Glial Fibrillary Acidic Protein Autoimmunity After Aseptic Meningitis

A Report of 2 Cases

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Abstract

Objectives
We describe 2 patients with glial fibrillary acidic protein (GFAP) autoimmunity secondary to aseptic viral meningitis or meningoencephalomyelitis.

Methods
This study involved a retrospective chart review.

Results
Two female patients, 45 and 55 years of age, developed aseptic meningoencephalomyelitis or meningitis; in one patient, it was likely caused by herpes simplex virus 2. The patients were recovering from the infectious condition when they, 51 and 5 days after onset, had new symptoms with detection of GFAP antibodies in the CSF; CSF and serum samples from the initial lumbar punctures had been negative for GFAP antibodies. Both patients recovered with steroid treatment (in one case, plus rituximab; in the other, plus azathioprine) including resolution of MRI and CSF abnormalities.

Discussion
These 2 patients had GFAP autoimmunity secondary to viral meningoencephalomyelitis or meningitis. This suggests that GFAP astrocytopathy might not always be a primary disease entity; it may follow another brain injury that triggers this autoimmune response.

Introduction
Glial fibrillary acidic protein (GFAP) autoimmunity,1-5 manifesting as meningoencephalitis, is not rare and is at the same time enigmatic: The intracellular location of GFAP puts a direct pathogenic antibody effect into question. Differently from paraneoplastic conditions with intracellular antibodies, tumors are rarely found, and >70% of GFAP antibody–associated conditions respond to first-line immunotherapy.6

While no HLA association could be demonstrated,6 more than half of the patients have a prodromal febrile illness2,5,6 suggesting an infectious disease that (silently) involves the CNS, exposes brain proteins to the adaptive immune system, and triggers the generation of GFAP antibodies. One case with GFAP astrocytopathy subsequent to herpes simplex virus (HSV) encephalitis has been reported.7 In this study, we add 2 cases of GFAP autoimmunity after aseptic meningitis with initially negative GFAP antibodies.
Table  Laboratory, Imaging, Neuropsychological, and Laboratory Findings in Case 1

<table>
<thead>
<tr>
<th>Laboratory findings in blood</th>
<th>Normal range</th>
<th>Day 14</th>
<th>Day 51</th>
<th>Day 136</th>
<th>Day 292</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (mmol/L)</td>
<td>136–145</td>
<td>122*</td>
<td>128*</td>
<td>138</td>
<td>138</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>&lt;5</td>
<td>2.3</td>
<td>&lt;0.6</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>Leukocyte count (G/L)</td>
<td>3.0–9.6</td>
<td>5.4</td>
<td>4.39</td>
<td>16.07*</td>
<td>4.88</td>
</tr>
<tr>
<td>Lymphocyte count (G/L)</td>
<td>1.50–4.00</td>
<td>0.58</td>
<td>n.d.</td>
<td>0.79</td>
<td>1.41</td>
</tr>
</tbody>
</table>

**Imaging**

- **Brain MRI, day 15**: Hydrocephalus of unknown etiology. Frontal right and cerebellar left lesions, most likely cardioembolic old infarcts. Hemosiderin deposition at the tentorium cerebelli on the right side. Subdural hematoma on the right side.

- **CT thorax/abdomen, day 26**: Normal.

- **Spinal MRI, day 51**: Longitudinal, centrally localized T2 hyperintense lesion of the cervical and thoracic spinal cord from C4 to T5.

- **Brain and spinal MRI, day 124**: Brain unchanged. Spinal cord: normal.

- **Brain and spinal MRI, day 204**: Complete regression of spinal lesions.

- **Brain MRI, day 482**: Persisting pathologic widening of the ventricular system. Unchanged postischemic defects. No new lesions or pathologic contrast enhancement.

- **FDG-PET, day 482**: Metabolically active left palate tonsil, DD of inflammatory or neoplastic origin. Histopathology after tonsillectomy: acute cryptitis, no malignancy.

