【Grant-in-Aid for Scientific Research(S)】
Biological Sciences (Medicine, dentistry, and pharmacy Ⅱ)

Title of Project : Establishment of a New Disease Entity as Astrocytopathy, and Studies on the Pathogenesis and Treatment for Neuromyelitis Optica

Yasuto Itoyama
(National Center Hospital, National Center of Neurology and Psychiatry, Director General)

Research Area : Medicine, dentistry, and pharmacy
Keyword : Neuroimmunology

【Purpose and Background of the Research】

Neuromyelitis optica (NMO) is an intractable neurologic disease characterized by recurrent severe optic neuritis and transverse myelitis. Since NMO has been considered a type of multiple sclerosis (MS), and termed optic-spinal MS in Japan, there has been much confusion of its diagnosis and treatment. However, NMO-specific aquaporin 4 (AQP4) antibody was discovered through a collaborative study by our group and Mayo Clinic, and we have suggested that NMO is a distinct entity from MS. Moreover, we found an immunohistological loss of AQP4 in NMO lesions and proposed that NMO is a new disease entity as an immune-mediated astrocytopathy. The objectives of the present study are to establish this disease entity, elucidate the immunopathogenesis, and develop preventive measures and therapies for NMO.

【Research Methods】

1. Establishment of a New Disease Entity for NMO --Immune-mediated Astrocytopathy--

(1)Building clinical entity of NMO:We will analyze the clinical and laboratory data of over 700 NMO cases that we have collected. (2)Classification of brain lesions:Brain lesions in NMO will be classified to clarify the clinical manifestations and frequencies, and the relation with spinal cord lesions and they will be compared with MS.

2. Elucidation of Pathogenesis of NMO --Astrocytopathy targeting AQP4--

(1)Neuropathological analysis: We will examine astrocytic damage unique to NMO by light and electron microscopic analyses of the autopsied brain and spinal cord. (2)Analysis of cerebrospinal fluid (CSF):Levels of astrocyte proteins like glial fibrillar acidic protein and S-100 in CSF will be compared with those of myelin basic protein and neurofilament, for comparison of damage of astrocytes with those of myelins and neurons. (3)Experimental studies (in vitro):Cytotoxicity of AQP4 antibody to cultured astrocytes will be examined. B cell marker analysis and in vitro production of AQP4 antibody by lymphocytes will also be studied. (4)Experimental studies (in vivo):AQP4 antibody will be administered under various circumstances in experimental autoimmune encephalomyelitis will be examined, and the antibody's role in the formation of NMO-like lesions will be analyzed.

3. Prevention of NMO and establishment of therapy

(1)Why AQP4 antibody is produced and how the antibody penetrates the blood-brain barrier remain unclear. We will study viral infections and antigens homologous to AQP4 to reveal the mechanism of the antibody production. (2)Building diagnosis and treatment system:We will promote early diagnosis of NMO including AQP4 antibody tests, and develop therapies, such as low-dose corticosteroids to prevent relapse, and improve the patients' QOL.

【Expected Research Achievements and Scientific Significance】

The present study will be of great significance by clarification of the pathogenesis of astrocytopathy in NMO and by development of the preventive measures and new therapies. Since the proportion of NMO patients is higher in Japan and other Asian countries than those in Western countries, the patients and families long for the establishment of effective prevention and therapy of NMO.

【Publications Relevant to the Project】

- Misu T, Fujihara K, Kakita A, et al. Loss of aquaporin-4 in lesions of neuromyelitis optica: distinction from multiple sclerosis. Brain, 130:1224-1234, 2007.
- Takahashi T, Fujihara K, Nakashima I, et al. Anti-aquaporin-4 antibody is involved in the pathogenesis of NMO: a study on antibody titer. Brain, 130:1235-1243, 2007.

【Term of Project】 FY2010-2014

【Budget Allocation】 150,600 Thousand Yen

【 Homepage Address and Other Contact Information】

http://www.ms.med.tohoku.ac.jp/index.html