Multifocal Demyelinating Leukoencephalopathy Induced by Levamisole Therapy

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The neurotoxic effects of levamisole therapy have been rarely reported. In this article, we report two patients who developed multifocal demyelinating leukoencephalopathy (MDL) after levamisole treatment. Clinically, they had dizziness, nausea, vomiting, confusion, mental dullness, speechlessness, and memory impairment after the treatment. The total dosage of levamisole was 300 mg and 1800 mg, respectively. The onset of symptoms was acute or subacute, from a few hours to several weeks. Initial brain magnetic resonance imaging (MRI) demonstrated diffuse multifocal enhancing lesions in the subcortical white matter. After the withdrawal of levamisole, and during the follow-up period, the neurological and neuropsychological manifestations and serial brain MRI improved gradually. We conclude that levamisole treatment may induce MDL, and that the brain MRI changes may correlate well with the recovery of clinical features and neuropsychological findings. In addition, early steroid treatment is crucial, and the neurotoxic effect of levamisole is not dose-dependent and may be idiosyncratic or immune-mediated. *(Chang Gung Med J 2006;29(4 Suppl):90-6)*

Key words: multifocal demyelinating leukoencephalopathy, levamisole, neurotoxicity, MRI, neuropsychology.

Levamisole, an anthelmintic agent that targets the nicotinic acetylcholine receptors, is usually used as an immunostimulant in combination with 5-fluorouracil (5-FU) to treat colorectal cancer.[1-5] The neurotoxic effects related to levamisole and 5-FU include fatigue, myalgia, dizziness, vertigo, nausea, vomiting, diarrhea, anxiety, depression, seizures, ataxia, and even disturbance of consciousness.[6-12] The brain magnetic resonance images (MRI) show multiple subcortical white matter lesions suggesting multifocal demyelinating leukoencephalopathy (MDL). However, most authors have concluded that the condition was mainly due to 5-FU neurotoxicity.[6-11] Only a few cases of MDL have been considered secondary to levamisole therapy.[12-15] Therefore, the exact etiologic agent and the pathogenesis of MDL remain unclear. We report two patients who developed MDL after levamisole therapy alone. We studied the clinical features and neuropsychological changes in these patients and correlated them with the neuroimaging changes after the discontinuation of levamisole.

CASE REPORT

Case 1

A 49-year-old man was admitted to our hospital on April 17, 2003, with speechlessness, a decline of

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mental status, dizziness, nausea, and vomiting. He had suffered from recurrent episodes of oral and genital ulcers and blurred vision over the past 3 years, and came to our outpatient clinic on March 3, 2003. Levamisole (150 mg daily for 3 days each week) was given under the impression of Behcet's syndrome. His family history was unremarkable. He had no history of vaccination, insect bite, or flu-like symptoms before the episode. On April 2, dizziness, headache, nasal congestion, nausea, and mild fever with a body temperature of 37.8°C was experienced. Two weeks later, he developed memory impairment, mental dullness, speechlessness, and gait disturbance. The duration of levamisole treatment before the onset of neurological symptoms was about 6 weeks, and the total dose was 1800 mg.

Neurological examinations revealed confusion as to time and place, with E4V3M6 on the Glasgow Coma Scale, and a dull mental response with little verbal output. He had primitive reflexes, including glabella signs and snouting reflexes. His neck was rigid, but Brudzinski's and Kernig's signs were not observed. The plantar responses were flexor. Cerebrospinal fluid examination revealed albuminocytologic dissociation, with white cells: 1/mm^3, red cells: 7/mm^3, total protein: 126.4 mg/dL, and a normal sugar level: 76 mg/dL. Electroencephalography (EEG) demonstrated diffuse intermittent slow waves in both hemispheres. A brain computed tomography (CT) scan on April 17 showed a low density at the right frontal lobe. On April 22, a brain MRI with gadolinium demonstrated diffuse multifocal enhancing lesions in the subcortical white matter of bilateral hemispheres and a large right frontal lesion (Fig. 1A). The lesions had low-signal intensity on T1-weighted images (T1WI) and high-signal intensity on T2-weighted images (T2WI).

