

Rapidly progressive dementia: Extending the spectrum of GFAP-astrocytopathies?

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Introduction

Glial fibrillary acidic protein (GFAP) is an astrocytic intermediate filament with manifold pathophysiological implications. In 2016, a novel astrocytopathy associated with GFAP-antibodies (AB), extending the nosologic spectrum defined by Aquaporin-4-AB (AQP4-AB)-mediated astrocytopathy, neuromyelitis optica¹ was described. GFAP astrocytopathy (GFAP-A) usually manifests after an unspecific, often viral prodrome as an acute to subacute meningoencephalomyelitis or isolated subforms thereof, with monophasic or relapsing course.² GFAP-A etiology ranges from paraneoplastic to parainfectious and idiopathic.¹ Remarkably, GFAP-A is frequently embedded in a context of overlapping autoimmunity, raising the question of an emerging clinicopathological spectrum.³ In the limited number of neuropathological investigations to date, GFAP-A was shown to be associated with microglial activation and perivascular inflammation sparing vascular walls.³

Diagnosis of GFAP-A relies on detection of GFAP-AB in CSF, since their presence in serum is less specific.⁴ In

Abstract

Autoimmune glial fibrillary acidic protein astrocytopathy (GFAP-A) is a steroid-responsive meningoencephalomyelitis, sometimes presenting with atypical clinical signs such as movement disorders or psychiatric and autonomic features. Beyond clinical presentation and imaging, diagnosis relies on detection of GFAP-antibodies (AB) in CSF. Using quantitative behavioral, serologic, and immunohistochemical analyses, we characterize two patients longitudinally over 18–24 months who presented with rapidly progressive neurocognitive deterioration in the context of GFAP-AB in CSF and unremarkable cranial MRI studies. Intensified immunotherapy was associated with clinical stabilization. The value of GFAP-AB screening in selected cases of rapidly progressive dementias is discussed.

tissue-based assays (TBA), the IgG staining pattern is mostly filamentous appearing and adjacent to pial, subpial, and subependymal portions of the CNS.⁴ MRI shows subcortical white and gray matter abnormalities in ~50–60% and myelitic changes in ~44% of patients. Moreover, subcortical radial perivascular contrast enhancement is commonly found.³ Cranial ¹⁸fluor-desoxy-glucose positron emission tomography (FDG-PET) in single GFAP-A cases has shown both subcortical *hypometabolism* and cortical *hypermetabolism*.⁴ Monophasic GFAP-A typically shows favorable response to corticosteroids; however, up to 50% of cases are steroid-dependent or relapsing, requiring escalation of immunotherapy.¹

Case Reports: Methods and Results

Both patients presented around their seventh decade with abrupt onset and rapidly progressive neurocognitive deficits over 4–6 months accompanied by autonomic and psychiatric abnormalities. Focal neurologic signs (especially visual, motor, or sensory disturbances, movement

disorders) or significant MRI abnormalities (e.g., regional post-gadolinium enhancement) of brain parenchyma, ophthalmic/ orbital structures, or vasculature were absent (Fig. 1A1–2 and C1–2). Given the clinical course consistent with rapidly progressive dementia, immune-mediated etiologies were considered as likely differential diagnoses,^{5,6} warranting CSF analysis and autoimmune panel screening. Consequently, GFAP-AB were detected in a three-step approach in both patients. First, screening (“anti neural antigen panel” (ANP), see Table 2) was performed by immunofluorescence testing (IFT) on unfixed primate cerebellum slices (4 μ m slice thickness, 30 min incubation time) using serum and CSF with a detection titer cut-off at 1:100. Subsequently, positive results were confirmed by IFT with anti-human IgG of HEK-cells (cell-based assay, CBA) specifically transfected with the GFAP α isoform incubated with patient serum as previously described⁷ (Labor Prof. Stöcker, Euroimmun) (Fig. 1B3 and D3). Since ANP revealed diverging GFAP-AB results in serum and CSF of patient 1, retesting using an independent high-sensitivity assay was performed in a specialized laboratory for autoimmune encephalopathies (H. P.) using IFT on unfixed mouse brain slices incubated with patients’ CSF samples overnight (Fig. 1B1–2 and D1–2). Using said assay, a staining pattern highly typical for GFAP could be detected in both cases. Only abnormal findings are reported; see Tables 1 and 2 for detailed description of results.

