Long-term Outcomes of CLIPPERS (Chronic Lymphocytic Inflammation With Pontine Perivascular Enhancement Responsive to Steroids) in a Consecutive Series of 12 Patients

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Background: Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) is a central nervous system inflammatory disease.

Objective: To describe the disease course of CLIPPERS.

Design: A nationwide study was implemented to collect clinical, magnetic resonance imaging, cerebrospinal fluid, and brain biopsy specimen characteristics of patients with CLIPPERS.

Setting: Academic research.

Patients: Twelve patients with CLIPPERS.

Main Outcome Measures: The therapeutic management of CLIPPERS was evaluated.

Results: Among 12 patients, 42 relapses were analyzed. Relapses lasted a mean duration of 2.5 months, manifested frequent cerebellar ataxia and diplopia, and were associated with a mean Expanded Disability Status Scale (EDSS) score of 4. Besides typical findings of CLIPPERS, magnetic resonance imaging showed brainstem mass effect in 5 patients, extensive myelitis in 3 patients, and closed ring enhancement in 1 patient. Inconstant oligoclonal bands were found on cerebrospinal fluid investigation in 4 patients, with an increased T-cell ratio of CD4 to CD8. Among 7 available brain biopsy specimens, staining was positive for perivascular CD4 T lymphocytes in 5 samples. Thirty-eight of 42 relapses were treated with pulse corticosteroid therapy, which led to improvement, with a mean residual EDSS score of 1.9 (range, 0-7). In 1 patient without untreated relapses, scores on the EDSS progressively increased to a score of 10 at death. Among 5 patients without long-term corticosteroid therapy, the mean annualized relapse rate was 0.5 (range, 0.25-2.8). Among 7 patients taking oral corticosteroids, no relapses occurred in those whose daily dose was 20 mg or higher. No progressive course of CLIPPERS was observed. Four patients with a final EDSS score of 4 or higher had experienced previous severe relapses (EDSS score, ≥5) and brainstem and spinal cord atrophy.

Conclusions: CLIPPERS is a relapsing-remitting disorder without progressive forms. Long-term disability is correlated with the severity of previous relapses. Further studies are needed to confirm that prolonged corticosteroid therapy prevents further relapses.

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pions) on magnetic resonance (MR) imaging, and (3) T-lymphocytic infiltrate with perivascular predominance in brain biopsy specimens. Pittock et al1 suggested
that CLIPPERS diagnosis could be made without brain biopsy if clinical and MR imaging features of the disease were present and if alternative diagnoses were excluded. Since then, 15 additional cases of CLIPPERS have been reported.2-10

We describe 12 patients with CLIPPERS who were consecutively identified through a nationwide study. The aims of the present study were to further analyze the clinical features, disease course, MR imaging, cerebrospinal fluid (CSF) findings, and brain biopsy specimen characteristics of patients with CLIPPERS and to propose a therapeutic management.

METHODS

The study inclusion criteria were the following: (1) recurrence of brainstem symptoms, (2) punctuate and curvilinear gadolinium-enhancing lesions involving the pons or middle cerebellar peduncle on MR imaging, (3) clinical and radiological response to corticosteroids, and (4) no evidence of alternative CNS disease. A brain biopsy specimen was obtained if clinical or MR imaging criteria were not fulfilled. Twelve patients from 9 university multiple sclerosis centers were included to assess multiple sclerosis diagnosis. Early in the disease course, multiple sclerosis diagnosis was clearly excluded in all 12 patients. For each patient, data were retrospectively analyzed since the multiple sclerosis diagnosis was clearly excluded in all 12 patients. Twelve patients from 9 university multiple sclerosis centers were included to assess multiple sclerosis diagnosis. Early in the disease course, multiple sclerosis diagnosis was clearly excluded in all 12 patients. For each patient, data were retrospectively analyzed since the onset of their disease. Two of 12 patients included herein were previously described.2,9

CLINICAL EVALUATIONS

The following patient characteristics were collected: sex, age at onset, and personal and family history of autoimmune disease. Neurological and systemic signs during relapses and relapse duration and severity using the Expanded Disability Status Scale (EDSS) were analyzed. Based on patients' EDSS scores after the treatment of relapses, their disease was categorized as resistant to corticosteroids (when the EDSS score was unchanged) or as responsive to corticosteroids (when the EDSS score stabilized or improved). Patients' EDSS scores were obtained at the following time points: during relapses, between relapse-free periods (residual EDSS score), and at the end of the follow-up period (last EDSS score). Fatigue, weight loss (>10% of the initial body weight), and depression (according to Diagnostic and Statistical Manual of Mental Disorders [Fourth Edition] criteria) were considered possible systemic features. Acute treatment included high doses of corticosteroids (oral or intravenous). When corticosteroid treatment was continued for more than 2 months, it was considered long-term corticosteroid therapy. Patients were categorized as not receiving long-term corticosteroid therapy or as receiving long-term corticosteroid therapy.