The neurological symptoms were initially considered as a manifestation of neuro-Behcet's disease and had been treated with methylprednisolone 16 mg and levamisole 150 mg daily since April 18. Unfortunately, his consciousness deteriorated, with E4V1M5 on the Glasgow Coma Scale. He was mute and his mental status became dull during the following 3 weeks. Repeated biochemistries showed an erythrocyte sedimentation rate (ESR): 40 mm/hr, ALT: 626 U/L, AST: 162 U/L, and alkaline phosphatase (Alk-P): 220 U/L. Antibodies for herpes simplex virus (HSV) were all negative, and protein electrophoresis revealed no oligoclonal band. The follow-up brain MRI scan on May 8 disclosed an enlargement of the multifocal irregular white matter lesions (Fig. 1B). Therefore, a neurotoxic effect due to levamisole was suspected; levamisole therapy was ceased and a short course of intravenous dexamethasone therapy (20 mg daily for 7 days) was started, followed by methylprednisolone 24 mg daily. On May 22, the patient could follow orders and gradually improved clinically and neuropsychologically.

One month later, he was orientated to time, place, and person, and he could talk to others and ambulate without assistance. Laboratory examinations revealed an improvement in liver function, including AST, ALT and Alk-P. The repeated brain MRI scan on May 26 showed that the bilateral multifocal cerebral white matter lesions were decreased in size and number. On June 6, he had clear consciousness, but the Mini-Mental Status Examination (MMSE) score was 14 (total score 30), and the neuropsychological tests for executive functions, including the organization of complex figures, working memory, short-time memory retrieval, and reading, were still impaired. On July 3, the MMSE score was 25 and neuropsychological tests showed a prominent improvement, but abstraction, concept forming ability, mental search speed, and semantic category retrieval were still impaired. On July 12, the follow-up brain MRI scan demonstrated prominent sulci and cortical atrophy, and the previous multiple subcortical white matter lesions were in regression (Fig. 1C), as compared with the previous scans. On Dec. 3, the cognitive function tests showed a MMSE score of 30, and a near complete recovery showed in other neuropsychological tests. During a two year period of follow-ups, no other brain abnormalities were noted, except for one episode of genital ulcers.

Case 2

A 38-year-old man had repeated ulcers on the oral mucosa for several years. On Feb. 5, 2004, he visited a dentist. Erosive lichen planus was suspected, and levamisole 150 mg daily was given for 2 days. However, within a few hours of the treatment, he complained of dizziness, confusion, and even getting lost. Lethargy, and an impairment of orientation were experienced in the following few days. These symptoms fluctuated until March 19, when drowsiness, loss of memory, and bitemporal headache were

