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# Glial Fibrillary Acidic Protein Astrocytopathy: Review of Pathogenesis, Imaging Features, and Radiographic Mimics

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## ABSTRACT

**SUMMARY:** Glial fibrillary acidic protein (GFAP) astrocytopathy is a recently described autoimmune inflammatory disorder of the CNS characterized by the presence of specific antibodies targeting the intracellular filament protein in mature astrocytes. The pathogenesis is heterogeneous and poorly understood, with around 20%–34% of cases occurring as a paraneoplastic syndrome, most frequently associated with ovarian teratomas. It presents clinically as acute or subacute encephalomyelitis, and the diagnosis relies on imaging and detection of GFAP-Immunoglobulin (GFAP-IgG) in the CSF. Characteristic imaging findings include linear perivascular enhancement in the white matter extending in a radial pattern. Other imaging findings include periependymal enhancement, longitudinally extensive cord signal changes, intramedullary enhancement, optic neuritis, and papillitis. There is significant imaging overlap with other neuroinflammatory diseases like neuromyelitis optica spectrum disorder and lymphoproliferative conditions. GFAP astrocytopathy is characteristically responsive to steroids with, however, a significant rate of relapse. Currently, literature on this novel entity is limited with no established diagnostic criteria or standard treatment regimen. This comprehensive review explores the clinical, radiographic, and histopathologic aspects of GFAP astrocytopathy, shedding light on its complex nature and potential diagnostic challenges. The paper highlights the neuroimaging findings with a focus on differentiating GFAP astrocytopathy from other neuroinflammatory disorders.

**ABBREVIATIONS:** ADEM = acute disseminated encephalomyelitis; AQP4 = aquaporin 4; CLIPPERS = chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids; IFA = immunofluorescence assay; IgG = Immunoglobulin G; GFAP = glial fibrillary acidic protein; MOGAD = myelin oligodendrocyte glycoprotein antibody-associated disease; NMOSD = neuromyelitis optica spectrum disorder; OCT = optical coherence tomography; PACNS = primary angiitis of the CNS; SLIPPERS = supratentorial lymphocytic inflammation with parenchymal perivascular enhancement responsive to steroids; WBC = white blood cell

Autoimmune CNS disorders are immunotherapy-responsive conditions characterized by the presence of specific antibodies that bind to intracellular or plasma membrane antigens.[1] In 2016, a novel entity, "autoimmune glial fibrillary acidic protein (GFAP) astrocytopathy," emerged to describe a corticosteroid-responsive inflammatory disorder affecting various parts of the CNS, spanning from the optic nerve to the spinal cord. This condition was strongly associated with the presence of GFAP-specific Immunoglobulin G (IgG) autoantibodies in the CSF or serum.[2] The diagnostic confirmation of autoimmune GFAP astrocytopathy relies on identifying GFAP-specific IgG in the CSF through tissue-based and cell-based assays.[3] GFAP, a structural protein found in the intermediate filaments of astrocytes, plays a pivotal role in this disorder's pathogenesis, though the exact mechanisms remain incompletely understood.[4] It is hypothesized that the condition is autoimmune in nature, with involvement of CD8+ cytotoxic T cells.[5] The GFAP antibody only serves as the biomarker for the inflammatory changes and itself does not induce any pathologic changes.[5] Additionally, there is a notable association with paraneoplastic syndrome, with around 20%–34% of patients having associated neoplasms, most frequently associated with ovarian teratoma.[6] Similar to other autoimmune encephalides, GFAP astrocytopathy can be triggered by viral encephalides, like herpes encephalitis. This is secondary to neuronal breakdown following viral infections and subsequent release of antigens. Histopathologic features of GFAP astrocytopathy are poorly described at present, with few reports describing inflammatory changes in local tissues with mononuclear infiltration by macrophages and $CD8^+$ T cells.[5]

GFAP expression is highest in the perivascular regions of the brain and around the central canal of the spinal cord, with the autoantibodies in GFAP astrocytopathy leading to lymphocytic inflammation in these areas, corresponding to enhancement seen on MR imaging. The most common clinical pattern is that

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From the Department of Radiology (D.S., S.B., A.D., G.B., V.G., N.S., P.V., A.A.), Mayo Clinic, Jacksonville, Florida; and Department of Radiology, Perelman School of Medicine (S.M.), University of Pennsylvania, Philadelphia, Pennsylvania.

Please address correspondence to Amit Agarwal, MD, Senior Associate Consultant, Department of Radiology, Mayo Clinic, Jacksonville, FL 32256; e-mail: amitmamc@gmail.com; @amitagarwalmd; @mayoradiology

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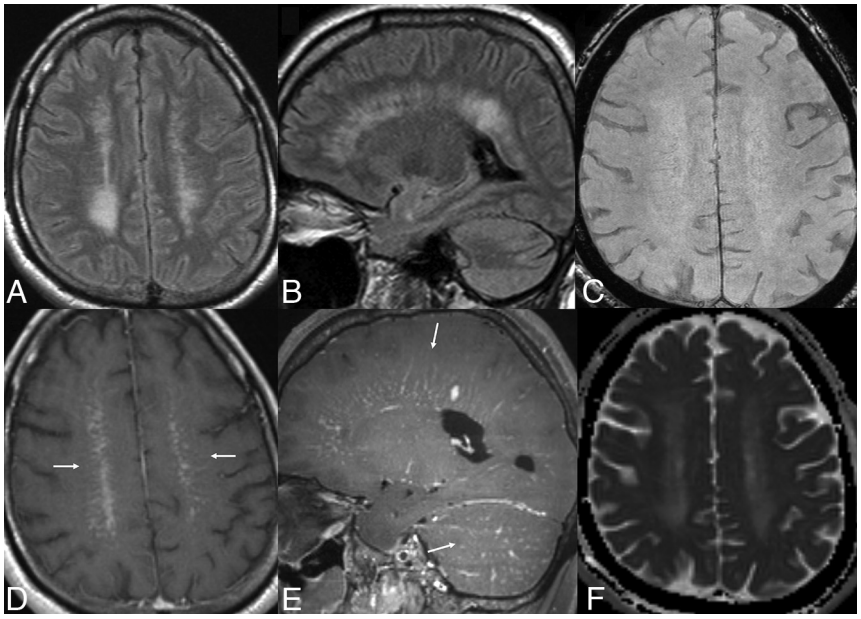