Patient 1

This patient complained of disorientation and memory loss accompanied by an anxious depression, insomnia, and constipation over the preceding 6 months. Neuropsychological assessment revealed impairments especially in linguistic, visuoconstructive, and executive domains ($z = -3.2$ to -1.8). Serum ANP detected GFAP-AB (titer 1:1000). Cranial FDG-PET disclosed fronto-parieto-occipital hypometabolism (Fig. 1A3). CSF analysis revealed elevated protein levels and marginally decreased β -amyloid-42. Intravenous methylprednisolone pulse therapy (IVMP, 1000 mg/d for 3 days) was administered. At 5-month follow-up, neurocognitive deficits persisted, hence, five sessions of plasmapheresis and rituximab 1000 mg every 6 months were initiated. At 1.5-year follow-up, linguistic deficits had markedly improved ($z = -1.6$ vs. $z = -0.84$) and cognitive flexibility worsened while all other domains remained stable ($z = -3.4$ to -0.84).

Patient 2

This patient reported disorientation, hallucinations, and long-term memory impairment, accompanied by anxious depression, insomnia, and reduced libido over the

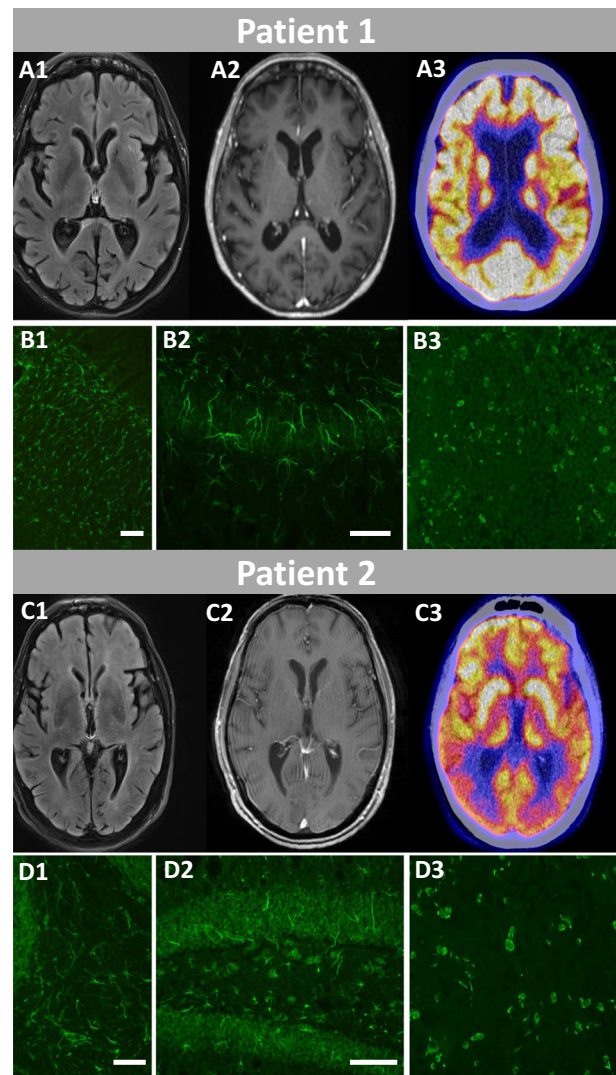


Figure 1. Clinical and molecular imaging findings. *Patient 1:* (A1–2) Representative axial C-MRI images in T2w and T1w-Gd techniques disclose no parenchymal, vascular, or blood–brain barrier abnormalities. (A3) Axial FDG-PET overlayed on computed tomography (CT) showing subtle left occipital hypometabolism with otherwise normal cortical and subcortical tracer uptake. (B) Indirect immunofluorescence testing (IFT) with anti-human IgG of patient CSF samples incubated with unfixed mouse corpus callosum (B1) and hippocampus (B2) slices as well as (B3) confirmatory testing using IFT with anti-human IgG on patient serum incubated with acetone-fixed HEK293-cells specifically transfected with GFAP α subunit (CBA, titer 1:1000). (B1 and 2) shows characteristic filamentous, astrocytic staining pattern of GFAP-AB. Scale bar = 100 μ m. *Patient 2:* (C1–2) Representative axial C-MRI images in T2w and T1w-Gd techniques showing mild microangiopathic white matter hyperintensities but no further parenchymal, vascular, or blood–brain barrier abnormalities. C3, Axial FDG-PET overlayed on CT showing left hemispheric dominant occipito-temporal hypometabolism and pronounced striatal hypermetabolism. (D) Indirect IFT shows characteristic astrocytic staining pattern of GFAP-AB (method see B, scale bar = 100 μ m). D3, CBA confirms the presence of CSF anti-GFAP antibodies (titer 1:10, method see B3). GFAP, glial fibrillary acidic protein; CBA, cell-based assay.

