Widespread inflammation in CLIPPERS syndrome indicated by autopsy and ultra-high-field 7T MRI

ABSTRACT

Objective: To examine if there is widespread inflammation in the brain of patients with chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) syndrome by using histology and ultra-high-field MRI at 7.0T.

Methods: We performed a detailed neuropathologic examination in 4 cases, including 1 autopsy case, and studied 2 additional patients by MRI at 7.0T to examine (1) extension of inflammation to areas appearing normal on 3.0T MRI, (2) potential advantages of 7.0T MRI compared to 3.0T MRI in reflecting widespread inflammation, perivascular pathology, and axonal damage, and (3) the possibility of lymphoma.

Results: In the autopsy case, perivascular inflammation dominated by CD4+ T cells was not only detected in the brainstem and cerebellum but also in brain areas with normal appearance on 3.0T MRI, including supratentorial regions and cranial nerve roots. There was no evidence of lymphoma in any of the 4 patients. The 7.0T MRI in clinical remission also revealed supratentorial lesions and perivascular pathology in vivo with contrast-enhancing lesions centered around a small venous vessel. Ultra-high-field MRI at 7.0T disclosed prominent T1 hypointensities in the brainstem, which were not seen on 3.0T MRI. This corresponded to neuropathologic detection of axonal injury in the autopsy case.

Conclusion: Our findings suggest more widespread perivascular inflammation and postinflammatory axonal injury in patients with CLIPPERS.

GLOSSARY

CLIPPERS = chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids; H&E = hematoxylin & eosin; mRS = modified Rankin Scale; MS = multiple sclerosis; T2*W = T2*-weighted; TE = echo time; TR = repetition time; T1W MPRAGE = T1-weighted magnetization-prepared rapid gradient echo; SWI = susceptibility-weighted imaging; VIBE = volumetric interpolated brain examination.

Features of chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) include subacute brainstem symptoms, MRI appearance with multiple punctate or curvilinear gadolinium enhancements, and a clear response to immunosuppressive treatment. Since the original case series, several cases have been described, some of which suggest that the CLIPPERS MRI appearance can be seen in other inflammatory disorders, such as primary angiitis of the CNS or multiple sclerosis (MS). Recently, cases have been reported with development of lymphoma after the initial diagnosis of CLIPPERS.

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Table Demographics, clinical symptoms, treatment, and timing of MRI or neuropathologic investigations of patients in this study

<table>
<thead>
<tr>
<th>Patients</th>
<th>Sex/age, y</th>
<th>Time and symptoms at diagnosis</th>
<th>Clinical state at MRI</th>
<th>Treatment at biopsy</th>
<th>Treatment at MRI</th>
<th>Time between symptom onset and MRI/autopsy/biopsy</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1 (autopsy and 3.0T MRI)</td>
<td>M/62</td>
<td>2008: Diplopia, dysphagia, dysarthria, ataxia</td>
<td>Rem</td>
<td>Prednisone</td>
<td>Prednisone</td>
<td>3.0T MRI: 1 week; autopsy: 3 mo</td>
<td>NA</td>
</tr>
<tr>
<td>Patient 2 (biopsy 1)</td>
<td>M/23</td>
<td>1999: Nystagmus, ataxia, anorexia</td>
<td>NA</td>
<td>None</td>
<td>NA</td>
<td>Biopsy: 27 mo</td>
<td>17</td>
</tr>
<tr>
<td>Patient 3 (biopsy 2)</td>
<td>F/58</td>
<td>2007: Ataxia, dysarthria, paresthesia (hands and feet)</td>
<td>NA</td>
<td>Prednisone; methotrexate</td>
<td>NA</td>
<td>15 mo</td>
<td>17</td>
</tr>
<tr>
<td>Patient 4 (biopsy 3)</td>
<td>M/42</td>
<td>2010: Tetraparesis, proximal paraparesis, dysarthria, diplopia, ataxia</td>
<td>NA</td>
<td>Prednisone</td>
<td>NA</td>
<td>Biopsy: 5 mo</td>
<td>17</td>
</tr>
<tr>
<td>Patient 5 (3.0T and 7.0T MRI)</td>
<td>F/48</td>
<td>2013: Hemiparesis, double vision, gait instability, dysarthria, facial pain</td>
<td>Rem</td>
<td>Rem</td>
<td>Prednisone; methotrexate</td>
<td>7.0T MRI: 13 mo</td>
<td>NA</td>
</tr>
<tr>
<td>Patient 6 (3.0T and 7.0T MRI)</td>
<td>F/73</td>
<td>2010: Fatigue, diplopia, ataxia, dysarthria</td>
<td>Rem</td>
<td>Prednisone; methotrexate</td>
<td>3.0T MRI: 49 mo; 7.0T MRI: 49 mo</td>
<td>18</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: NA – not applicable; Rel – Relapse; Rem – Remission.
developed subacute dysarthria, horizontal nystagmus, diplopia, jerky eye movements, ataxia, tetraspasticity, and paraparesis (table). CSF showed mild pleocytosis and no persisting oligoclonal bands. Brain biopsy indicated parenchymal and perivascular inflammatory infiltrates predominantly composed of CD3+ T cells. MRI showed multiple punctate gadolinium-enhancing lesions in the cerebellum, brainstem, and midbrain. No systemic autoantibodies were found. Symptoms and MRI lesions rapidly responded to methylprednisolone. He was treated with methotrexate and azathioprine, and had only a single relapse.
during the follow-up period of 19 months (mRS 2). The patient committed suicide.17