**FIG 1.** Characteristic MR imaging findings of GFAP astrocytopathy in a 68-year-old man with history of prostatic adenocarcinoma. Multiple foci of linear T2/FLAIR hyperintensity (*A* and *B*) are noted in the periventricular white matter with corresponding perivascular radial pattern enhancement (*D* and *E, arrows*). Similar pattern of enhancement is also noted in the cerebellum (*D, arrow*). SWI (*C*) is normal and ADC map (*F*) reveals T2 shine through artifacts in the periventricular white matter with no restricted diffusion. Patient had elevated WBC count of 200/mm$^3$ in his CSF (lymphocyte predominant). Positive titer for GFAP-IgG was noted on CSF analysis by using cell-binding assay. Patient received methylprednisolone 1g daily for 5 days, with remarkable clinical recovery just after the first dose and was subsequently placed on oral taper. Near-complete radiographic response was noted on the follow-up MR imaging (2 weeks) along with negative GFAP IgG titers (Online Supplemental Data).

of meningoencephalitis (with or without myelitis) and rarely as isolated myelitis. The extensive involvement of the CNS leads to a diverse array of clinical manifestations, including headaches, fever, seizures, encephalopathic and myelopathic symptoms, visual impairment, and psychiatric disorders. Common visual symptoms include blurred vision or transient visual obscurations due to optic disc edema (papillitis) and, less commonly, as painful optic neuritis. Coexisting neoplasm (most commonly ovarian teratoma) and systemic autoimmune inflammatory conditions are seen in around 20% of cases.[6] The diagnosis relies on detection of GFAP-IgG in CSF, along with supporting imaging findings. Given this wide spectrum of clinical symptoms, accurate interpretation of imaging findings becomes crucial for diagnosis and management decisions.[3,4] Common MR imaging features include parenchymal enhancement and T2 hyperintensities. The characteristic imaging findings in GFAP astrocytopathy include linear perivascular and periventricular enhancement extending in a radial pattern with associated white matter T2/FLAIR hyperintensities (Fig 1, Online Supplemental Data). Punctate and nodular patterns of enhancement can also be seen in the supra- and infratentorial brain along with leptomeningeal and ependymal enhancement. Diffusion-weighted and SWI sequences do not reveal any changes. Findings also include longitudinally extensive cord T2-hyperintensities with patchy intramedullary enhancement, periependymal and leptomeningeal enhancement, and optic disc papillitis. There is, however, a significant imaging overlap with other neuroinflammatory conditions (like neuromyelitis optica spectrum disorder [NMOSD]) and lymphoproliferative disorders.[1,2,7] This article aims to provide an overview of the expected MR imaging findings in this condition, while also delving into the histopathology and potential differential diagnoses for the identified lesions. The Online Supplemental Data highlight the common radiographic mimics of GFAP astrocytopathy with description of their epidemiologic, clinical, pathologic, and radiographic features.

## EPIDEMIOLOGY AND CLINICAL FEATURES

Epidemiologic studies on autoimmune GFAP astrocytopathy is still limited, as it was discovered in 2016.[6] Although the disease is majorly underdiagnosed due to the lack of a standardized diagnostic criteria, there has been increased recognition and more literature available in recent years. Four large series on this have been published, with two from Mayo Clinic, USA, one from Italy, and one from China. These series have reported onset at any age (median 44–50 years), with children accounting for around 10% of cases and with no racial predilection. Men and women are affected equally, except when associated with ovarian teratomas.[1,3,7] In the largest study from existing literature, by Xiao et al,[8] the median age of onset among 324 patients was identified to be 45 years (8 to 103 years), with slight predominance in females. It is important to note that around 34% of patients, in a study by Flanagan et al,[6] had a wide range of associated neoplasms, with ovarian teratoma being the most common, and others being adenocarcinomas, gliomas, head and neck squamous cell carcinomas, and multiple myeloma.[6,8] The clinical features of autoimmune GFAP astrocytopathy vary greatly, as it affects different regions of the CNS. The initial phase of GFAP astrocytopathy is characterized by fever, headaches, fatigue, nausea, and neck pain. In one of the largest studies performed, by Kunchok et al,[9] 55% of the patients presented with syndromic meningoencephalitis and 40% of patients presented with meningoencephalomyelitis. The meningoencephalitis symptoms included delirium, headaches, neck stiffness, vomiting, tremors, blurred vision, seizures, and psychiatric symptoms, while myelopathic symptoms included sensorimotor dysfunction. Visual symptoms also are a common manifestation of GFAP astrocytopathy, with heterogeneous manifestations ranging from optic neuritis, optic disc edema, and disc papillitis.[4] Optic disc edema (usually bilateral) is the most common manifestation. This can be detected and quantified with various tests, including fundus photographs, fundus fluorescein angiography, and optical coherence tomography (OCT). OCT is a noninvasive, noncontact testing technique that can be used to quantify disc edema based on retinal nerve fiber