Table 1. Synopsis of clinical findings.

	Patient 1	Patient 2
Initial symptoms	Intermittent disorientation and navigational problems. Short-term memory deficits and practical deficits	Intermittent disorientation, hallucinations, avolition, impairment of long-term and episodic more than short-term memory
Vegetative symptoms	Insomnia, night sweats, weight loss and anorexia, hyposmia, chronic constipation, asthenia	Insomnia, diurnal somnolence, weight loss due to anorexia, constipation, meteorism, reduced libido and erectile dysfunction
Psychiatric symptoms	Anxiety, depression, avolition	
Concomitant diagnoses	Major depressive disorder, chronic constipation, left bundle branch block, meningioma	Major depressive disorder, SIADH, arterial hypertension, hypogonadotropic hypogonadism
Neurological examination	Disoriented to time. No other abnormalities	
Neuropsychological assessment (CERAD-Plus)	Impairments in semantic ($z = -2.1$) and phonematic fluency ($z = -1.6$), word finding ($z = -1.8$), performance ($z = -3.1$), visuoconstruction ($z = -3.2$), visual memory ($z = -2.9$). Visuomotor slowdown ($z = -2.9$). The Frontal Assessment Battery (FAB) moderate frontal-executive deficits. No evidence of depressiveness (9 points with a cut-off of 11), mild anxiety symptomatology (11 with cut-off at 11)	Impairments in learning performance ($z = -2.7$), consolidation performance ($z = -4.0$), recognition performance ($z = -4.6$), intrusion ($z = -2.9$), naming performance ($z = -1.9$), semantic and phonematic fluency ($z = -3.5$ and $z = -3.3$), figural memory ($z = -2.7$), visuoconstruction ($z = -2.9$), visuomotor speed, sustained attention ($z = -2.7$)
Neuropsychological assessment at follow up (1.5–2 years)	Improvements in phonematic fluency ($z = -0.84$). Deterioration in cognitive flexibility. All other domains stable. No depressive symptoms (9 points with a cut-off of 11) or pathological anxiety symptoms (6 points with cut-off at 11)	CERAD-Plus Improvements in consolidation performance ($z = -1.2$), recognition ($z = 0.81$) intrusion ($z = 0.68$), naming ($z = -0.49$), semantic fluency ($z = -0.79$), phonematic fluency ($z = 0.52$), visuoconstruction ($z = 0.75$), visuomotor speed ($z = -0.64$), sustained attention ($z = 0.16$)

preceding 4 months. Neuropsychological assessment revealed severe impairments ($z = -4.6$ to -2) in most domains. Blood work showed moderate hyponatremia consistent with SIADH and hypogonadotropic hypogonadism. Serum ANP was negative ($<1:10$) and isolated antinuclear antibodies detectable (titer 1:80). Cranial FDG-PET showed cortical *hypometabolism* besides striatal *hypermetabolism* (Fig. 1C3). CSF showed lymphocytic pleocytosis ($28/\text{mm}^3$). CSF ANP detected GFAP-AB (titer 1:10); a second CSF TBA disclosed a staining pattern highly typical for GFAP (Fig. 1B1–2). IVMP (1000 mg/d for 3 days), followed by five sessions of immunoadsorption and steroid taper were initiated. Incomplete remission and persisting pleocytosis ($15/\text{mm}^3$) at 3-month follow-up prompted initiation of rituximab 1000 mg. Two years later, all neuropsychological results were within normal limits ($z = -1.2$ to $+0.81$).

Eighteen and 9 months after initial treatment, GFAP-AB were undetectable in serum of patient 1 (CSF unavailable) and serum and CSF of patient 2. Repeat FDG-PET revealed no neoplasms in both.

