NMDA receptors, which raises levels of NO and peroxynitrite. NO facilitates the release of neurotransmitters, including glutamate as a retrograde messenger, which further stimulate the NMDA receptors (11). Under this hypothesis, levetiracetam administration may act by releasing NMDA sensitization through reducing excessive glutamate release as well as the antioxidant property (8, 9), thus inhibiting the NO level (10). We suggest that levetiracetam administration may be helpful for relieving MCS symptoms in a subset of patients. Levetiracetam administration has been reported as effective for SSD, although the mechanism is still unknown (12). A recent MR spectroscopy study clarified the presence of glutamatergic overactivation in somatization disorder, a form of SSD (13). These studies may indicate that a subset of SSD cases have glutamatergic overactivation, which levetiracetam can normalize. The clinical significance of this observation is limited to this single case. A double-blind study is required to clarify the activity of levetiracetam for MCS.

CONFLICT OF INTEREST

Dr. Jin has received honoraria for consulting from Otsuka Pharmaceutical Co., Ltd. (Tokyo, Japan) and UCB Japan Co. Ltd. (Tokyo, Japan). Dr. Nakasato has received honoraria for consulting from UCB Japan Co. Ltd. (Tokyo, Japan). Drs. Nakasato and Jin confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. Drs. Kakisaka, Fujikawa, Kitazawa, and Kato declare no conflict of interest.

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