**Neuropsychological bedside tests**

<table>
<thead>
<tr>
<th>Date</th>
<th>Day 14</th>
<th>Day 36</th>
<th>Day 51</th>
<th>Day 70</th>
<th>Day 76</th>
<th>Day 91</th>
<th>Day 292</th>
</tr>
</thead>
<tbody>
<tr>
<td>MoCA (n: ≥26 points)</td>
<td>20/30*</td>
<td>22/30*</td>
<td>19/30*</td>
<td>20/30*</td>
<td>28/30</td>
<td>30/30</td>
<td>29/30</td>
</tr>
</tbody>
</table>

**CSF findings**

<table>
<thead>
<tr>
<th>Date</th>
<th>Day 14</th>
<th>Day 16</th>
<th>Day 19</th>
<th>Day 30</th>
<th>Day 51</th>
<th>Day 124</th>
<th>Day 292</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell count (cells/µL) (n &lt; 4/µL)</td>
<td>81*</td>
<td>62*</td>
<td>138*</td>
<td>88*</td>
<td>42*</td>
<td>14*</td>
<td>3</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>89%</td>
<td>n.d.</td>
<td>89.5%</td>
<td>n.d.</td>
<td>97.5%</td>
<td>91.5%</td>
<td>n.d.</td>
</tr>
<tr>
<td>Lactate (mmol/L) (n 1.7–2.6 mmol/L)</td>
<td>2.8</td>
<td>2.4</td>
<td>2.3</td>
<td>n.d.</td>
<td>3.4*</td>
<td>3.2*</td>
<td>1.7</td>
</tr>
<tr>
<td>CSF/serum glucose ratio (n ≥0.5)</td>
<td>0.7</td>
<td>0.4*</td>
<td>0.3*</td>
<td>n.d.</td>
<td>0.4*</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>CSF/serum albumin ratio (×10²) (n &lt; 7.7)</td>
<td>17.4*</td>
<td>n.d.</td>
<td>12.6*</td>
<td>n.d.</td>
<td>21.5*</td>
<td>6.0</td>
<td>6.3</td>
</tr>
<tr>
<td>Protein (mg/L) (n 200–500/µL)</td>
<td>1,100*</td>
<td>640*</td>
<td>774*</td>
<td>n.d.</td>
<td>1,390*</td>
<td>457</td>
<td>460</td>
</tr>
<tr>
<td>Oligoclonal bands*</td>
<td>Type 3*</td>
<td>n.d.</td>
<td>Type 3*</td>
<td>n.d.</td>
<td>Type 3*</td>
<td>Type 2*</td>
<td>Type 1</td>
</tr>
<tr>
<td>Virus PCRs in the CSF*</td>
<td>neg.</td>
<td>n.d.</td>
<td>EBV (+)</td>
<td>n.d.</td>
<td>neg.</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>Anti-GFAP CBA CSF (neg.: &lt;1:2)</td>
<td>neg.</td>
<td>n.d.</td>
<td>pos.</td>
<td>n.d.</td>
<td>pos.*</td>
<td>pos.*</td>
<td>pos.*</td>
</tr>
<tr>
<td>Anti-GFAP IFT CSF (neg.: not even in undiluted CSF demonstrable)</td>
<td>neg.</td>
<td>n.d.</td>
<td>n.d.</td>
<td>pos.</td>
<td>(1:32)*</td>
<td>pos.</td>
<td>(1:128)*</td>
</tr>
</tbody>
</table>

*Abnormal values.

**Abbreviations:** CBA = cell-based assay; CRP = C-reactive protein; EBV = Epstein-Barr virus; GFAP = glial fibrillary acidic protein; HSV = herpes simplex virus; IgG = immunoglobulin G; IgM = immunoglobulin M; IIFT = indirect immunofluorescent tissue-based assay (mouse brain); LP = lumbar puncture; MoCA = Montreal Cognitive Assessment; n = normal; n.d. = not determined; neg. = negative; pos. = positive.

*O CB type 1 = no oligoclonal bands in the CSF and serum, i.e., no intrathecal IgG production; OCB type 2 = oligoclonal IgG bands only in the CSF, i.e., intrathecal IgG production; OCB type 3 = oligoclonal bands in the CSF and serum with additional bands in the CSF, i.e., intrathecal IgG production.

Neural autoantibodies were tested both in the CSF and serum (Laboratory Krone, using Euroimmun assays): GAD65, NMDAR, GABA_A R, GABA_B R, IgLON5, AMPAR 1/2, DPPX, LG1, CASPR2, glycine receptor, mGlur5, and mGlur1, amphiphysin, CV2CRMPS, Ma2/Ta (PNMA2), Rl, Y0, Hu, Recoverin, Sox1, Titin, Zic4, and DNER/Tr.

**Virus PCRs in the CSF:** HSV-1, HSV-2, cytomegalovirus, enterovirus, varicella zoster virus, and human herpes virus-6 negative; PCR for EBV on day 19, weakly positive, i.e., <100 copies/mL, on days 14 and 51, negative.