Discussion

These cases are highly atypical for GFAP-A not only in that they lack typical clinicoradiological features, but also in that

the clinical picture was dominated by a rapidly progressive dementia with psychiatric and autonomic features, leading to a medical consultation within 4 and 6 months from symptom onset. With (potentially treatable) autoimmune etiologies being among the most frequent causes of rapidly progressive dementias with presentations <6 months from onset,^{5,6} and up to 76% of patients with autoimmune encephalitis present with rapidly progressive cognitive deterioration early in the disease course, CSF work-up including autoimmune panel was warranted in both cases. Due to a persisting clinical suspicion based on aforementioned red flags and in accordance with recent recommendations,⁸ initially divergent serum and CSF GFAP-AB results of patient 1 prompted independent re-testing. To this end, a CSF TBA with higher sensitivity was carried out, which ultimately yielded staining results strongly suggestive for GFAP-AB in both cases. Despite obvious methodological differences influencing sensitivity and the GFAP-typical staining pattern in the second TBA using CSF, the reason for differing results in patient 1 can ultimately not be determined on ground of the available data. However, in case of GFAP-autoimmunity, encephalitic manifestations are independent of CSF GFAP-AB titers and seem to occur in a majority of cases with GFAP-AB positivity in serum even in absence of detectable CSF titers.^{2,9}

Table 2. Synopsis of laboratory results.

	Patient 1	Patient 2
Blood work	Within normal limits	Mild hyponatremia (<128 mmol/L)
Serum antineural antibody panel IFT (ANP, Prof. Stoecker, Luebeck)	Anti-GFAP IgG 1:1000 (unfixed primate cerebellum slices (4 μ m) and confirmation on GFAP-a subunit transfected HEK cells)	Anti-GFAP IgG negative
	Amphiphysin, CV2, PNMA2 (Ma-2), Ri, Yo, Hu, recoverin, SOX1, titin, Zic4, GAD65, Tr (DNER), LGI1, CASPR2, VGKC RIA, NMDA-RAMPA-R, GABA-B, GAD65, Hu, Ri, Yo, amphiphysin, CV2 (CRMP-5), Ma1/Ma2, ANNA-3, PCA-2, Tr (DNER), ZIC4, IgLON5, AGNA, SOX-1, recoverin, aquaporin-4, MOG, glycine receptors, DPPX, ITPR1, CARPVIII, flotillin 1/2, mGluR1, mGluR5, MBP, MAG negative	
Virus serology	HAV-IgG positive, HBs Ag CIA negative, HBc Ab CIA, HBs-Ab CIA, HCV Ab CIA negative, VZV IgG EIA positive, VZV IgM EIA negative	HBs Ag CIA, HBc Ab CIA, HBs-Ab CIA, HCV Ab CIA negative, Tick-borne encephalitis (FSME) screen: IgG EIA positive, IgM EIA negative, HIV 1/2 CIA negative
Serum antibody assays	N. A.	ANA speckled 1:80, ANCA, Sm/RNP, Sm, SS-A, SS-B, Scl-70, CENP-B, Jo-1, Anti-DNA Abs negative
CSF analysis	Clear macroscopical CSF before and after centrifugation. Cell count: 1/mm ³ ; Erythrocytes: 2/mm ³ , protein 56 mg/dL (<50 mg/dL), isoelectrical fixation: diffuse, polyclonal/normal, lactate 2,3 mmol/L, tau-protein 435 pg/mL (<450 pg/mL), p-tau 56 pg/mL (<61 pg/mL), β -amyloid 1–42,437 pg/mL (>450 pg/mL)	Clear macroscopical CSF before and after centrifugation. Cell count: 28/mm ³ (lymphocytes 97%, monocytes 2%, Granulocytes 1%) (<5/mm ³), erythrocytes: 2/mm ³ , protein 81 mg/dL (<50 mg/dL), isoelectrical fixation: positive OCB, lactate 3 mmol/L (<2.3 mmol/L), tau-protein 173 pg/mL (<450 pg/mL), p-tau 28 pg/mL (<61 pg/mL), β -Amyloid 1–42,726 pg/mL (>450 pg/mL)
CSF anti neural antibody panel (ANP, Prof. Stoecker, Luebeck)	Anti-GFAP IgG negative (frozen, unfixed primate cerebellum slices [4 μ m])	Anti-GFAP IgG 1:10 (frozen, unfixed primate cerebellum slices [4 μ m] and confirmation on GFAP-a subunit transfected HEK-cells)
	Amphiphysin, CV2, PNMA2 (Ma-2), Ri, Yo, Hu, RECOVERIN, SOX1, titin, Zic4, GAD65, Tr (DNER), LGI1, CASPR2, VGKC RIA, NMDA-RAMPA-R, GABA-B, GAD65, Hu, Ri, Yo, amphiphysin, CV2 (CRMP-5), Ma1/Ma2, ANNA-3, PCA-2, Tr (DNER), ZIC4, IgLON5, AGNA, SOX-1, recoverin, aquaporin-4, MOG, glycine receptors, DPPX, ITPR1, CARPVIII, flotillin 1/2, mGluR1, mGluR5, MBP, MAG negative	
Tissue-based assay in CSF (Prof. H. Pr��b, Charit�� Berlin)	GFAP-specific binding pattern (unfixed mouse brain slices)	GFAP-specific binding pattern (unfixed mouse brain slices)