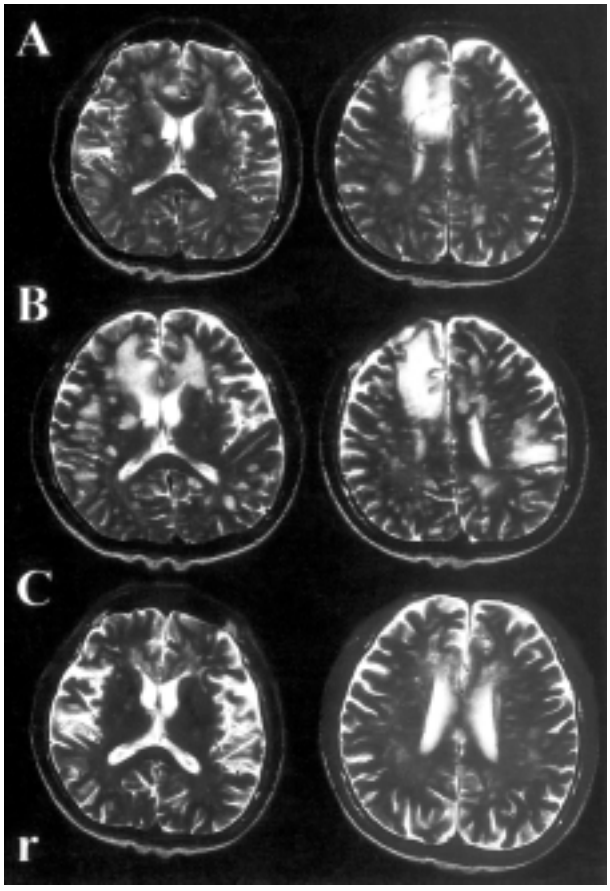

Fig. 1 Serial brain MRI on T2-weighted images in patient 1, with multifocal demyelinating leukoencephalopathy after levamisole therapy. (A) Initial brain MRI on April 22, 2003 revealed a high signal intensity lesion in the right frontal lobe and multifocal subcortical white matter lesions in the bilateral hemispheres. (B) The follow-up brain MRI on May 8 demonstrated a deterioration of the multifocal subcortical white matter lesions. (C) The repeated brain MRI on July 12 showed an improvement with a decrease in size and number of the bilateral cerebral white matter lesions.

observed. On March 23, he could not work or dress himself, and he had progressive memory impairment, incoherent speech, and poor concentration. The total dosage of levamisole was 300 mg. The patient was referred to Chang Gung Memorial Hospital.

On admission to the hospital (March 27), his consciousness was clear. His neck was supple, without either Kernig's sign or Brudzinski's sign. He had impairments in left-right discrimination, calculation, finger agnosia, and naming. His recent memory and cortical sensation, including two-point discrimination in both hands, were impaired. The cranial nerve function, plantar response, and tendon reflexes were normal. The hemograms and other laboratory tests were normal. The cerebrospinal fluid examinations revealed lymphocyte 2/mm^3 sugar: 55 mg/dL, total protein: 56.9 mg/dL, and lactate: 12.4 mg/dL. The protein electrophoresis, immunoelectrophoresis, and herpes simplex virus antigens were all normal. Brain CT disclosed multiple small low attenuation lesions at the left putamen and centrum semiovale regions. In addition, brain MRI also demonstrated multiple small, low-signal intensity areas in the bilateral hemispheres and cerebellum on T1WI, with high signal intensity on T2WI (Fig. 2A). After contrast medium injection, abnormal enhancement was noted in the two hemispheres, the cerebellum, and the pons. In the magnetic resonance angiography, the intracranial large vessels were patent. The EEG showed intermittent diffuse theta waves in the bilateral hemispheres. The studies for metastatic lesions, including whole body bone scan, liver and renal echograms, and tumor markers, were normal.

After admission, his condition continued to deteriorate. He demonstrated confusion as to time, place, and person, silly laughter, dressing apraxia, right and left indiscrimination, acalculia, finger agnosia, agraphia, urinary incontinence, and apathy. Because of the history of levamisole adminstration, MDL was impressed. Therefore, an intravenous administration of dexamethasone 20 mg daily was started on March 30. The condition improved rapidly. The Mini-Mental test scores were 6 on March 31, and improved to 26 on April 3 (total score: 30). He was able to follow verbal orders on April 2, and two weeks later, his orientation to time, place, and person was normal, and dyscalculation, apraxia, agnosia, and memory were also improved. The F-18 fluorodeoxylglucose (FDG) positron emission tomography on April 3 still showed a diffuse decrease of uptake in the bilateral cerebral hemispheres, cerebellum, and basal ganglia. The follow-up brain MRI scan on April 12, showed a resolution of the multiple hyperintensity lesions in the two hemispheres, the cerebellum, and even the brainstem in T2WI (Fig. 2B). On April 27, the T2 high signal intensity lesions showed continued improvement after one month of corticosteroid treatment (Fig. 2C).

