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ANTI-MOG ANTIBODIES WITH LONGITUDINALLY EXTENSIVE TRANSVERSE MYELITIS PRECEDED BY CLIPPERS

Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) is an inflammatory brainstem syndrome of uncertain etiology, with distinct radiologic features.¹ Autoimmunity has been postulated, although specific CNS antibodies have not been reported. Our patient initially presented with classical clinicoradiologic features of CLIPPERS. Five months later, she developed a longitudinally extensive spinal cord inflammatory lesion affecting mainly the conus, and had antibodies to myelin-oligodendrocyte glycoprotein (MOG). Although neuromyelitis optica spectrum disorders (NMOSD) with brainstem involvement may feature in the broad differential diagnosis of CLIPPERS, this is the first report describing an overlap with the anti-MOG phenotype of NMOSD, and highlights that CLIPPERS may not be a distinct nosologic entity.

Case report. A 36-year-old woman presented with a 2-week history of dizziness, left facial paresthesia, allodynia, and altered intraoral sensation. Shortly before admission, she developed slurred speech, gait ataxia, and double vision. There were no constitutional symptoms suggesting systemic illness.

Examination revealed diplopia, horizontal nystagmus on left gaze, dysarthria, and left-sided facial weakness. Visual acuities and fundal appearances were normal, as were tone, power, sensation, and sphincter function. Limb reflexes were brisk, without clonus. Her gait was ataxic.

Brain MRI showed patchy pontocerebellar signal change (figure, A–D), consistent with CLIPPERS.¹ CT of the chest/abdomen/pelvis was normal. CSF showed 2 lymphocytes/ μ L and elevated protein (686 mg/L). Microscopy, culture, and viral PCR were negative. Flow cytometry identified reactive T cells (CD4:CD8 ratio 3:1). CSF oligoclonal bands were negative. Angiotensin converting enzyme levels were normal, and antinuclear antibody screening was negative.

As symptoms were progressing, we commenced treatment with high-dose steroids (3 days IV methylprednisolone; thereafter 1 mg/kg/day prednisolone). Subsequently, the clinical findings and imaging appearances improved markedly (figure, E).

With full symptom resolution, steroids were slowly weaned and discontinued 5 months after initial admission. Two weeks later, the patient developed progressive painful tightness in both legs, altered perineal sensation, difficulty climbing stairs, and transient urinary retention requiring catheterization. She had a spastic paraparesis, pyramidal weakness, brisk 4-limb reflexes, crossed adductor jerks, and bilateral patellar and ankle clonus. Left leg pinprick and temperature sensation were reduced. Upper limb, cranial nerve, and cerebellar examination results were normal.

MRI showed residual pontine changes and a new long cord lesion involving the conus (figure, F).

CSF studies revealed 18 lymphocytes, elevated protein (554 mg/L), and again a reactive picture without clonality on flow cytometry. Oligoclonal bands remained negative.

Aquaporin-4 (AQP4) antibodies were negative, but serum anti-MOG immunoglobulin G1 antibodies were positive using a cell-based assay using full-length human MOG.

Our patient received further pulsed and maintenance steroids. One month later, her myelopathic symptoms had fully resolved.

Discussion. The initial presentation of a steroid-responsive brainstem encephalitis with curvilinear and nodular pontocerebellar enhancement and T-cell-predominant CSF leukocytosis suggested CLIPPERS syndrome.¹

Alternative diagnoses included autoimmune or parainfectious disorders, neoplasia (particularly primary CNS lymphoma), vasculitis, and infection. Central pontine myelinolysis can occasionally enhance, but there were no precipitating factors, and the lesion appearances are atypical. Behçet or sarcoidosis can cause multifocal lesions, but there were no systemic features raising suspicion of these (e.g., orogenital ulceration, uveitis, skin, joint, or respiratory involvement). Paraneoplastic antibodies were not screened; however, the subsequent clinical course was not suggestive of a paraneoplastic etiology. Given unequivocal and rapid improvement with steroids, brainstem biopsy to exclude malignancy was believed to be of unacceptably high risk.

Although often monophasic, CLIPPERS can relapse after discontinuation of immunotherapy and

(A, B) T2-weighted MRI shows axial slices through pons. There is diffuse but patchy signal change in pons (A, dark arrow), extending into the cerebellar peduncles (B, white arrow) with some associated swelling but without substantial mass effect or hydrocephalus. (C, D) T1-weighted MRI shows curvilinear, punctate, and nodular gadolinium contrast enhancement most severe adjacent to the surface but extending into the center of the pons (C, white arrow) and cerebellar peduncles (D, white arrow). There was no restricted diffusion and no supratentorial lesions. (E) Nine weeks later, the pontine lesion no longer demonstrates contrast enhancement and there was a reduction in the extent of abnormal high T2 signal in the pons and middle cerebellar peduncles. (F) Five months after initial presentation, following steroid withdrawal, MRI spine shows a new longitudinally extensive lesion with intrinsic enhancement and edema within the conus medullaris, spanning 3 vertebral segments (T11-L1, arrows indicate top and bottom extent of lesion).

the ideal treatment regimen is unknown.² Our patient's conus lesion developed shortly after ceasing steroids. Cervical cord inflammation is described in CLIPPERS, with lesions decreasing in frequency with increasing distance from the pons.^{3,4} Longitudinally extensive thoracolumbar cord lesions have not been previously reported, hence this substantially altered our differential diagnosis, prompting anti-MOG antibody testing.

Anti-MOG antibodies have been reported in acute disseminated encephalomyelitis, pediatric multiple sclerosis, and recently in seronegative NMOSD.^{5,6} NMOSD associated with MOG antibodies often presents with a steroid-responsive monophasic disease, bilateral concurrent optic neuritis, or myelitis. In contrast to anti-APQ4-mediated disease, conus involvement, as in our patient, is common.^{5,6}

Anti-MOG antibodies may reflect a bystander phenomenon after tissue damage in the CNS.⁷ We cannot exclude the possibility that our patient developed antibodies subsequent to her initial pontine inflammation, as anti-MOG antibodies were not checked at original presentation. While some CLIPPERS cases

are associated with elevated autoimmune antibodies, anti-MOG antibodies have not been reported.² Their potential relevance and an etiologic link between these rare disorders is demonstrated here by the development of myelitis following cessation of steroid treatment for a typical CLIPPERS phenotype. This also suggests that CLIPPERS is a syndrome rather than a distinct disease process.

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