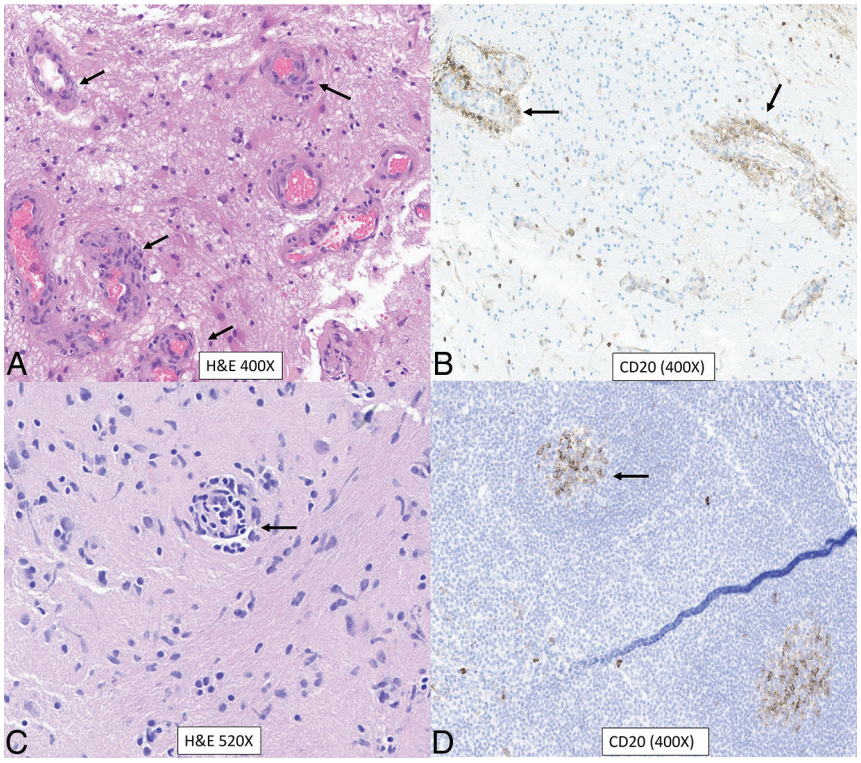


**FIG 2.** Histopathologic findings in 2 different patients with GFAP astrocytopathy (*A* and *B*) and intravascular CNS lymphoma (*C* and *D*). Hematoxylin-eosin (*A*) and CD20 (*B*) staining of brain biopsy in a patient with subacute course of encephalitis and CSF positive for GFAP autoantibodies shows extensive infiltration of inflammatory cells (*A* and *B, arrows*) mainly around the vessels with no evidence of transmural vessel wall inflammation (vasculitis). Similar stains in a different patient (*C* and *D*) show plugging of the lumen of small vessels by large atypical cells (*C, arrow*) that are positive for CD20 (*D, arrow*) and negative for CD3, consistent with intravascular large B cell lymphoma.

layer thickness, which is increased in disc edema. Comprehensive descriptions of visual pathway involvement in this condition are lacking, however, GFAP antibody evaluation should be performed in patients with encephalitis and optic disc edema. Visual symptoms are associated with a higher relapse risk and often require longer immunosuppressive therapy.[10] The above clinical presentation and CSF findings of low glucose, high protein, and elevated white blood cells (WBCs) make it difficult to differentiate it from infectious causes, particularly tuberculous meningitis. Other less frequently described patterns include a chronic relapsing course of the disease, parkinsonism, and rapidly progressive dementia.[11,12] It can rarely present clinically with area postrema–like syndrome, with spinal cord lesions, absent classic medulla oblongata lesions, and positive GFAP-IgG in CSF.[13] Overall, it is a great clinical mimic of infectious, psychological, and neurologic disorders, making it a difficult diagnosis. However, given its characteristic rapid response to immunosuppressive therapy, it is important to raise the possibility of this condition, based on neuroimaging features (Online Supplemental Data).

## PATHOPHYSIOLOGY

Glial fibrillary acidic protein is the major intracellular intermediate filament in the brain (astrocytes) responsible for the cytoskeleton in glial cells that provides mechanical strength and shape to the cells and helps in their functioning.[14] GFAP expression is essential for normal white matter architecture and the integrity of the blood–brain barrier, and the astrocytes provide both structural and functional support for neurons. In addition, GFAP can be found in the nonmyelinating Schwann cells (peripheral nerves) and glial cells of the enteric nervous system. GFAP also plays a vital role in astrogliosis after CNS injury or neurodegenerative conditions. The precise pathophysiologic mechanism of autoimmune GFAP positive astrocytopathy is yet to be fully understood, however, several mechanisms have been proposed based on biologic markers.[15] While the presence of autoantibodies against GFAP within the CNS defines this condition, the precise chain of events leading to astrocytopathy remains unclear. Given the protein location within the astrocytic cytoplasm, GFAP antibodies in the CSF and/or serum are merely biomarkers of cytotoxic T cell–mediated immunity, as the antibodies cannot bind to the intracellular antigen.[5] This also suggests that there must be an underlying triggering event exposing intracytoplasmic GFAP to the immune system, leading to the production of autoantibodies. Various triggering events have been identified in the literature. These events include Epstein–Barr virus (EBV) infection, traumatic brain injury, other autoimmune disorders, herpes simplex virus encephalitis, dengue, syphilis, and COVID-19 infection.[11] GFAP astrocytopathy induced by viral encephalitis usually follows a bimodal pattern, the first peak being due to the viral invasion, followed by the second peak driven by the autoantibodies.[16] Cancer has also been identified as one such trigger, as it may lead to paraneoplastic syndrome. Approximately 20%–34% of the patients have been discovered to exhibit concurrent tumors, with ovarian teratoma being the prevailing type, in one study accounting for nearly 34% of all neoplasms.[6,8] Coexisting autoimmune diseases are seen in approximately 20% of patients with GFAP astrocytopathy, and include type 1 diabetes mellitus, autoimmune thyroid disease, and rheumatoid arthritis.[6,8]

CSF studies have shown the presence of cytotoxic T cells further providing credence to the theory that the damage is mediated by the cellular response.[15] Evidence for the cellular response theory may be identified through immunohistochemical studies that demonstrate abundant perivascular cell infiltration (Fig 2), consistent with the perivascular enhancing patterns on imaging findings seen early in the disease process.[9] Other peculiar findings in patients with GFAP astrocytopathy include the presence of coexisting autoantibodies, such as NMDA IgG, AQ4-IgG, and antineuronal nuclear antibodies in the CSF. Conversely, there are reported cases of patients presenting similar clinical and imaging

findings who test negative for antibodies in both their CSF and serum. This further adds to the intrigue regarding the pathogenesis of this disorder. Nevertheless, a comprehensive understanding of the underlying pathophysiology of GFAP astrocytopathy remains elusive, highlighting the need for further research in this area.[17,18]

## MOLECULAR MARKERS AND HISTOPATHOLOGY

The diagnosis of GFAP astrocytopathy hinges on the identification of GFAP antibodies in the CSF of a symptomatic patient.[18] These antibodies may also be present in the patient's serum, but studies have revealed a lower serum positivity rate among patients with GFAP-specific antibodies in the CSF. This lower sensitivity and specificity in serum tests highlight the importance of relying on CSF positivity for diagnosis. Nevertheless, the presence of serum GFAP antibodies should prompt a comprehensive evaluation of the patient's clinical symptoms and imaging investigations.[19] It is again worth noting that the GFAP antibodies themselves are nonpathogenic and serve as markers of T cell–mediated autoimmune responses.[5] Various methods can be employed to detect these CSF antibodies, including cell-based assays, Western blot, or indirect immunofluorescence assays. Among these, cell-based assays have demonstrated greater accuracy compared with indirect immunofluorescence assays. Therefore, in cases where indirect immunofluorescence assays yield negative results, despite classic clinical symptoms and MR imaging findings, GFAP astrocytopathy should not be ruled out.[4]