Patients examined by 7T MRI (patients 5 and 6). Two additional patients with CLIPPERS were included in the 7.0T MRI study.

Patient 5 is a 48-year-old woman who developed subacute numbness in the left half of her body, double vision, gait instability, dysarthria, facial pain, numbness of the oral cavity, and fatigue over a period of 2 weeks in September 2013 (table). During the weeks before the onset of these symptoms, she had noted frontal headaches. The patient was admitted to another hospital in October 2013, where a cranial 1.5T MRI demonstrated multiple small T2 hyperintense lesions with punctate and curvilinear contrast enhancement in the pons and cerebellum, and a bigger right cerebellar lesion. As this case has not been published before, the brain MRI findings of this patient are shown in figure e-1 at Neurology.org/nn. A spinal cord MRI demonstrated a small longitudinal contrast-enhancing lesion in the cervical cord. The cerebellar lesion was biopsied in October 2013. Histologic analysis revealed cerebellitis with prominent CD4+ T-cellular infiltrates, compatible with CLIPPERS syndrome. There were no signs of lymphoma. Antinuclear antibodies, antibodies to extractable nuclear antigens, and antineutrophil cytoplasmic antibodies as well as antibodies to aquaporin-4 were negative. She was initially treated with high-dose IV methylprednisolone (1 g/day for 3 days followed by 1 g/day for 5 days) and subsequently with oral prednisolone (starting dose 25 mg/day with a subsequent taper to 5 mg/day) and azathioprine (3 × 50 mg), which was changed to methotrexate in May 2014, when a cranial MRI demonstrated constant to minimally progressive CLIPPERS lesions. At the time of the 7.0T MRI examination, she was treated with prednisolone (5 mg daily) and methotrexate (15 mg weekly), and had residual facial paresthesiae but no clinical signs of new disease activity.

Patient 6 is a 73-year-old woman who was diagnosed with CLIPPERS in October 2010 and whose clinical and paraclinical details were previously reported in detail.18 The patient had mildly elevated antinuclear antibodies (1:320) and double-stranded DNA antibodies (immunoglobulin G). Antibodies against aquaporin-4 and extractable nuclear antigens were negative. At the time of the 7.0T MRI examination, she was treated with methylprednisolone (4 mg daily) and methotrexate (15 mg weekly) and was in clinical remission.