LABORATORY TESTS

All patients underwent laboratory screening that included complete blood cell count, renal and liver function, creatine kinase and low-density lipoprotein cholesterol levels, C-reactive protein level, erythrocyte sedimentation rate, serum protein electrophoresis, immunofixation, thyroid hormone levels, and urinalysis. Autoimmune serological evaluations included antinuclear and anti–extractable nuclear antigen antibodies, rheumatoid factor, complement levels, cryoglobulinemia, antineutrophil cytoplasmic antibodies, lupus anticoagulant, anti–beta2-glycoprotein 1 and anti-cardiolipin antibodies, angiotensin-converting enzyme, anti–aquaporin 4 antibody, thyroid autoantibodies, and onconeural antibodies (anti-Yo, anti-Hu, anti-Ri, anti-Tr, anti-Ma2, anti-amphiphysin, and anti-CV2 antibodies). Five patients were screened for anti-GQ1b antibody. Virological and bacteriological examination included hepatitis C virus, hepatitis B virus, human immunodeficiency virus, VDRL test, and Treponema pallidum hemagglutination, and Borrelia burgdorferi serological evaluations were systematically performed. Results for all these laboratory tests were normal or negative. All patients underwent CSF analysis, including immunoelectrophoresis. Cerebrospinal fluid lymphocyte phenotyping was performed in 4 patients.

IMAGING

Brain MR imaging (1.5 T) was performed, including T1-weighted, T2-weighted, fluid-attenuated inversion recovery, T2-weighted gradient-echo images, and diffusion-weighted images, as well as apparent diffusion coefficient, time-of-flight MR angiography, and gadolinium-enhanced T1-weighted imaging. All patients underwent at least 1 spinal cord MR imaging session, including gadolinium-enhanced T1-weighted imaging. Localization, size, gadolinium enhancement, and mass effect of the lesions were analyzed during relapses. Based on changes in the size or number of lesions after the treatment of relapses (using T2-weighted and gadolinium-enhanced T1-weighted sequences), lesions were categorized as resistant to corticosteroids (when lesions were unchanged) or as responsive to corticosteroids (when the size or number of lesions decreased or gadolinium enhancement decreased or disappeared). At the end of the follow-up period, the presence of atrophy, black holes, and cystic cavities was assessed. Thoracoabdominopelvic computed tomography and whole-body positron emission tomography with 18F-fluorodeoxyglucose were performed in all patients, and these findings were normal.

PATHOLOGICAL INVESTIGATIONS

In 7 patients, cerebral biopsy specimens were obtained. Histological sections were stained with hematoxylin–eosin, with Bielschowsky stain, and for the following antigens: CD3, CD20, CD68, CD38, CD138, CD1a, beta-amyloid, neurofilament, and glial fibrillary acid protein. In 5 patients, histological sections were also stained for CD4, CD8, and granzyme B.

RESULTS

SYMPTOMS AND CLINICAL SIGNS DURING RELAPSES

Twelve patients (9 men and 3 women) of white race/ethnicity met the diagnostic criteria for inclusion in the study. Their clinical features are summarized in the Table. The mean age at the onset of symptoms was 46.5 years (age range, 13-64 years). After a mean follow-up period of 5.5 years (range, 0.5-34 years), 42 relapses (mean, 0.63 annual relapses per patient) had occurred. Relapses consisted of isolated brainstem signs (33 relapses), brainstem and spinal cord signs (8 relapses), and isolated spinal cord signs (1 relapse). Cerebellar ataxia (in 31 relapses), diplopia (in 16 relapses), and gaze-evoked nystagmus (in 13 relapses) were the most frequent symptoms during relapses. At the end of the follow-up period, all patients had experienced at least 1 relapse with brainstem signs, and 4 of 12 patients had experienced at
DURATION, SEVERITY, AND RESPONSE TO CORTICOSTEROID TREATMENT DURING RELAPSES

Of 42 relapses, 38 relapses were treated with high doses of corticosteroids (intravenous methylprednisolone acetate in 29 relapses and oral prednisone in 9 relapses). Four relapses (in 3 patients) were not treated, with variable evolution that included recovery without sequelae (patient 5), recovery with sequelae (patient 4), and worsening to an EDSS score of 10 at death (patient 3).