In line with diagnostic criteria for NMOSD, Huang et al[19] proposed that diagnostic criteria for GFAP astrocytopathy should include the documentation of antibodies, along with specific clinical manifestations such as unexplained fever, tremors, headaches, encephalopathy, seizures, psychosis, ataxia, optic nerve abnormalities, and other meningoencephalitic symptoms. Although standard diganostic criteria are not yet established, classic MR imaging findings, like linear enhancement of periventricular white matter, are needed to support the diagnosis. This diagnosis should also prompt screening examinations for tumor factors and infection-related biomarkers as well. While GFAP antibodies are valuable in diagnosing GFAP astrocytopathy, they are not as useful for monitoring treatment outcomes. Researchers like Kimura et al[15] have identified CSF biologic biomarkers such as S100B and neurofilament light chain that can be used for diagnosis and prognosis assessment in patients with GFAP astrocytopathy. These markers were found to be significantly elevated in GFAP astrocytopathy, differentiating it from other disorders like multiple sclerosis, varicella zoster meningitis, and NMOSD, which do not exhibit similar concentration increases. Several other antibodies may be seen coexisting with GFAP antibodies in up to 40% of patients with GFAP astrocytopathy. The most common antibodies associated with GFAP antibodies include NMDAR–IgG, which was seen in 22% of 102 patients, with aquaporin-4 (AQP4)-IgG being the second most common. Interestingly, patients with coexisting antibodies tend to exhibit different characteristics. Those positive for both AQP4-IgG and GFAP-IgG tend to present at an earlier age. It was also noteworthy that patients with GFAP, NMDAR, and AQP4 antibodies in the CSF had a high probability of also having an ovarian teratoma. Other findings seen on CSF evaluation in the study by Flanagan et al[6] include the lymphocyte predominant elevation (78.5% of the patients), increased protein levels (80% of patients), and CSF oligoclonal bands. These findings collectively offer valuable insights into the biomarkers associated with GFAP astrocytopathy, enhancing our understanding of this complex autoimmune disorder.

Pathologic examinations have provided crucial insights, though conducted on only a limited number of patients, and have consistently revealed signs of inflammation. Notably, studies conducted by Yang et al[20] have unveiled astrogliosis accompanied by the proliferation of CD3+ and CD20+ inflammatory cells clustered around blood vessels. Moreover, biopsies performed on 4 patients have unveiled compelling evidence of inflammation characterized by the infiltration of lymphocytes, monocytes, and neutrophils within the perivascular space. Intriguingly, these signs of inflammation persist without conclusive evidence of vasculitis.[6] These histologic findings may be differentiated from the histologic findings of radiographic differentials like intravascular lymphoma or primary angiitis. Intravascular lymphoma presents with neoplastic cells that can be seen packing the lumen of small or intermediate-sized blood vessels of the brain (Fig 2).[21] Similarly, primary angiitis of the CNS classically presents with transmural inflammation and may also show different histopathologic patterns like granulomatous, lymphocytic, and necrotizing vasculitis (Online Supplemental Data).[22]

## NEUROIMAGING PATTERN

Brain and spinal MR imaging are important tools for investigating GFAP astrocytopathy due to the high prevalence of imaging abnormalities in affected individuals. The incidence of MR imaging abnormalities in patients with this condition ranges from nearly 44% to around 66% of the total cases.[4-6,9,23] On T2-weighted MR imaging, diffuse periventricular hyperintense lesions are a common feature, but the hyperintensity can also extend to regions such as the brainstem, thalamus, basal ganglia, centrum semiovale, and limbic structures, corresponding to the GFAP-enriched CNS regions.[4] Kimura et al[11] have suggested that the bilateral T2 hyperintensity of the posterior part of the thalamus is a characteristic feature of GFAP astrocytopathy. The most characteristic finding described in literature is linear perivascular radial enhancement perpendicular to the ventricles in the white matter, observed in around 44% of patients in the study by Xiao et al (Fig 1).[8] The classic linear radial enhancement was demonstrated by Long et al[7] to correspond to the areas of extensive perivascular inflammation seen in the brain biopsies of patients positive for GFAP antibodies. The enhancement is sometimes punctate or solid nodular in appearance (Fig 3) and extends beyond the periventricular region, occasionally appearing in patterns like leptomeningeal, cranial nerves, serpentine, and ependymal enhancements (Online Supplemental Data). Enhancement patterns mimicking tumefactive and nontumefactive demyelinating plaque have also been described (Online Supplemental Data).[4,23] Posterior fossa involvement is less common, though similar radial enhancement patterns can be seen in the cerebellum, with other findings including cerebellar atrophy without any T2 hyperintensity in some instances (Fig 4). Other findings include unilateral or bilateral optic nerve swelling with optic disc head enhancement (papillitis) (Fig 5).[2] Symmetric bilateral T2