Neuropathologic examination. Three-micrometer sections from formalin-fixed, paraffin-embedded tissue blocks were stained with hematoxylin & eosin (H&E) and for CD45 (clone: 2B11&PD7/26 ventana-LCA, Ventana Medical Systems, Tucson, AZ), CD3 (clone: 2G6, Ventana Medical Systems), CD4 (SP35, Ventana Medical Systems), CD8 (clone: C8/144B, Dako, Glostrup, Denmark), CD20 (clone: clyL26, Ventana Medical Systems), and neurofilament heavy-chain (NF smi31, Affinity, Exeter, UK). Selected sections from brainstem and insular cortex were double-stained for CD3 and NF. Adjacent sections were stained for Luxol fast blue and H&E. Adjacent formalin-fixed tissue section from brainstem tissue (autopsy) as well as sections from 3 additional brainstem biopsies were similarly stained for light-chain restriction (kappa-smi and lambda-smi, smlg reaction, Dako), the zinc-finger transcription factor, B-cell lymphoma 6 protein (Bcl-6, clone: LN22 NovoCastra, Leica Biosystems, Newcastle, UK), the large B-cell lymphoma marker, Multiple Myeloma Oncogene 1 (MUM-1, IRF4, Dako), and the precursor B lymphoma marker, CD10 (clone: 56C6-CALLA, NovoCastra, Leica Biosystems). All immunohistochemical stainings were performed using the BenchMark Ultra IHC staining system (Ventana Medical Systems). For detection, ultraView Universal DAB Detection Kit was applied (Ventana Medical Systems). Toliudine blue was used as counterstaining. Lymphoma stainings were assessed by a skilled lymphoma pathologist. Digital images were obtained at a magnification of 5× or 10× (brainstem) or 10× (cerebellum, parietal cortex, insular cortex/basal ganglia, nerve root, and biopsies 1–3) using a Leica microscope (Leica 4000B LED, Leica Microsystems, Wetzlar, Germany) equipped with a Leica digital camera (Leica DFC420, Leica Microsystems).

Ultra-high-field MRI data acquisition and postprocessing. Ultra-high-field MRI were acquired using a 7T whole body MRI scanner (Magneton, Siemens, Erlangen, Germany) equipped with a birdcage volume coil used for transmission. The imaging protocol included 2D T2-weighted (T2*W) fast low angle shot (echo time [TE] = 25.0 ms, repetition time [TR] = 1.820 ms, spatial resolution = 0.2 × 0.2 × 2 mm3, supratentorial coverage), pregadolinium and postgadolinium 3D T1-weighted magnetization-prepared rapid gradient echo (T1W MPRAGE) (TE = 2.98 ms, TR = 2.300 ms, inversion time = 900 ms, spatial resolution = 1.0 × 1.0 × 1.0 mm3, whole brain coverage), and 3D flow-compensated gradient echo–based susceptibility-weighted imaging (SWI) (TE = 14 ms, TR = 25 ms, flip angle = 12°, spatial resolution = 0.5 × 0.5 × 1.0 mm3, supratentorial and infratentorial coverage). For infratentorial imaging, postgadolinium volumetric interpolated brain examination (VIBE) sequence was used (TE = 3.3 ms, TR = 19.7 ms, spatial resolution = 0.5 × 0.5 × 1.0 mm3).

To identify vascular structures within contrast-enhancing CLIPPERS lesions, we calculated the sum of (1) coregistered T1W MPRAGE with supratentorial T2*W images, and (2) coregistered VIBE with infratentorial SWI images using the image calculator function of the MIPAV software package (version 7.0.1, Bethesda, MD).

RESULTS Perivascular inflammation in CLIPPERS extends to areas with normal appearance on 3.0T MRI: Analysis of the autopsy case. First, we investigated inflammation in different brain regions corresponding to gadolinium-enhancing and normal-appearing brain areas on 3.0T MRI (autopsy tissue of patient 1): brainstem and cerebellum were compared to parietal and insular cortex (figure 1). Perivascular accumulation of CD45+ lymphocytes (figure 1, B, G, L, and Q) with predominance of CD3+ T cells (figure 1, C, H, M and R) and CD4+ T cells were detected in brainstem and cerebellum as expected (figure 1, D and N). CD4+ T cells also infiltrated the parenchyma, which was most pronounced in the brainstem (figure 1D). Accumulation and infiltration by CD8+ T cells were less pronounced (figure 1, E and Q), and only a few CD20+ B cells were observed in close proximity to the vessel wall (figure 1, F and P). However, insular and parietal cortex with normal appearance on 3.0T MRI revealed a similar, albeit less prominent perivascular accumulation of CD4+
T cells (figure 1, I and S), fewer CD8+ T cells (figure 1, J and T), and a very limited number of CD20+ B cells (figure 1, K and U). CD4+ T cells also infiltrated the parenchyma the insular cortex (figure 1S). Perivascular inflammation was also found in the roots of cranial nerves (figure 1, V and W). These data suggested that brain areas with normal appearance on 3.0T MRI may be affected by inflammation in CLIPPERS syndrome.