During relapses, the mean time between the onset of symptoms and the maximum EDSS score was 2.5 months (range, 0.25-18 months). The mean EDSS score during relapses was 4 (range, 3-10), and the mean residual EDSS score after relapses was 1.9 (range, 0-7). In 38 relapses treated with corticosteroids, progressive EDSS score worsening was seen until pulse corticosteroid therapy was initiated (Figure 1). During 2 relapses in patient 6, very high corticosteroid doses (intravenous methylprednisolone [1 g once daily] for 6 days and 10 days, respectively) were needed to obtain clinical improvement. For all relapses, corticosteroid treatment was successful. Clinical improvement was observed within 2 weeks following the start of corticosteroid therapy and had a similar course in intravenously and orally treated patients.

At the end of the follow-up period, the mean EDSS score was 3.8 (range, 0-10), with only one asymptomatic patient (patient 11, with an EDSS score of 0). These results are summarized in Figure 2 and Figure 3.

LONG-TERM CORTICOSTEROID THERAPY

Patients 1 through 5 did not receive long-term corticosteroid therapy, and patients 6 through 12 received long-term corticosteroid therapy. The follow-up results in patients 1 through 5 suggest the natural history of this disease (Figure 2). The mean annualized relapse rate was 0.5 (range, 0.25-2.8).

In patients receiving long-term corticosteroid therapy, no relapse occurred when the daily dose was 20 mg or higher. As seen in patient 11 and patient 12, relapse-free periods were longer when corticosteroid weaning was slower (Figure 3).

Comparison was difficult because of a difference in the mean follow-up period between patients not receiving long-term corticosteroid therapy (130 months; range, 16-408 months) vs patients receiving long-term corticosteroid therapy (20 months; range, 6-53 months). Severe relapses (defined as an EDSS score of ≥5) were more frequent in patients not receiving long-term corticosteroid therapy (severe relapse occurred in 3 patients) than in patients receiving long-term corticosteroid therapy (severe relapse occurred in 1 patient), and long-term evolution was more severe in patients not receiving long-term corticosteroid therapy.
therapy (3 patients had a last EDSS score of ≥6.5) than in patients receiving long-term corticosteroid therapy (1 patient had a last EDSS score of 4.5).

Relapsing-remitting evolution was constant in all 12 patients. No progressive form was observed.

MONOCLONAL ANTIBODY AND IMMUNOSUPPRESSIVE MEDICATIONS

Three of 12 patients received additional immunosuppressive drugs. These included 1 cycle of anti-CD20 monoclonal antibody (intravenous rituximab [375 mg/m²] twice weekly for 4 weeks) (in patient 5) and 6 intravenous cycles of cyclophosphamide (1 g monthly for 6 months) (in patient 4 and patient 12). Among these 3 patients (patients 4, 5, and 8), only patient 4 experienced a relapse 1 month after immunosuppressive treatment.

NEUROIMAGING

A mean of 7 (range, 4–16) brain MR imaging sessions per patient was performed. Each patient underwent MR imaging during and after each relapse.

Distributions of lesions seen on T2-weighted and gadolinium-enhanced T1-weighted images during relapses are shown in eFigure 1 (http://www.archneurol.com). During relapses, MR imaging revealed brainstorm involvement in all patients and showed characteristic punctuate and curvilinear gadolinium enhancement in the pons or middle cerebellar peduncle (eFigure 2). In most cases, the gadolinium-enhancing lesions decreased in number as the distance from the pons increased. They predominantly involved pontocerebellar and corticospinal tracts. These abnormalities were seen from the first relapse in all patients except patient 5, in whom typical MR imaging features of CLIPPERS were observed at 9 years after the onset of disease (during a 12th relapse). The mean size of the gadolinium-enhancing lesions was 1 to 3 mm (eFigure 1); few lesions exceeded 3 mm. Gadolinium-enhancing lesions exceeding 3 mm had a typical nodular aspect (Figure 4A). Only one lesion with closed ring enhancement was observed (Figure 4B). Increased T2-weighted signal was present in the corresponding gadolinium-enhancing lesions but often exceeded 3 mm, with a tendency to confluence (Figure 4C and D). Lesions affected white matter (ie, corticospinal tract and corpus callosum) and gray matter (ie, dentate nucleus, basal ganglia, and hippocampus), although cortical and cerebellar cortex and red nucleus were spared. Cerebellar, supratentorial, and spinal cord involvement were seen in 10 patients, 8 patients, and 4 patients, respectively. Juxtacortical (but not cortical) lesions were seen in 4 patients (Figure 4E and F). Spinal cord involvement was variable, ranging from small punctuate lesions at 1 vertebral level (patient 10) to large confluent lesions involving a maximum of 3 vertebral levels (patients 4, 5, and 8) (Figure 4G and H). Pons or middle cerebellar peduncle swelling was seen in 5 patients (Figure 4I).
Using gadolinium-enhanced T1-weighted imaging, response to corticosteroid therapy was observed during all relapses. Using T2-weighted imaging, response to corticosteroid therapy was observed during all relapses except 2. At the end of the follow-up period, additional MR imaging features were noted, including brainstem atrophy, spinal cord atrophy, and black hole in the cerebellum (Figure 4J, K, and L). Cystic aspect, leptomeningeal or pachymeningeal involvement, microbleeds, or decrease in the apparent diffusion coefficient was not observed.