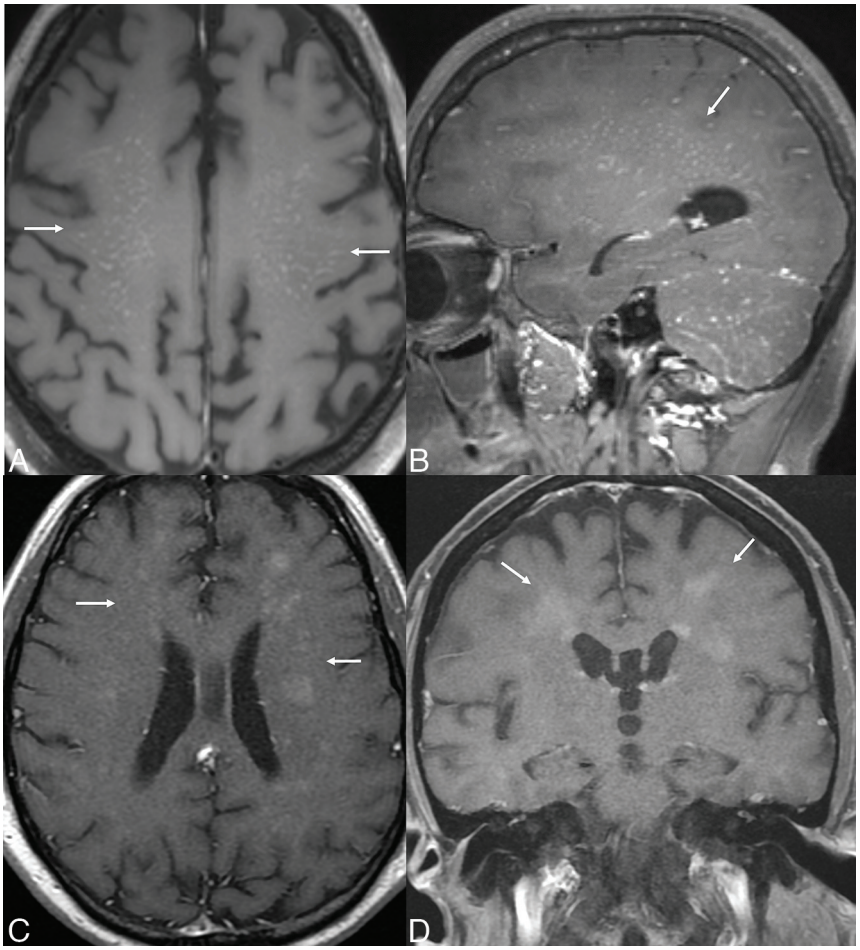


**FIG 3.** Common patterns of enhancement on MR imaging in 2 different patients with GFAP astrocytopathy. Contrast-enhanced MR imaging in 2 different patients with no significant prior history. Multiple foci of punctate enhancement noted in supratentorial and cerebellar white matter in a 42-year-old man (*A* and *B*, *arrows*). Multiple solid nodular foci of enhancement in the supratentorial white matter involving the centrum semiovale and corona radiata noted in a 35-year-old woman (*C* and *D*, *arrows*). Radiographic differentials in both cases included vasculitis, lymphoma, and neurosarcoidosis. The final diagnosis of GFAP encephalitis was made based on positive CSF and serologic titers of GFAP autoantibodies.

hyperintensity may also be observed in the posterior bulbopontine region on T2/FLAIR imaging. In some rare cases, patients have exhibited restricted diffusion in the splenial corpus callosum. On SWI, the brain parenchymal lesions do not reveal any iron deposition or microbleeds.[4–6]

Spinal MR imaging in patients presenting with myelitis often demonstrates extensive longitudinal T2 hyperintensity, spanning more than 3 vertebral segments in approximately 50% or more patients (Fig 5). Gadolinium-enhanced T1-weighted images of the spine may reveal linear pericentral, leptomeningeal, punctate, or patchy enhancement.[4,6] A French cohort study with 46 patients emphasized a higher incidence of spinal involvement, particularly in the cervical and thoracic regions.[4] Long et al's[7] investigation revealed consistent central gray matter involvement in all cases of GFAP-related myelitis. Typically, spine lesions are not diffuse and are predominantly confined to the central or peripheral regions of the cord.[2]

GFAP astrocytopathy has a monophasic course in most patients (around 83% in a French cohort study) with rapid clinical and radiographic response after immunotherapy, despite severe clinicoradiographic findings at the onset.[4] Response to steroids is a hallmark of the disease, though transition to a steroid-sparing drug may be needed in cases of relapse (20%) (Online Supplemental Data). Postimmunotherapy, an earlier reduction is seen in the meningeal enhancement rather than the nonenhancing white matter and cord lesions (T2 hyperintensities).[2] It has been suggested that this early reduction in meningeal enhancement be used to evaluate the response to therapy and to assess treatment efficacy, after the acute phase of therapy has been completed.[2] MRA and digital subtraction angiograms conducted in patients yielded normal results and are usually performed to rule out other differentials such as vasculitis.[6] However, SPECT scans in 7 patients evaluated by Kimura et al[11] by using 99mTc-hexamethylpropyleneamine oxime (4 patients) or 123I-N-isopropyl-p-iodoamphetamine (3 patients) demonstrated a notable decrease in cerebral blood flow in the frontal lobes. In contrast, Long et al's[7] study utilizing PET-CT in a GFAP antibody-positive patient exhibited striking hypermetabolism in the cerebral cortex and cerebellum, alongside diffusely increased uptake in the spinal cord. Some patients with GFAP astrocytopathy also exhibit abnormal results on electrophysiologic assessments of their visual evoked response and auditory brainstem response, further highlighting the diverse neurologic manifestations of this condition.[7,24]

Completely normal imaging of the neuraxis is uncommon in GFAP astrocytopathy. In patients with clinical symptoms of meningoencephalitis and unremarkable or nonspecific imaging features, the diagnosis primarily hinges on identification of specific GFAP antibodies in the serum and CSF. GFAP$\alpha$-IgG, when detected in CSF, is highly specific (near 100%) for GFAP astrocytopathy, sometimes with paraneoplastic etiology. If immunofluorescence assay (IFA) pattern suggests GFAP, then IFA titer and GFAP cell-binding assay are performed, which offer higher sensitivity. In one of the largest series (Flanagan et al),[6] CSF IFA was positive in 94% of patients of GFAP astrocytopathy, with elevated titers ranging from 1:4–8192 (median 1:128). The alpha subunit IgG had the highest sensitivity (100%) by using cell-based assay. These tests are highly specific (near 100%), with all the control CSF specimens (105 out of 105) in the study being negative on IFA and only 1 patient being false-positive for GFAP$\alpha$ on cell-based assay.[6] This antibody is rarely found in healthy individuals.