**No evidence of lymphoma and prelymphoma state: Analysis of 4 cases.** Next, brainstem samples (patients 1–4) were analyzed for the possibility of lymphoma or prelymphoma. We found no evidence for monoclonal cell expansion using staining for light chain restriction (figure 2, A–B, F–G, K–L, and P–Q) and lymphoma markers CD10, Bcl-6, and MUM-1 (figure 2, C–E, H–J, M–O, and R–T). Follow-up of the 3 biopsy cases (patients 2–4; mean of 75 months) did not indicate clinical or paraclinical evidence of lymphoma either.

**Ultra-high-field MRI reveals perivascular lesions outside the brainstem/cerebellum and tissue damage.** Since pathologic examination indicated perivascular inflammation in brain areas with normal appearance on 3.0T MRI, albeit less pronounced than in brainstem and cerebellum, we next examined 2 patients with CLIPPERS by 7.0T MRI during clinical remission. Contrast-enhancing lesions (n = 20) were only depicted in patient 5. Of those, 2 lesions were found in a supratentorial localization affecting (n = 1) or bordering (n = 1) the thalamus (figure 3D). Cortical gray matter lesions were not observed on supratentorial T2*W images.

To visualize the perivascular distribution of lesions, we fused contrast-enhanced T1W and supratentorial T2*W images with a volume resolution...
of 0.08 mm³ to display small T2*W hypointense venous structures within gadolinium-enhancing hyperintense CLIPPERS lesions (figure 3). Indeed, a distinct venous vessel could be seen within the center of the thalamic CLIPPERS lesion in vivo (figure 3C). Due to technical limitations, a different approach with a lower spatial resolution of 0.25 mm³ was used for infratentorial areas. Even with this approach, a very small venous vessel could be depicted within 8 of 10 contrast-enhancing CLIPPERS lesions on fused postgadolinium VIBE and SWI (data not shown).

In addition, 7.0T T1W MPRAGE depicted numerous T1W hypointense lesions within the pons and cerebellum (figure 4, E–G) in patient 5, which were not visible on conventional 3.0T MRI (figure 4, A–D), indicating severe tissue destruction within postinflammatory CLIPPERS lesions (figure 4). Multiple pontine postinflammatory T1W hypointense lesions were also found in patient 6 by using T1W imaging at 7.0T (data not shown). Corresponding to the 7.0T MRI findings, neurofilament and myelin staining revealed axonal injury and myelin loss in brainstem areas with severe inflammation of the autopsy case (figure 4, H and I). Preservation of axons and myelin was seen in areas with limited inflammation (figure 4, J and K).

**DISCUSSION** In this article, we describe neuropathologic as well as high-field/ultra-high-field MRI features of 6 patients with CLIPPERS syndrome. The diagnosis of CLIPPERS syndrome was supported by (1) postcontrast T1-weighted MRI with typical punctate, nodular, or curvilinear and occasionally more confluent gadolinium-enhancing lesions, (2) perivascular inflammation in the brainstem dominated by T cells, (3) clinical course with several steroid-responsive relapses, and (4) absence of other diseases. In addition to punctate and curvilinear lesions, case 5 had a larger confluent lesion in the cerebellum. Similar lesions were previously described in patients with CLIPPERS and a biopsy of the cerebellar lesion of case 5 demonstrated histopathologic features of CLIPPERS.

We found widespread perivascular inflammation in brain areas with normal appearance on 3.0T MRI in an autopsy case of CLIPPERS syndrome. The inflammatory pattern of these regions was similar to the original and later neuropathologic descriptions of the disease characterized by pronounced CD4+ T-cell infiltration of brain tissue and less predominant angiocentric CD8+ T-cell and CD20+ B-cell inflammation. Although T2W and gadolinium-enhancing lesions were found only in the pons, midbrain, and cerebellar regions, inflammation could be seen as distant as the parietal cortex and even involved the cranial nerve roots. The degree of inflammation, however, showed a gradient of less inflammation with greater distance from the primarily affected areas (brainstem > cerebellum > insular cortex > parietal cortex), suggesting that the inflammation seen on conventional 1.5T–3.0T MRI only depicts the most severely
affected brain regions. Consistent with these neuropathologic findings, cognitive impairment such as dys-executive syndromes, language disturbance, frontal release signs and cortical atrophy were described in a case series of CLIPPERS syndrome, suggesting that cortical involvement may be more prominent than initially thought.2

