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Multiple Sclerosis after Allergen-Specific Immunotherapy and Influenza Vaccination

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Introduction

The safety of influenza vaccination in patients with multiple sclerosis (MS) has been confirmed by several clinical and MRI studies [1–3]. In addition, the frequency of autoreactive T cells against myelin protein did not increase in patients with MS after influenza vaccination [4]. However, caution has been advised for patients with high disease activity [5]. We describe a patient who developed MS after influenza vaccine was given in association with ongoing allergen-specific immunotherapy for allergic rhinitis.

Case Report

A 43-year-old woman with a 2-year history of allergic rhinitis had received allergen-specific immunotherapy against house dust and Japanese cedar once weekly for 6 months. On October 24, 2001, she underwent both influenza vaccination and allergen-specific immunotherapy simultaneously. Ten days later, she experienced back pain and then loss of vision in the left eye and moderate left lower limb weakness. CSF examination showed no oligoclonal bands, but the cell count (70/μl; normal, <5/μl) and myelin basic protein content (1,080 pg/ml; normal, <102 pg/ml) were elevated. MRI demonstrated hyperintense signals in the left optic nerve, the lower left pons, and the left cervicothoracic cord. After gadolinium contrast administration, T₁-weighted sequences showed a decreased enhancement in the left optic nerve. Diagnostic possibilities included either

acute demyelinated encephalomyelitis or a first attack of MS. Complete recovery followed intravenous corticosteroid treatment. Two days after additional allergen-specific therapy on January 11, 2002, she again developed visual loss in the left eye. Vision again improved with intravenous corticosteroid therapy. The patient was then diagnosed with clinically definite MS. After this second episode, allergen-specific immunotherapy was discontinued, and no relapse of MS was recognized during the 15-month follow-up.

Three-Color Flow Cytometry

After the first episode of MS symptoms, we serially studied expression of chemokine receptors, CXCR3 and CCR4, on the surface of peripheral CD4⁺ T cells using three-color flow-cytometric analysis. Peripheral blood mononuclear cells isolated by density gradient centrifugation were stained with combinations of fluorochrome-conjugated specific antibodies against CD3, CD4, CD8 (Pharmingen, San Jose, Calif., USA), CXCR3, and CCR4 (R&D System, Minneapolis, Minn., USA). Stained cells were counted by flow cytometry on a Becton-Dickinson FACS instrument. Recent study has shown a biased Th1/Th2 balance in MS using the analysis of chemokine receptor expression [6]. CXCR3 is expressed on T-helper (Th)1 cells, while CCR4 is expressed on Th2 cells [7, 8]. Thus, the CXCR3/CCR4 ratio is considered a measure of Th1/Th2 balance. Before discontinuing allergen-specific immunotherapy, this ratio exceeded 2, but it decreased by discontinuation of allergen-specific immunotherapy (table 1). Nine months later, the CXCR3/CCR4 ratio still remained below 2 (table 1).

Discussion

MS is a demyelinating disease characterized by chronic inflammation and progressive immune-mediated destruction of the myelin sheath. Many studies have shown correlations between disease progression in MS and Th1 responses. Th1 cytokines including IFN-γ, IL-2, and TNF-α are thought to be crucial for the initiation and amplification of focal brain inflammation and direct myelin damage in MS [9]. On the other hand, the Th2 response is recognized to lead to IgE production, which mediates allergic disease. Allergen-specific

Table 1. CXCR3 and CCR4 expression on peripheral CD4⁺ T cells and CXCR3/CCR4 ratio

	2001	2002				2003
	Dec. 27	Jan. 18	Feb. 15	June 18	Oct. 18	Jan. 8
CXCR3, %	18.4	18.0	20.0	21.9	21.4	18.2
CCR4, %	9.06	7.5	11.8	11.6	11.5	13.9
CXCR3/CCR4 ratio	2.03	2.40	1.69	1.89	1.86	1.31

The percentage of CD4⁺ T cells expressing chemokine receptors were calculated within the T-lymphocyte population.

immunotherapy, which is highly effective in some patients with these diseases including allergic rhinitis, has been demonstrated to decrease IL-4 production by CD4⁺ T cells, and to shift cytokine responses from a Th2 to a Th1 pattern [10, 11]. In the present case, myelin-specific T cells may have been induced by influenza vaccination in the background of an ongoing Th1-biased response mediated by allergen immunotherapy. To our knowledge, this is the first report of MS after treatment with allergen-specific immunotherapy in combination with influenza vaccination. Yet, this case evidences that in some MS patients caution may be applied since MS might be exacerbated by allergen-specific immunotherapy. Because allergen-specific immunotherapy and influenza vaccination are likely to coincide occasionally in other patients, further studies are needed to determine the implications of our findings.

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Simultaneous Occurrence of a Central and a Peripheral Positional Nystagmus during the Dix-Hallpike Manoeuvre

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Peripheral positional nystagmus in the context of posterior canal benign paroxysmal positional vertigo (BPPV) is a common otological disorder. This case report describes its possible and coincidental association with a central positional down-beating nystagmus (DBN) in a patient with obvious neurological disorder.

A 57-year-old man was referred in February 1999 because he had insidiously developed a severe gait disturbance and dysarthria over the last few years. His neurological status had recently aggravated with the apparition of brief positional vertigo, occurring mainly on rising from bed or rolling on the right side when lying flat. His past history was limited to a right ocular traumatism in 1959 with enucleation in 1991. He had no familial history of neurological disease.

Neurological examination revealed a cerebellar ataxia with bilateral dysmetria during finger-to-nose and heel-to-knee tests as well as a marked dysequilibrium with broad-based and ataxic gait. Speech was slurred. Oculomotor examination showed a mild saccadic pursuit. There was no spontaneous nystagmus in the different positions of gaze with or without fixation (Frenzel's glasses). Left Dix-Hallpike and straight head-hanging manoeuvres triggered an immediate and short-lived DBN. Right Dix-Hallpike testing triggered a similar DBN, but after 3–5 s, the nystagmus changed to a strong rotatory up-beating nystagmus in which the upper pole of the eye beat toward the right ear. This latter nystagmus was associated with definite vertigo and both lasted for approximately 10 s. Pure tone audiometry and brainstem auditory-evoked responses were normal. Brain MRI scan showed severe cerebellar and pontine atrophy. There was no Chiari malformation (fig. 1). Cerebrospinal fluid as well as large serum investigations were normal.

The patient was reassessed two more times in June 1999 and April 2002. He had no definite positional vertigo, particularly when rolling on the right side in a supine position, although he complained of slight and short light-headedness triggered by all types of head movements. On these two visits, the right, left and straight head-hanging manoeuvres only revealed an immediate and short-lived positional DBN; the previous rotatory up-beating nystagmus could not be elicited. On the last visit, neurological examination had further deteriorated and showed a bilateral pyramidal syndrome with hyperactive deep tendon reflexes and Babinski's sign on both sides. There was no extra-pyramidal syndrome nor orthostatic hypotension.

The patient initially presented with a cerebellar ataxia and further deteriorated with brainstem involvement. Imaging confirmed an atrophy of the cerebellum as well as the pons. In the absence of any history of similarly affected relatives, the final diagnosis is highly suggestive of an olivopontocerebellar form of multiple system atrophy. The unique feature in this patient was the positioning examination which revealed 2 different types of nystagmus. Firstly, a central positional nystagmus as the nystagmus was immediate, purely vertical and DBN, triggered by right, left and straight head-hanging ma-

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