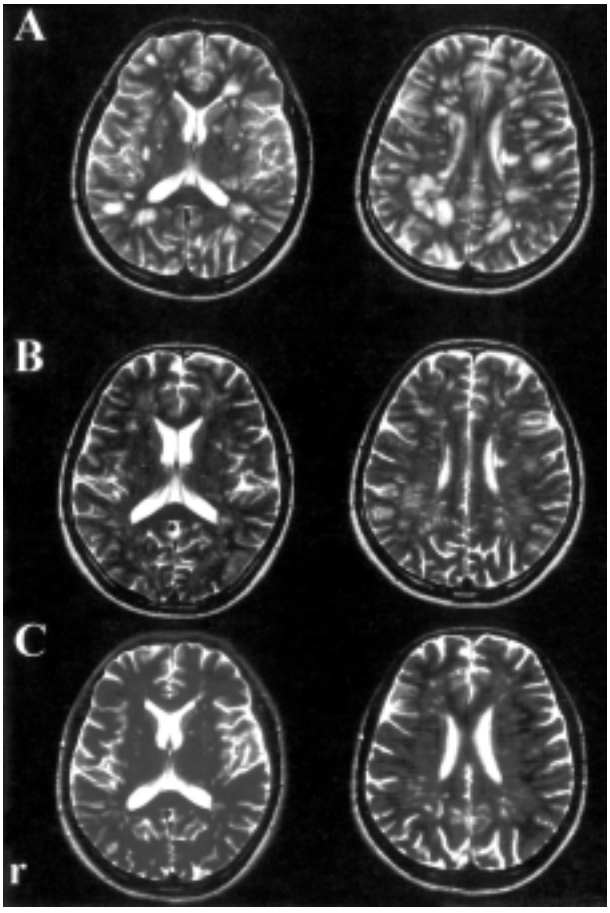

Fig. 2 Serial brain MRI on T2WI in patient 2, with multifocal demyelinating leukoencephalopathy after levamisole therapy. (A) Initial brain MRI on March 29, 2004, showed multiple small high-signal intensity lesions in the subcortical white matter areas of the bilateral hemispheres and basal ganglia. (B) The repeated brain MRI on April 12 revealed a resolution of the high signal lesions. (C) The follow-up scans in April 27, disclosed a nearly complete recovery of the subcortical white matter and basal ganglion lesions.

DISCUSSION

We report the clinical features and MRI changes after levamisole therapy in two patients with either Behcet's disease or erosive lichen planus. We followed up the clinical manifestations and MRI changes after the discontinuation of levamisole therapy. There has been an association between MDL and a combination therapy of 5-FU and levamisole in patients who have received this treatment as an adjuvant therapy for colorectal cancer;[1-5] most of these patients recovered after discontinuing the therapy. Although the pathogenetic role in MDL is unclear, most researchers have considered that 5-FU was the most plausible agent.[6-11] However, Chen et al.[12] reported a patient with colon carcinoma who developed MDL after a combination therapy with 5-FU and levamisole. Despite continuation of 5-FU, resolution of the MDL on MRI occurred when levamisole was stopped. The data indicate that levamisole is possibly the main causative agent. To our knowledge, there have been only 3 cases who demonstrated MDL due to the neurotoxic effects of levamisole.[13-15]

In our patients, the onset of levamisole neurotoxicity was acute or subacute, and the course was progressive, with a latency of 4-6 weeks, which was slightly earlier than that in previous studies.[5-15] The dosages of levamisole in our patients were 300 and 1800 mg, respectively, which were much less than those reported previously, with ranges between 1500 mg and 5400 mg.[5-15] The data indicate that the neurotoxic effect may be idiosyncratic or immune-mediated, instead of dose-dependent. In our patients, the neurological manifestations included dizziness, headache, general malaise, vertigo, lethargy, confusion, memory impairment, dysphasia, gait disturbance, and cortical function impairments. In a large study with levamisole treatment alone, 6 out of 447 patients (1.3%) developed dizziness, headache, vertigo, fatigue, blurred vision, diplopia, impaired coordination, impaired thinking, and even seizures.[4] Other neurological manifestations included ataxia, paresthesia, focal weakness, coma, and even death.[5-15]

The brain MRI scans showed multiple subcortical white matter lesions, which had a non-homogeneous enhancement after contrast medium administration. The brain MRI findings were very similar to those of previous studies in which subcortical white matter lesions were numerous in the periventricular areas, and mainly of an elliptical shape with the long axis perpendicular to the ventricle surface.[13-15] In addition, the improvement in brain MRI findings were well correlated with the clinical features.