CSF FINDINGS

Twenty-nine CSF samples were obtained from 12 patients. Twenty-six were obtained during relapses, and 3 were obtained between relapses.

In 26 CSF samples obtained during relapses, elevated protein level was the most frequent abnormality.
Protein levels were between 0.05 and 0.1 g/dL in 18 samples, greater than 0.1 g/dL in 1 sample, and normal (≤0.05 g/dL) in 7 samples (to convert protein level to grams per liter, multiply by 10.0). White blood cell counts were greater than 50/µL in 3 samples, between 3 and 49/µL in 11 samples, and normal (≤3/µL) in 12 samples (to convert white blood cell count to ×10⁹/L, multiply by 0.001). Intrathecal synthesis of oligoclonal bands (OBs) was observed in 6 of 26 samples during relapses (in patients 3, 4, 5, and 9). The presence of OBs varied during relapses (observed during relapses 1 and 2 in patient 3, relapse 2 in patient 4, and relapses 9 and 12 in patient 5); they disappeared in later events (relapse 3 in patient 3 and relapses 10 and 11 in patient 5). The CSF T-cell ratio of CD4 to CD8 was obtained in 4 patients, showing a high ratio (normal range, 1.6-2.4) in 3 of them (3.4 in patients 2 and 12 and 5.8 in patient 9).

Three CSF samples obtained between relapses showed mild elevated protein level (0.07 g/dL) in 1 sample and mild pleocytosis in 2 samples (5-9/µL, with lymphocyte predominance). Oligoclonal bands were not observed.

Patients 1, 3 through 7, and 9 underwent stereotactic brain biopsy (6 in the posterior fossa and 1 in the frontocerebral hemisphere), without adverse effects. All biopsy specimens revealed parenchymal and perivascular inflammatory infiltrates without demyelination, granulomatous inflammatory, or necrotizing vasculitis pattern. These infiltrates were predominantly composed of T cells (CD3 positive) in 6 patients and of T cells (CD3 positive) and microglia (CD68 positive) in patient 7. Histological sections from 5 patients with marked T-lymphocyte infiltration were also stained for CD4, CD8, and granzyme B and showed increased CD4 T cells associated with few CD8 T cells and very little or absent granzyme B (Figure 5). Some microglia were observed in 6 samples, some B cells (CD20 positive) in 3 samples, some plasmocytes (CD38 or CD138 positive) in 2 samples, some neutrophils in 2 samples, and reactive
gliosis (glial fibrillary acid protein positive) in 2 samples. The results of immunohistochemistry for CD1a were negative. No evidence of β-amyloid deposits was seen. In 2 of 7 biopsy specimens (from patients 5 and 6), axonal swelling and torpedoes, together with some focal secondary demyelination, were observed in the vicinity of inflammatory perivascular lesions; it was not possible to make conclusions about the other 5 patients.

