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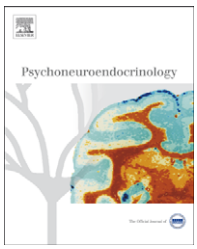

Blood-brain barrier damage as a risk factor for corticosteroid-induced psychiatric disorders in systemic lupus erythematosus

Katsuji Nishimura[a,*], Masayoshi Harigai[b], Masako Omori[a], Eri Sato[c], Masako Hara[c]

[a]*Department of Psychiatry, Tokyo Women's Medical University School of Medicine, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan*
[b]*Clinical Research Center and Department of Rheumatology, Tokyo Medical and Dental University School of Medicine, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan*
[c]*Institute of Rheumatology, Tokyo Women's Medical University School of Medicine, 10-22 Kawada-cho, Shinjuku-ku, Tokyo 162-0054, Japan*

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Summary
To clarify the incidence of and risk factors for corticosteroid-induced psychiatric disorders (CIPDs) in patients with systemic lupus erythematosus (SLE), we conducted a prospective study of 161 consecutive episodes in 155 inpatients with a SLE flare who were treated with corticosteroids. A subgroup of these patients, those who experienced a total of 22 episodes with current overt central nervous system manifestations of SLE (CNS-SLE), were excluded from follow-up. Results of clinical, laboratory, and neurologic tests (including electroencephalography, magnetic resonance imaging of the brain, and cerebrospinal fluid [CSF] analysis), performed within a week before corticosteroid administration, were assessed with regard to development of CIPDs. Within 8 weeks of corticosteroid administration, a diagnosis of CIPD was made for 14 (10.1%) of 139 episodes in 135 patients with a non-CNS-SLE flare. Using multiple logistic regression analysis, we identified positive $Q_{albumin}$ (CSF/serum albumin ratio; an indicator of blood-brain barrier [BBB] damage) (odds ratio [OR], 33.3; 95% confidence interval [CI], 3.64–304; $p = 0.002$) and low serum levels of complements (OR, 0.91; 95% CI, 0.83–1.00; $p = 0.047$) as independent risk factors for CIPDs. Positive $Q_{albumin}$ was detected in 45% (5 of 11) of episodes in which CIPDs developed. Compared with episodes in which no psychiatric events occurred, a higher level of $Q_{albumin}$ was found in episodes in which CIPDs developed, and an even higher level was noted in

*Corresponding author. Tel.: +81 3 3353 8111; fax: +81 3 3351 8979.
E-mail address: knishimura@psy.twmu.ac.jp (K. Nishimura).

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episodes with active CNS-SLE (Jonckheere-Terpstra test, $p<0.001$). Although no causal links have been proven, the results from the present study raise the possibility that BBB damage may be associated with SLE- and corticosteroid-induced behavioral changes.

1. Introduction

Corticosteroids are the cornerstone of treatment for various inflammatory and immunologically mediated disorders, such as systemic lupus erythematosus (SLE). Despite widespread use, corticosteroid treatment is frequently associated with adverse psychiatric effects, including affective disorders, psychotic disorders, and delirium (Wolkowitz et al., 1997; Patten and Neutel, 2000). SLE is associated with a high incidence of psychiatric manifestations (West, 1994; Ainiala et al., 2001; Brey et al., 2002; Hanly et al., 2004).

It is unknown whether this association is a direct consequence of systemic autoimmunity and inflammation (e.g., entry of immune cells and molecules into the central nervous system [CNS]), an indirect effect (e.g., an epiphenomenon associated with accumulation of toxic metabolites), or a consequence of immunosuppressive therapy with corticosteroids (Kohen et al., 1993; Denburg et al., 1994; Wolkowitz et al., 1997)—because of similar or identical psychopathology (ACR Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature, 1999; Patten and Neutel, 2000) and because no diagnostic gold standard of CNS manifestations of SLE (CNS-SLE) exists (West, 1994; ACR Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature, 1999). Hypoalbuminemia has been demonstrated to be a risk factor for corticosteroid-induced psychiatric disorders (CIPDs) in SLE patients (López-Medrano et al., 2002; Chau and Mok, 2003), but the proposed mechanism remains speculative.

In general, brain damage or disease of any etiology may predispose a person to substance-induced psychiatric disorders such as delirium (Lipowski, 1990). Several abnormal findings associated with CNS involvement in SLE, including abnormal electroencephalographic findings, magnetic resonance images of the brain, and cerebrospinal fluid (CSF) findings, are observed in SLE patients, regardless of whether they exhibit current overt neuropsychiatric symptoms (West, 1994). Although this clinical or subclinical CNS involvement due to SLE might predispose a patient to CIPDs, to our knowledge, no clinical studies from this viewpoint have been reported.

The purpose of the present study was to clarify the incidence of and risk factors for CIPDs in SLE patients, especially with regard to potential CNS involvement in SLE.

2. Methods

2.1. Study design

First, to identify the incidence of CIPDs in SLE patients, we prospectively followed for 8 weeks consecutive inpatients with a non-CNS-SLE flare who were treated with corticosteroids. Second, to identify risk factors for CIPDs, we evaluated clinical, laboratory, and neurologic variables within a week before corticosteroid administration and compared them between groups that developed CIPDs and those that did not. Finally, to evaluate potential CNS involvement in SLE in patients developing CIPDs, we compared neurologic variables for these patients and for patients with active CNS-SLE.

2.2. Study population

From August 1999 to December 2004, we prospectively followed consecutive SLE patients who were treated with corticosteroids for the first time or in augmented doses in the Rheumatologic Unit of Tokyo Women's Medical University Aoyama Hospital. In total, 161 courses of corticosteroids were administered for 161 episodes of first or recurrent manifestations of SLE in 155 patients (150 women, 5 men). Six patients required a second hospitalization because of another manifestation of SLE, and received a second course of therapy during the study period. Of the 161 episodes, 75 (47%) occurred in patients whose SLE had not been previously treated with corticosteroids. The mean dosage of corticosteroids administered was 50.8 mg/day (standard deviation [SD], 19.6; range, 15–150) or 0.98 mg/kg/day (SD, 0.40; range, 0.27–2.59) as prednisolone. In addition, IV methylprednisolone pulse therapies were initially conducted in 48 (30%) of 161 episodes: 0.5 g/day for 3 days in 20 episodes and 1 g/day for 3 days in 28 episodes. Patients who showed any symptoms due to CNS-SLE at the time of administration of corticosteroids were excluded from follow-up, whereas patients with only peripheral neurologic symptoms were included. All patients in this study were Japanese and fulfilled the American College of Rheumatology 1982 revised criteria for SLE (Tan et al., 1982).

2.3. Definition of CIPDs and psychiatric evaluation

CIPDs were defined as new-onset psychiatric symptoms that developed within 8 weeks of initiation or augmentation of corticosteroid therapy and that resolved completely through a reduction in corticosteroid dosage and without additional immunosuppressive agents, as defined in a previous study (Chau and Mok, 2003). The psychiatric events in our unit were evaluated at regular intervals (once a week) by experienced psychiatrists (K.N. and M.O.) using the criteria for substance-induced disorders in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) (American Psychiatric Association, 1994). Except for substance-induced sexual dysfunction and sleep disorder, the following phenomenological subtypes of substance-induced psychiatric disorders from the DSM-IV were used: substance-induced delirium, persisting dementia, persisting amnestic disorder, psychotic disorder, mood disorder, and anxiety disorder. According to the DSM-IV, the disturbances