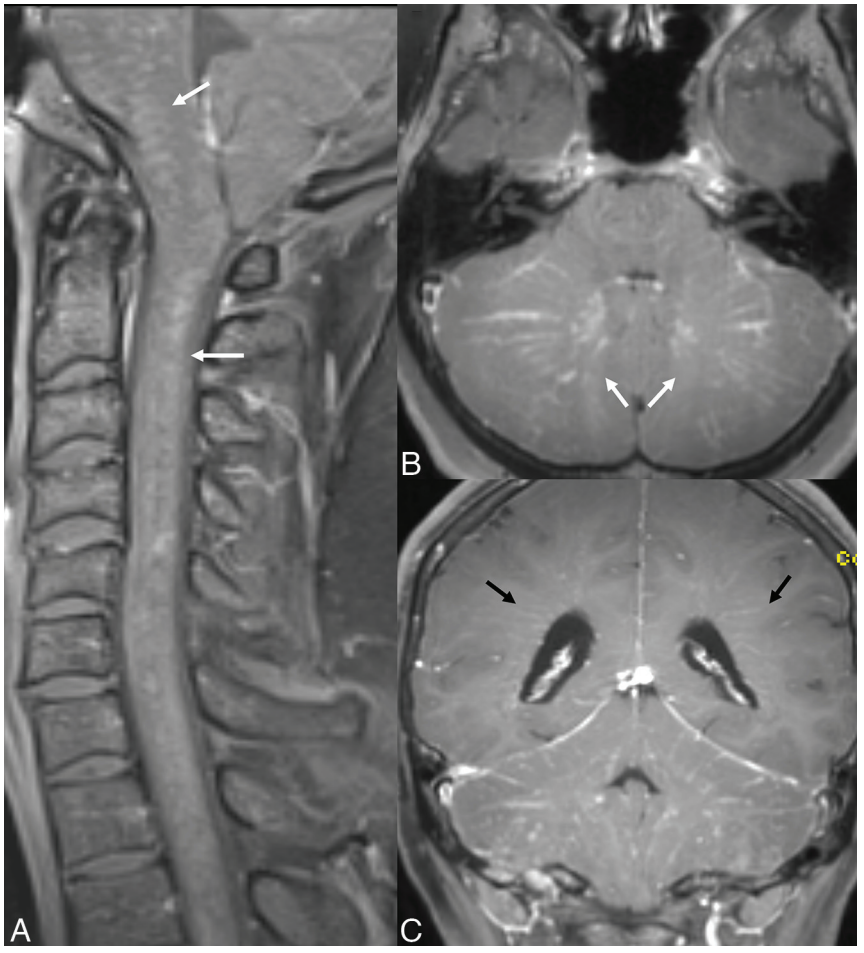


**FIG 4.** GFAP astrocytopathy in a 65-year-old man with predominant cerebellar, brainstem and spinal cord involvement. Multiple contrast-enhanced MR images reveal patchy striated enhancement in the brainstem, cervical cord (*A*, *arrows*), and the cerebellum (*B*, *arrows*). Enhancement involves primarily the central cord (*A*) with radial linear pattern in the cerebellar white matter and brainstem (*B* and *C*). Mild periventricular linear enhancement is also noted in the supratentorial white matter (*C*, *black arrows*), though less pronounced than the cerebellar enhancement. The final diagnosis of GFAP encephalomyelitis was made based on positive CSF and serologic titers of GFAP autoantibodies. Patient had a long-standing history of Crohn disease and ankylosing spondylitis and showed marked improvement in symptoms (ataxia and cognitive changes) after rituximab therapy.

GFAP evaluation is now a routine component of the "autoimmune CSF panel" at major laboratories. Rarely, brain biopsy may be needed in equivocal cases, though the histopathologic findings only confirm the inflammatory pattern with no feature specific for GFAP astrocytopathy.[1,6]

## RADIOGRAPHIC MIMICS

It is imperative to recognize that within the domain of neuroimaging, GFAP astrocytopathy is not the exclusive pathology that can manifest with linear perivascular enhancement or long segment cord signal changes. Several other neurologic disorders may present with similar radiologic features, necessitating a meticulous approach to distinguish GFAP astrocytopathy from its mimics. Given the significant imaging overlap, the neuroradiologist can at best provide some common differentials. However, with a multidisciplinary approach, greater knowledge about the epidemiologic and clinical features along with correlation with serologic/CSF biomarkers, an accurate diagnosis can usually be made (Online Supplemental Data). In this section, we discuss some of these common imaging differentials of GFAP astrocytopathy.

### *NMOSD and Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease*

NMOSD refers to closely related severe demyelinating diseases commonly associated with antibodies against AQP4 channels, classically presenting with optic neuritis and longitudinally extensive myelitis. Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) represents a group of inflammatory demyelinating disorders defined by the presence of IgG antibodies to myelin oligodendrocyte glycoprotein.[25] Despite clinical overlap with acute disseminated encephalomyelitis (ADEM), NMOSD, and MS, MOGAD is now considered to be a distinct entity, with presentations of ADEM more frequent in the pediatric population.[26] These conditions are strong radiographic mimics of GFAP astrocytopathy, sharing analogous signs of T2/FLAIR-hyperintense lesions, particularly within the brainstem and hypothalamus. Notably, the regions of T2 hyperintensity in NMOSD are typically periependymal.[27] Furthermore, all these conditions may present with longitudinally extensive T2 hyperintense spinal lesions, further complicating the diagnostic differentiation (Fig 5).[6,26,27] Spinal involvement in MOGAD is usually central, affecting both gray matter and central white matter, can be either long-segment or short-segment, and is commonly associated with leptomeningeal enhancement.[26] Cord involvement in NMOSD is usually long-segment with marked T2-hyperintense (higher than CSF) and T1-hypointense spotty lesions involving the central gray matter. Enhancement is common in all these conditions with variable patterns, including patchy "cloud-like" enhancement, thin ependymal enhancement, and ring enhancement seen in NMOSD.[27] Cord lesions in GFAP astrocytopathy are more commonly thin and linear occurring along the central canal with, however, limited utility in narrowing the differentials.[6] AQP4-IgG–positive patients preferentially present with bilateral long-segment posterior optic nerve involvement with chiasmatic extension whereas patients with MOGAD usually exhibit anterior optic nerve with perioptic involvement.[26] Pattern of optic nerve involvement in GFAP astrocytopathy is poorly described at present. With respect to brain lesions, while they are