**Bacterial culture:** broad-spectrum PCR, Borrelia burgdorferi IgG and IgM, Treponema pallidum.
Case Presentations

Case 1
A 55-year-old female patient was referred from an external hospital with meningoencephalomyelitis. The symptoms had begun 2 weeks earlier with fever, holocephalic headache, nausea, and behavioral changes and progressive gait disturbance. The patient had fever (38.9°C) with otherwise unremarkable vital signs, moderate cognitive dysfunction with disorientation in time, psychomotor slowing (Glasgow coma scale [GCS] 14), mild M4 paraparesis, ataxia of the lower extremities with gait ataxia, and a visual disturbance in the left eye due to a left-sided papilledema. The CSF sample in the external hospital revealed pleocytosis (no details given on patient transfer). The first lumbar puncture in this department was performed on day 14 after onset. For details on paraclinical findings, see Table. A retrospective panel testing for neural and glial antibodies in stored materials was negative in the serum and CSF (cell-based assay [CBA] and tissue-based assay [TBA], sagittal mouse brain sections assays from Euroimmun, Lübeck, Germany: CBA: N-methyl-D-aspartate receptor (NMDAR), γ-aminobutyric acid receptors A and B, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors 1/2, dipeptidyl-peptidase-like protein 6, leucine-rich glioma-inactivated protein 1, contactin-associated protein-like 2, glycine receptor, metabotropic glutamate 1 and 5 receptors, IgLON5, GFAP, and glutamic acid decarboxylase; immunoblot: amphiphysin, CV2, Ma2, Ri, Yo, Hu, Sox1, Zic4, and delta/notch-like EGF-related receptor. GFAP antibody positivity requires a CSF titer of ≥1:2 on TBA and CBA; TBA positivity is endpoint titrated. This follows the practice of the Mayo laboratory.1,8 We used an in-house staining protocol as previously described.9 GFAP antibody titers (titration on TBA) and CSF cell counts and OCB positivity over time are depicted in Figure 1. The patient was empirically treated with ceftriaxone and acyclovir. On day 19, she became drowsy and hypertensive up to 190/100 mm Hg. Lumbar puncture revealed an elevated CSF opening pressure of 40 cm H2O, an increased cell count, and an increased protein content with intrathecal production of IgG against herpes simplex virus type 1 and 2 (HSV-1/2). Because an MRI examination of the brain did not show signs of HSV-1 encephalitis and HSV-1 PCR was negative, HSV-2 meningoencephalomyelitis was suspected. Although CSF was also positive for Epstein-Barr virus (EBV) DNA, EBV was not considered primarily pathogenic because the patient was not chronically immunocompromised, EBV DNA was only detected on day 19 and at no other CSF study, and copy numbers were low (<100 copies/mL). However, we cannot exclude coinfection with EBV. Of note, this CSF sample already bound to the GFAP CBA at 1:2 (not further titrated) but did not give a corresponding pattern on mouse brain, so no GFAP antibody positivity could be diagnosed. Over the next few days, the patient vomited repeatedly and had elevated blood pressure and persistent moderate cognitive impairment. On day 37, she was transferred to rehabilitation and slowly recovered from disorientation in time, ataxic gait disturbance (mobile with bilateral gait assistance), and excessive anxiety.

On day 51, she deteriorated rapidly with temperatures up to 38.1°C, worsening of ataxia and cognitive impairment, and new-onset meningism and bilateral papillitis. In retrospect, GFAP antibodies were present in the CSF. Spinal MRI on day 71 revealed longitudinally extensive, central myelitis (Figure 2A). Upon a methylprednisolone pulse (1g/d for 5 days, days 71–76), followed by a slow taper, the patient improved within days regarding ataxia, cognition, and imaging (Figure 2A). Upon reduction of prednisolone from 10 to 5 mg/d on day 121, she deteriorated overnight, with left abducens paresis, left leg paresis with gait ataxia, and subfebrile

Figure 1 Graphical Depiction of the Disease and Treatment Courses

<table>
<thead>
<tr>
<th>Days since disease onset</th>
<th>CSF cells/µL</th>
<th>GFAP abs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1,024</td>
<td>1,024</td>
</tr>
<tr>
<td>2</td>
<td>1,024</td>
<td>1,024</td>
</tr>
<tr>
<td>3</td>
<td>1,024</td>
<td>1,024</td>
</tr>
<tr>
<td>4</td>
<td>1,024</td>
<td>1,024</td>
</tr>
<tr>
<td>5</td>
<td>1,024</td>
<td>1,024</td>
</tr>
</tbody>
</table>

Light green, viral meningoencephalomyelitis or meningitis; red, GFAP astrocytopathy; yellow: steroids; purple, rituximab; green, azathioprine. CSF cell counts and GFAP antibody titers in CSF are indicated by circles and triangles, respectively; brain symbols: time point of MR images in Figure 2; arrows: time points when GFAP antibodies were for the first time detected—previous values were determined in retrospect in stored samples. (A) Patient 1 (B) Patient 2. To depict the value “0” on the logarithmic axes, “1” was added to all values. Abs, antibodies; GFAP, glial fibrillary acidic protein; neg, negative; OCB, CNS-specific oligoclonal bands; pos, positive.
temperatures up to 37.8°C. Upon another methylprednisolone pulse, she improved promptly the following day. In a follow-up CSF collection on day 124, GFAP antibodies were ordered for the first time and found positive. This prompted the retrospective study of stored samples. Starting 6 months after onset, the patient has been stable with normal cognition and only mild gait unsteadiness.