Since our pathologic examinations revealed widespread inflammatory changes in brain tissue appearing normal on conventional 3.0T MRI, we performed ultra-high-field 7.0T MRI in 2 additional CLIPPERS cases to investigate such possibilities in vivo. Indeed, these efforts revealed contrast-enhancing lesions in supratentorial locations, supporting widespread inflammation in brain areas, in contrast to the only other autopsy report published recently.19 The number of such contrast-enhancing lesions was, however, limited, which is likely due to the immunosuppressive treatment: MRI changes in CLIPPERS respond rapidly to immunosuppression.1,3,20,21 Remarkably, when combining T1W and supratentorial T2*W images with a resolution as good as 0.08 mm3, we could show a vascular structure within most contrast-enhancing lesions. The 7.0T MRI thus enabled visualization of perivascular inflammation, the neuropathologic hallmark of CLIPPERS, in vivo. The hypointense appearance of these intralesional vascular structures on T2*W and SWI images indicates the presence of a paramagnetic material. Thus, these intralesional vascular structures are most likely small veins filled with paramagnetic deoxyhemoglobin.22 A central intraleonal vein was previously reported to be a characteristic finding in MS lesions.11,12,14,16 On the contrary, a central vein is

Figure 4  Comparison of 7.0T and 3.0T MRI (patients 5 and 6)

T1-weighted images of patient 5 at 3.0T and 7.0T are shown. Owing to substantially increased signal-to-noise ratio, 7.0T T1-weighted magnetization-prepared rapid gradient echo delineates numerous T1-weighted hypointense lesions within the pons and cerebellum (arrowheads, E–G). In contrast, corresponding areas appear normal (C, D) or only marginally hypointense on T1-weighted images at 3.0T (circle, A, B). T1-weighted hypointensity within non-contrast-enhancing chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids lesions may indicate postinflammatory structural brain damage including axonal loss on top of demyelination. Immunohistochemical stainings of autopsy case for neurofilament (NF) revealed massive axonal injury in the inflammatory lesion of the brainstem (H; CD3 red, NF brown) compared to insular cortex with limited inflammation (J). The presence of phosphorylated NF in the perinuclear cytoplasm of neurons suggests retrograde neuronal degeneration due to axonal injury in the lesions (H). Similarly, severe loss of perivascular myelin was found in areas of severe inflammation (I), compared to areas with limited inflammation (K), with Luxol fast blue and hematoxylin & eosin. 7.0T – 3D T1-weighted magnetization-prepared rapid gradient echo at 7.0T, echo time = 2.98 ms, repetition time = 2,300 ms, inversion time = 900 ms, spatial resolution = 1.0 × 1.0 × 1.0 mm3; 3.0T – standard T1-weighted axial images (B–D) and T1-weighted magnetization-prepared rapid gradient echo at 3.0T (A). 3.0T and 7.0T MRI examinations were performed 3 days apart. Magnification 10× (H–K). Scale bar = 100 μm.
We found perivascular inflammation predominated by CD4+ T cells even in areas with normal appearance on 3.0T MRI and extending to the cranial nerve roots, suggesting widespread inflammation in CLIPPERS syndrome, though most prominent in the primarily affected brainstem. We found no evidence of lymphoma in our 4 investigated patients. When applying ultra-high-field MRI at 7.0T, supratentorial lesions could be confirmed, and most of the contrast-enhancing lesions contained a vessel structure indicating the pathologic hallmark of CLIPPERS syndrome in vivo. The 7.0T MRI also indicated prominent T1W hypointensities suggesting tissue injury, which could not be seen on 3.0T MRI but corresponded to axonal injury and loss of myelin in the autopsy specimen. One limitation of the study might be the application of immunosuppressive treatment at the time of biopsy or MRI examination (table 1).

**AUTHOR CONTRIBUTIONS**
Morten Blaabjerg: design and conceptualization, clinical data, analysis and interpretation of the data, drafting and revising the manuscript. Klemens Ruprecht: MRI design and conceptualization, clinical data, analysis and interpretation of the data, drafting and revising the manuscript. Tim Sinnecker: MRI analysis and interpretation of the data, revising the manuscript. Daniel Kondziella: clinical data, interpretation of the data, revising the manuscript. Bjørn Morell Kern-Jespersen: clinical data, interpretation of the data, revising the manuscript. Mette Lindelof: clinical data, interpretation of the data, revising the manuscript. Hans Lasmann: pathological analysis and interpretation of the data, revising the manuscript. Friedemann Paul: MRI design and conceptualization, analysis and interpretation of the data, drafting and revising the manuscript. Zsolt Illes: design and conceptualization, analysis and interpretation of the data, drafting and revising the manuscript.

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