The expanding phenotype of CLIPPERS : Is it a disease or a syndrome?

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Expanding phenotype of CLIPPERS indicates it to be a disease or a syndrome?

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Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) is a newly named condition of pontine-centric inflammatory disorder.[1)] The cardinal feature of the disease is punctate gadolinium enhancement "peppering" the pons on magnetic resonance imaging (MRI). The unique MRI features

have attracted many neurologists' attention and several case reports were followed.[2)-5)] Biopsied pontine pathology of the original study revealed a marked perivascular and parenchymal CD3-postive T cell inflammation without any specific pathology.[1)] However, because of a lack of specific biomarker and a long term follow-up, nosological position of CLIPPERS is still to be established.

The paper by Simon and colleagues[6)] (see page XX) report five additional cases of CLIPPERS with detailed pathology and long term evaluation in this issue, expanding the clinical, neuroimaging and pathological phenotype; (1) Cognitive impairment was seen in four of five cases accompanied with cerebral atrophy in three of them. (2) MRI lesions distributed not only the pons but also the brachium ponti and cerebellum, later culminating in severe atrophy of cerebellum and brachium ponti. (3) prominent CD4-positive T lymphocytic as well as histiocytic infiltrate involving both small arteries and veins but with few B cells. Neuro-axonal injury was also found while there was no evidence of vasulitis (destruction of the vessel wall with fibrinoid necrosis).[6)] Based on the distribution of MRI lesions, they propose an amendment of the title to Chronic Lymphocytic Inflammation with *Pontocerebellar* Perivascular Enhancement Responsive to Steroids (CLIPPERS).[6)] Lesions may occur in the spinal cord, basal ganglia or cerebral white matter. Perivascular gadolinium enhancement pattern and

steroid-responsiveness indicate autoimmune/inflammatory nature of this condition. These authors[6] and others[1] carried out extensive laboratory and pathological surveys excluding specific causes for the conditions, such as sarcoidosis, histiocytosis, lymphoma, granulomatosis, multiple sclerosis, isolated angiitis of the CNS, Lyme disease, Whipple disease, Bickerstaff brainstem encephalitis, Behcet's disease and Sjögren syndrome, suggesting CLIPPERS is an independent disease entity.

However, there appears to be some overlap with other autoimmune/inflammatory brainstem-predominant encephalitis, especially, brainstem type of neuro-Behcet's disease and Sjögren syndrome. Pittock and colleagues[1] found no evidence of systemic illness while Simon and colleagues[6] reported additional subclinical systemic findings in some cases, namely anti-nuclear antibody, SS-A, lymphocytic conjunctival infiltrate, lymphocytic sialadenitis, and parotid uptake on gallium scan. Neuro-Behcet's disease is well known to frequently affect pons and cerebellum. Neruo-Behcet's disease occasionally presents without apparent mucocutaneo-ocular manifestations,[7, 8] showing progressive cerebellar ataxia and prominent pontine and cerebellar atrophy. Such patients can also be benefitted by early steroid therapy. Cognitive impairment first described by Neil and colleagues[6] in CLIPPERS is also frequently encountered in Behcet's disease. On MRI, enhancement

of lesions in the pons and middle cerebellar peduncles frequently show mottled non-confluent pattern similar to that of CLIPPERS.[9)-11)] On chronic stage, severe atrophy of the basis pontis and cerebellum is common. Pathologically, Behcet's disease shows perivascular infiltration of T cells and macrophages/monocytes with few B cells, mainly involving venules but also occasionally small arteries.[12)] Examinations of needle reaction, HLA-DR51, and IL-6 in the cerebrospinal fluid are warranted for differentiating brainstem type of neuro-Behcet's disease from CLIPPERS. So far all cases with CLIPPERS have been reported from Western countries. Behcet's disease is prevalent in Mediterranean countries, Middle East, and Japan. It is interesting to know if there is any racial preponderance for this condition.

Cerebellar and brainstem involvement has also been repeatedly reported in Sjögren's syndrome,[13)-15)] while sicca symptoms may not be clinically overt. MRI features of brainstem involvement in primary Sjögren syndrome occasionally presents punctate gadolinium-enhancing foci peppering the pons, middle cerebellar peduncles, cerebellar hemispheres and vermis, and mesencephalon, which are quite similar to those of CLIPPERS.[15)] Subclinical involvement of exocrine glands found in some CLIPPERS cases[6)] suggests a possibility that pontocerebellar involvement of CLIPPERS could be the first manifestation of certain systemic diseases, such as Sjögren's syndrome. Since

sicca symptoms are frequently subclinical, and SS-A or SS-B could be negative in Sjögren's syndrome, minor salivary gland biopsy may be recommended. Thus, CLIPPERS could be a syndrome with heterogeneous etiologies.

One curious finding is that T2-high lesions did not significantly extend beyond the boundaries of the contrast enhancement of individual lesions.[6)] This suggests vasogenic edema is scarce while marked gadolinium enhancement of the lesions indicates disruption of the blood brain barrier. Better explanation for this discrepancy is a matter of future investigations. On the other hand, pontine and cerebellar atrophy later emerged is prominent, suggesting severe neuro-axonal loss in this condition. Diffuse cerebral atrophy also developed in some cases along with cognitive dysfunction. Neurons are likely to be targeted by CLIPPERS. Since anti-neuronal auto-antibodies were not detected in this condition, CD4-positive T cells and histiocytes may play unique roles for causing such MRI features and late parenchymatous atrophy. Cerebrospinal fluid assays on cytokines and chemokines may give an insight to the nature of inflammation in this condition.

Without any specific biomarker, it would require careful exclusion of other conditions for diagnosing CLIPPERS. Nonetheless, clinical neurologists should be aware of this condition, because early introduction of steroids benefit suffers, regardless

of CLIPPERS being a disease or a syndrome.

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