The pathogenesis of levamisole neurotoxicity is still not fully understood. Levamisole has immunomodulatory effects, such as the enhancement of antibody production, augmentation of cellular immune responses and chemotaxis, enhancement of

phagocytosis of polymorphonuclear leukocytes, and the increase in delayed type hypersensitivity reactions.[16,17] In experimental studies, treatment with levamisole could induce an augmentation of virus-induced inflammatory demyelination in genetically susceptible mice.[18] Previous experimental studies in Brown Norway rats showed that levamisole administration led to a dose-dependent rise in serum interferon-γ and a fall in the serum immunoglobulin E level.[19] In addition, a detailed analysis of cytokine gene expression revealed an up-regulation of interferon-γ and a down-regulation of interleukin-4 messenger RNA. Furthermore, a marked up-regulation of interleukin-18, which had a potent activity in stimulating interferon-γ production, was also found. The data indicated that levamisole can induce interleukin-18 gene expression, resulting in a resetting of the immune balance to the type 1 response. Therefore, it is believed that levamisole can enhance an immune response to damage myelin.

Prompt diagnosis is very important, because some demyelinating lesions might potentially become permanent with axonal depletion and cavitation. In addition, the differential diagnosis among levamisole-induced MDL, metastatic brain lesions, and other leukoencephalopathies such as multiple sclerosis, acute disseminated encephalitis, and progressive multifocal leukoencephalopathy, is crucial. In patients such as our patient 1, who had a Behcet's disease, it is sometimes difficult to differentiate between neuro-Behcet disease and levamisole-induced MDL. However, a continuous deterioration after prolonged use of Levamisole, and a rapid improvement after a cessation of levamisole treatment, and no more brain abnormalities in the 2-year follow-up period, made the diagnosis of neuro-Behcet's disease unlikely. In patient 2, the important differential diagnosis included metastatic brain lesions. Although the whole body bone scan, liver and renal echograms, and tumor markers were normal, FDG positron emission tomography can provide more information for a primary focus on metastatic lesions. In addition, the diffuse decrease of uptake in the cerebral hemispheres, cerebellum, and basal ganglia indicated the diffused nature of the MDL. Furthermore, it is particularly interesting that levamisole has been used in the treatment of multiple sclerosis.[20] The administration of glucocorticoid may be helpful in the rapid clinical recovery and radiographic resolution of MDL.

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因 levamisole 治療引起多發性脫髓鞘白質病變

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因單獨使用 levamisole 治療而引起神經毒性作用很少被報導。在本文中，我們報告 2 位病患因使用 levamisole 治療而導致多發性脫髓鞘白質病變之臨床表徵、神經心理和核磁共振掃描結果。臨床上病患有頭昏、噁心、嘔吐、意識模糊、心智遲鈍、無法言語和記憶障礙。兩位病患所使用的 levamisole 之劑量分別是 300 毫克和 1800 毫克。症狀的出現常常是急性或亞急性由數小時至數週內發生。早期腦磁振掃描呈現在白質內有廣泛性多發性之顯影劑可加強之病灶。在停止 levamisole 治療後，神經學和神經心理學表現有漸漸好轉的趨勢。同時磁振掃描也呈現穩定的進步。結論：levamisole 治療可引發多發性脫髓鞘白質病變，腦磁振掃描和神經臨床檢查和神經心理學結果可以相互印證。此外早期類固醇治療是很重要，而 levamisole 之神經毒性與藥物劑量並無一致性，而可能與特異體質或免疫有相關。(長庚醫誌 2006;29(4 Suppl):90-6)

關鍵字：多發性脫髓鞘白質病變，levamisole，神經毒性，磁振掃描，神經心理學。

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