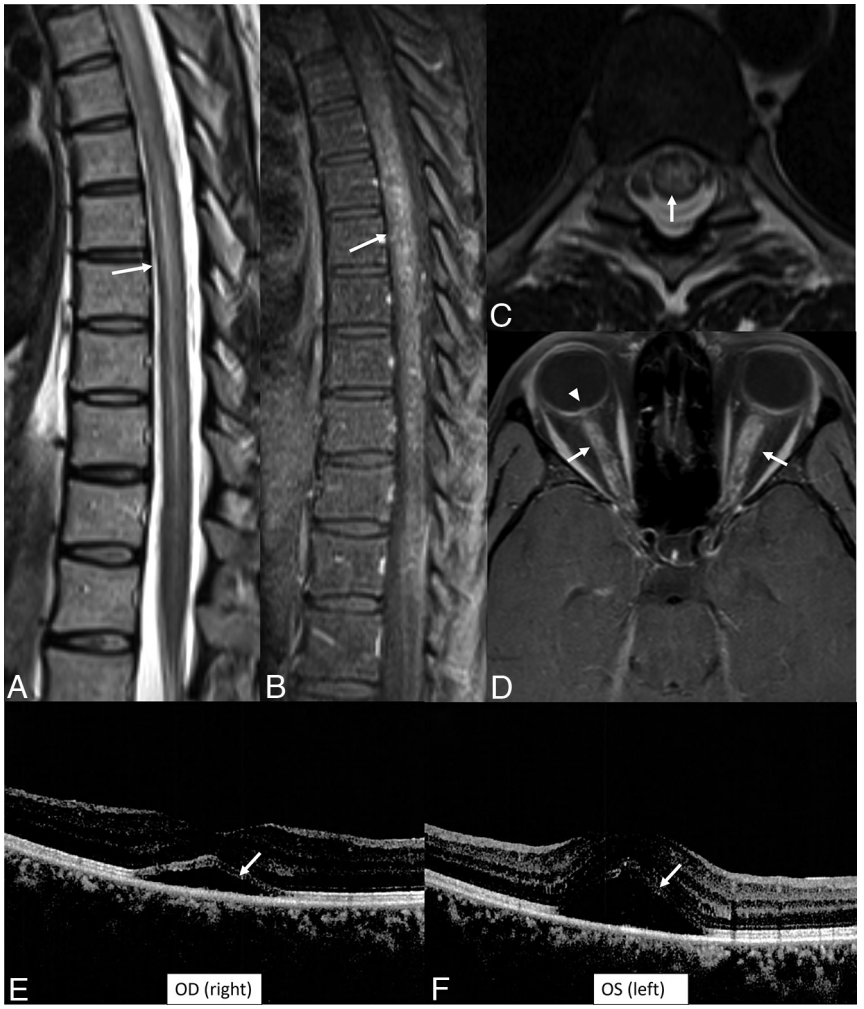


**FIG 5.** GFAP astrocytopathy in a 34-year-old woman with longitudinally extensive transverse myelitis and optic neuritis mimicking NMOSD. Patient was admitted in neurology with acute onset vision changes and sensorimotor symptoms in the lower limbs. Long segment T2 hyperintensity is noted involving the central cord (*A*, *arrow*) with patchy enhancement (*B*, *arrow*) and sparing of the cord periphery (*C*, *arrow*). Contrast-enhanced image of the orbits (*D*) reveals intense patchy enhancement involving the entire intraorbital segments of bilateral optic nerves (*D*, *arrows*) and the right optic disc head (*D*, *arrowhead*) suggesting acute optic neuritis with papillitis. OCT examination reveals increased peripapillary retinal nerve fiber layer thickness (left > right) with subretinal fluid (*E* and *F*, *arrows*). GFAP astrocytopathy was confirmed based on CSF antibody positivity and brain biopsy. CSF titers were negative for AQP4 with absence of oligoclonal bands. She underwent plasmapheresis and IV solumedrol treatment and saw rapid improvement in her symptoms.

less common in individuals with NMOSD, when they do occur, they tend to exhibit a predilection for the periependymal region in the dorsal brainstem, often involving the area postrema.[27] The classic periventricular radial enhancement is far more commonly observed in GFAP astrocytopathy.[28] The final diagnosis thus relies on epidemiologic features and serologic/CSF biomarkers.

### *Lymphoproliferative Conditions*

Numerous lymphocytic inflammatory and neoplastic conditions have similar radiographic presentation as GFAP astrocytopathy. Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) is a relatively new inflammatory disease characterized by a lymphocytic perivascular inflammatory pattern with a predilection for the pons, with characteristic curvilinear regions of "pepperlike" enhancement on imaging.[29] Supratentorial lymphocytic inflammation with parenchymal perivascular enhancement responsive to steroids (SLIPPERS) has similar pathologic findings and is considered to be the same entity with different anatomic predilection.[29] These conditions show T cell–predominant inflammatory cell infiltrates directed against an antigenic epitope in perivascular regions, primarily to exogenous antigens (such as viral infections) rather than a response to intracellular pathogens. The brainstem is particularly vulnerable to immune attack, similar to the pattern seen in Bickerstaff encephalitis and neuro-Behçet disease. The pathogenesis of these conditions is still unclear, with no characteristic serologic or CSF markers. CLIPPERS and SLIPPERS show excellent response to corticosteroids, similar to GFAP astrocytopathy.[29,30] Lymphoid granulomatosis is an uncommon lymphoproliferative disorder occurring in immunocompetent patients, with involvement of the lungs and CNS, characterized by the presence of large, positive EBV B cells, T cell infiltration, and tissue necrosis. Imaging features include punctate or linear T2 hyperintensities with contrast enhancement in perivascular distribution. Larger lesions may show solid nodular or peripheral enhancement patterns with varying amounts of perilesional edema.[31,32] Intravascular large B cell lymphoma is a rare form of non-Hodgkin lymphoma characterized by proliferation of neoplastic lymphocytes within small to medium-sized blood vessels that may or may not show parenchymal extension. The tumor cells occlude the blood vessels, resulting in patchy hemorrhagic and ischemic changes with stroke-like symptoms.[21] The most characteristic findings include multifocal hyperintense T2/FLAIR lesions with restricted diffusion (infarct-like lesions) throughout the cerebral hemispheres.[33] Lymphomatous tumor cells that extend into the perivascular brain parenchyma can form solid clusters of parenchymal enhancement (Fig 6). They are usually located deep within the white matter or close to the cortex, and frequently in the periventricular region.[34] Ependymal and leptomeningeal enhancement can be seen. These lesions are dynamic in nature, with resolution of some lesions and appearance of new lesions on temporal imaging.[21] These lesions can show rapid response to steroids, making it further challenging to