PROGNOSTIC CRITERIA

Patients 3 through 6 had a severe last EDSS score of 4.5 or higher. Patients 4 and 5 had brainstem and spinal cord atrophy, and all 4 patients experienced 1 or more severe relapses (EDSS score, ≥5). The other 8 patients had a less severe course. Annualized relapse rates, CSF findings, and brain biopsy results did not differ between the 2 groups of patients.
This study furthers our understanding of CLIPPERS. During a mean follow-up period of 5.5 years, 42 relapses were observed in 12 patients. During relapses, symptoms occurred progressively during a mean duration of 2.5 months. The mean EDSS score during relapses was 4. All patients had a relapsing-remitting disease course, with a mean annualized relapse rate of 0.5. Although all relapses were sensitive to high doses of corticosteroids, two-thirds of relapses left sequelae (mean EDSS score, 1.9). Progressive clinical worsening was seen during relapses until corticosteroid treatment was started. One patient who did not receive corticosteroid treatment died. No relapses occurred among 7 patients whose long-term daily dose of corticosteroids was 20 mg or higher. Relapse-free periods were longer when corticosteroid weaning was slower. Secondary progression was not observed. When a patient with signs of CLIPPERS fails to respond to corticosteroids, other diagnoses should be considered (eg, low-grade glioma or primary central nervous lymphoma). No secondary progression was seen between relapses. The median EDSS score at the end of the follow-up period was 3.

Several previously undescribed MR imaging features were seen in some of our patients during relapses, including pons or middle cerebellar peduncle swelling, closed ring enhancement, and normal initial MR imaging. At the end of the follow-up period, additional MR imaging features were seen in some patients, primarily extensive spinal cord involvement, followed by spinal cord atrophy and black holes. Pontocerebellar atrophy was also seen, confirming recently reported cases of CLIPPERS. In contrast to previous findings, brainstem mass effect was observed during some relapses in the present study. Therefore, mass effect is not typical but does not exclude CLIPPERS diagnosis. Notably, cavitary aspects were not found herein, in contrast to the study by Duprez and Sindic.

Oligoclonal bands were present in 4 of 12 patients, only during relapses. Evolution of OBs is variable; they can appear or disappear during and following relapses in the same patient, confirming CSF findings previously described in 2 isolated cases of CLIPPERS. The T-cell ratio of CD4 to CD8 in CSF (not analyzed previously) was increased in 3 of 4 CSF samples herein.

Brain biopsy specimens in our patients demonstrated classic T-cell infiltrates. Staining for CD4, CD8, and granzyme B showed increased CD4 T cells in 5 of 7 samples, similar to findings by Simon and colleagues in their recent publication reporting 5 cases of CLIPPERS. Relapses with an EDSS score of 5 or higher and brainstem or spinal cord atrophy seemed to be associated with severe long-term disability. In contrast, annualized relapse rates of relapses, CSF findings, and brain biopsy results in our patients were unrelated to final EDSS scores.

These data suggest that pulse corticosteroid treatment has to be started as early as possible during a relapse to limit clinical worsening during the relapse, followed by progressive tapering. High-dose (>20 mg once daily) long-term corticosteroid therapy seems to prevent further relapses. To avoid corticosteroid-related adverse effects, other immunosuppressive treatment may be proposed. In some reported cases of CLIPPERS, effective immunosuppressive maintenance treatment to prevent relapses (after complete corticosteroid withdrawal) was described using methotrexate in 4 patients and cyclophosphamide in 1 patient. Three of our patients (2 patients with cyclophosphamide and 1 patient with anti-CD20 treatment) became relapse free after add-on immunosuppressive treatment. However, one of these (patient 4) experienced a new relapse at 16 months after pulse cyclophosphamide therapy, suggesting that cyclophosphamide only suspends the symptoms. The efficacy of other immunomodulatory or immunosuppressive therapies (ie, hydroxychloroquine sulfate, mitoxantrone hydrochloride, immune globulin intravenous pentetate, azathioprine, and mycophenolate mofetil) has not been proven.

The pathogenesis of CLIPPERS is unknown. Characteristic imaging patterns of punctuate enhancement involving white matter and gray matter, together with perivascular inflammatory infiltrate in brain biopsy specimens, favor an inflammatory disorder with a vascular or perivascular tropism. Considering the anatomic arrangement of small intra-axial veins of the CNS, the predominant involvement of brainstem structures might be related to a primary CNS venous inflammatory disorder. To explain the particular features of CLIPPERS, Pittock and colleagues suggest a specific immune-mediated process directed against an epitope localized in the pons. The appearance or disappearance of OBs during and following relapses in the same patient suggests an immune process different from that described in multiple sclerosis. Effectors of the inflammatory process seem to be T lymphocytes, with a predominant involvement of brainstem structures, as seen in CSF samples and brain biopsy specimens in the present study. Further studies are needed to confirm that prolonged corticosteroid therapy is the optimal means to prevent further relapses. 

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