Case 2
This 45-year-old female patient developed neck pain, which was symptomatically treated with diclofenac. The following day, her headache increased and would no longer respond to diclofenac. A day later, she developed meningism, photophobia, and fever (38°C). CSF investigations on days 3 and 5 revealed pleocytosis and no intrathecal immunoglobulin G (IgG) synthesis. No infectious etiology could be demonstrated. The second serum-CSF pair was sent for antibody testing, with negative results for the abovementioned common neural and glial antibodies including GFAP antibodies, with negative results. Viral meningitis was diagnosed. Acyclovir, aciclovir and ceftriaxone, and symptomatic treatment were administered. The patient improved. The course is depicted in Figure 1.

On day 8, her fever returned, together with evolving neuropsychiatric abnormalities: an inconsistent line of thought, sensory aphasia, and some days later, optic hallucinations. She displayed restlessness, hyperkinesia, and discrete facial and brachial myoclonia. In addition, she was sleepless. EEG revealed diffuse slowing. The parietal and cerebellar meninges enhanced gadolinium (Figure 2C). The diagnosis of a possible autoimmune encephalitis was made, and the patient was (without repeat antibody testing) treated with IV methylprednisolone for 5 days at 1 g/d, with oral tapering. The fever and the neuropsychiatric abnormalities subsided within days. During follow-up visits 3, 15, and 27 months after onset, the patient was neurologically and cognitively unimpaired.

Discussion
These 2 patients developed GFAP astrocytopathy after aseptic/viral meningoencephalomyelitis (case 1, likely HSV-2) and meningitis (case 2). The patients had 2 distinct disease periods. During the GFAP astrocytopathy, additional cognitive problems evolved in both patients. The characteristic but not always evident radial contrast-enhancing periventricular pattern was not observed in the brain and spinal cord MRI. However, case 1 showed longitudinally extensive, centrally localized myelitic abnormalities, which have been previously found in 6/8 cases with GFAP astrocytopathy with myelitis. Both patients recovered with steroids, including resolution of imaging and CSF abnormalities. The prompt and striking response to steroids is common in monophasic cases of GFAP astrocytopathy. In both cases, the CSF was more sensitive than the serum for GFAP antibody testing, as previously noted.

Is GFAP astrocytopathy always a consistent primary entity? CSF or high-titer serum antibodies against GFAP have been

Figure 2 Characteristic MR Images
observed in patients with defined distinct brain disorders such as anti-NMDAR encephalitis,}\(^1\) glioma,\(^6\) or progressive multifocal leukoencephalopathy.\(^6\) Thus, GFAP autoimmunity might occasionally arise secondarily to another brain disease that triggers an immune response against GFAP as in the case report on a post-HSV encephalitis occurrence.\(^7\) The infection-autoimmune condition sequence is notoriously difficult to demonstrate. GFAP antibody positivity during the second disease period does not exclude that the antibodies were already there from the beginning. By retrospective testing of stored CSF from the early days of the disease, we can prove that the GFAP antibodies arose secondarily. We conclude that, at least in a subgroup of patients, GFAP autoimmunity/astrocytopathy can be a sequelae of a preceding viral meningitis or meningoencephalomyelitis similar to what has been shown with antibodies against neural surface epitopes including the NMDAR after HSV encephalitis.\(^12\)-\(^14\)

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### Appendix

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<table>
<thead>
<tr>
<th>Name</th>
<th>Location</th>
<th>Contribution</th>
</tr>
</thead>
</table>
| Christian G. Bien, MD | Bielefeld University, Germany          | Drafting/review of the article for content, including medical writing for content; major role in the acquisition of data |}
| Thomas Büttner, MD    | Klinikum Emden, Germany                | Drafting/review of the article for content, including medical writing for content; major role in the acquisition of data |}
| Ina C. Reichen, MD    | University Hospital Zurich and University of Zurich, Switzerland | Drafting/review of the article for content, including medical writing for content; major role in the acquisition of data |}

### References

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