Although the clinical phenotype described in GFAP-A case series has successively been extended,¹⁰ the given presentation of GFAP-A has, to the best of our knowledge, not yet been reported. Progressive neurocognitive deficits resembling neurodegenerative dementia in GFAP-A are in line with growing evidence for astroglial dysfunction in neuropsychiatric conditions.¹¹ Indeed, accompanying encephalopathic signs are reported in up to 60% of GFAP-A cases.⁴ Quantitative behavioral testing in our cases however revealed a pattern of affected cognitive domains mainly consistent with Alzheimer's dementia. This contrasts the delirious encephalopathies described in recent and earlier descriptions of GFAP-autoimmunity^{4,12} which were either unspecifically and globally affecting

cognitive domains¹ or embedded in a wider neurological phenotype of movement disorders, seizures and hallucinations.¹²

Recent experimental evidence suggesting differential CNS tropisms of GFAP autoimmunity points toward dissociable phenotypes: acute meningitic-vasculitic and chronic relapsing encephalitic.¹³ Our observation may support the notion of a further evolving clinical spectrum of GFAP-A and of a potentially emerging chronic encephalitic subtype presenting as rapidly progressive dementia.

These cases further suggest that in the setting of rapidly progressive dementia presenting within 6 months of symptom onset, GFAP-AB screening may be a valuable

addition to autoimmune dementia panels,^{14,15} especially since given cases could mimic typical neurodegenerative dementia and may therefore go unrecognized and worse, untreated. Especially patient 1 showed features strongly suggestive of neurodegenerative dementia. However, detection of CSF GFAP-AB after re-testing and cognitive stabilization over 1.5 years associated with immunotherapy demonstrate a relevant, perhaps *secondary* autoimmunological component amenable to immunomodulation. In fact, this bears resemblance with IgLON5-disease as the prototype of overlapping autoimmunity and neurodegeneration,¹⁶ mostly presenting with sleep-related, autonomic, and neuropsychiatric symptoms, similar to our patients. These features map to the diencephalon, a somewhat pathognomonic lesion site in AQP4-AB astrocytopathy, IgLON5-disease and, less frequently, also in GFAP-A.^{4,10} However, with C-MRI being unremarkable in both our patients, functional rather than structural diencephalic deficits, ought to be postulated.

In contrast to IgLON5-disease, however, we observed lasting and quantifiable effects of intensified immunotherapy in our patients. Given similar prevalence estimates of GFAP, NMDA-R, and LGI-1 autoantibodies,⁹ we argue that GFAP-AB may serve as a valuable addition to autoimmune screening panels to identify immunotherapy-responsive forms of rapidly progressive cognitive impairment especially in the setting of negative testing for more well described autoantibodies associated with this phenotype.¹⁵ After all, identifying treatment potential in devastating neurocognitive deficits is pivotal from a clinical perspective.

Limitations

In this case study, two patients with a similarly unusual condition were identified retrospectively by the lead investigator over a time period of 2 years, in a tertiary referral center working up approximately 100 dementia cases per year. Therefore, conclusions pertaining to the general population of patients with dementia and/or autoimmunity must be drawn with care. Therefore, we aimed to ascertain highest possible validity of these findings by analyzing quantitative behavioral and multimodal gold standard immunohistochemical as well as clinical imaging data over a longitudinal course of 1.5–2 years.

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Conflict of Interests

The authors declare no conflicts of interest pertaining to the manuscript.

Ethics Approval and Consent to Participate and Disclose

Patients gave informed written consent to consent, disclose and for publication of this retrospective study.

Authors' Contributions

MF obtained and analyzed patient data, conceptualized, drafted, and revised the manuscript. JH analyzed patient data and drafted the manuscript. HP analyzed patient data and revised the manuscript. CWI and JV obtained patient data and revised the manuscript.

Data Availability

Non-identifiable data is available upon reasonable request to the corresponding author.

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