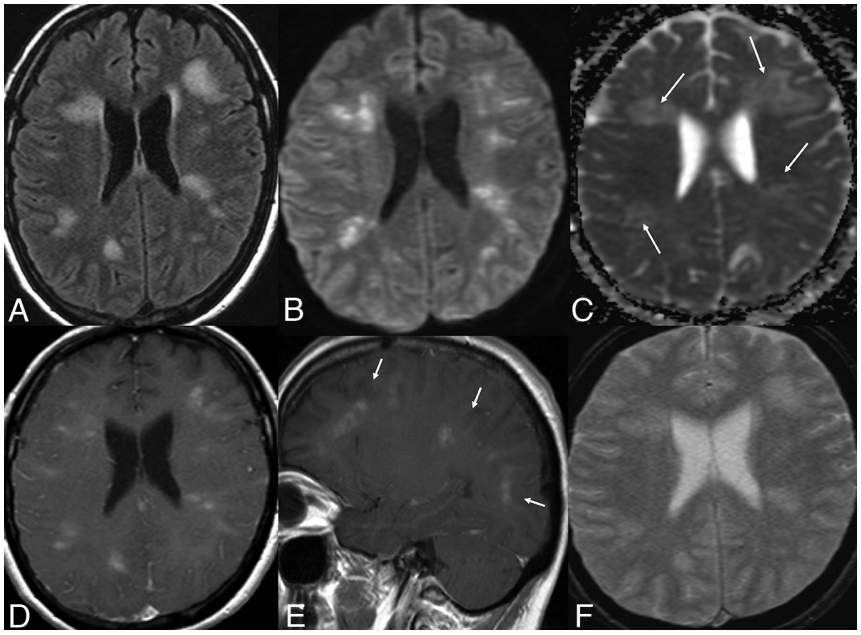


**FIG 6.** Intravascular large B cell lymphoma in a 57-year-old woman presenting with headaches, vision changes, and confusion. Multifocal discrete areas of T2/FLAIR hyperintensity (*A*) with corresponding restricted diffusion (*B*) with foci of low ADC values (*C*, *arrows*) noted in the supratentorial white matter with no significant mass effect. Contrast-enhanced axial (*D*) and sagittal (*E*) images reveal solid enhancement (*E*, *arrows*) corresponding to the areas of T2/FLAIR hyperintensities. No hemorrhagic changes are noted on SWI (*F*). Right frontal lobe biopsy revealed plugging of the lumen of multiple small vessels by large, atypical cells, which were positive for CD20 and PAX5 and negative for CD3 with BCL6 rearrangement in approximately 100% of nuclei consistent with intravascular lymphoma. No other organ involvement was seen on further work-up and the patient remains disease free, 4 years after the initial diagnosis, status post completion of 6 cycles of chemotherapy (MR-CHOP regimen).

differentiate from inflammatory conditions. This is a rapidly progressive condition with fatal outcome despite sensitivity to systemic chemotherapy.[34,35]

### *Neurosarcoidosis*

Neurosarcoidosis is a common chronic granulomatous disease with widely variable clinical and imaging manifestations and is usually in the list of radiographic differentials for most neuroinflammatory conditions. Common imaging findings include meningeal and cranial nerve enhancement, inflammatory enhancing lesions along the pituitary-hypothalamic axis, and parenchymal lesions.[36] Brain parenchymal involvement can be seen as an extension of leptomeningeal disease along the perivascular spaces, enhancing parenchymal nodules and nonenhancing foci of white matter T2 hyperintensities. Cerebrovascular complications are increasingly being recognized as a manifestation of neurosarcoidosis, including small-, medium-, and large-vessel vasculitis, as well as phlebitis and venous sinus thrombosis. Perivascular enhancement and small-vessel (including medullary) vasculitis can both result in classic radial periventricular enhancement on MR imaging (Online Supplemental Data), thus mimicking GFAP astrocytopathy. Leptomeningeal involvement in neurosarcoidosis presents as diffuse or nodular enhancement, with a predilection for the suprasellar and basal meninges, occasionally extending to the spinal cord.[36,37] Myelitis in neurosarcoidosis is usually seen to affect multiple spinal cord segments, often in a longitudinally extensive transverse myelitis pattern with variable intramedullary and meningeal enhancement.[36] Clinical features of multiple cranial neuropathies, associated pulmonary manifestation, and serologic markers are useful in demarcating this from other conditions.

### *Primary Angiitis of the CNS*

Primary angiitis of the CNS (PACNS) and CNS vasculitis associated with systemic autoimmune conditions can present as multifocal areas of enhancement and T2-hyperintensities in the cerebral parenchyma, like GFAP astrocytopathy. PACNS affects patients of all ages, but peaks at around 50 years. MR imaging findings include multiple infarcts of varying size involving different vascular territories.[38,39] Meningeal enhancement and microhemorrhages can commonly be seen. Although vessel wall imaging revealing concentric wall-thickening and enhancement and MR angiogram are helpful in the diagnostic work-up, DSA remains the criterion standard imaging technique (Online Supplemental Data). Multiple areas of narrowing and dilation of small and medium-sized vessels are typical imaging features with other less typical findings of fusiform arterial dilations, development of collaterals, and engorged medullary vessels.[38] The classic linear radial contrast enhancement seen in GFAP astrocytopathy can also be seen in various CNS vasculitis, however, angiogram studies are normal in the former.[6] The definite diagnosis of PACNS relies on biopsy that remains the standard of reference.[38] It is worth mentioning that certain atypical vasculitis disorders may lack typical angiographic changes observed in vasculitis cases but can exhibit signs of vasculitis upon biopsy.[40]

## CONCLUSIONS

Numerous new neuroinflammatory conditions have been described recently, secondary to robust advancements in molecular and genetic markers. GFAP is a unique novel encephalomyelitis where imaging plays a vital role, both in the diagnosis and management. This paper elucidates the distinctive imaging characteristics of GFAP astrocytopathy, encompassing its salient features, while concurrently delineating the differentials that may present with analogous radiographic findings. This review paper seeks to enhance the detection rate of this pathology, emphasizing its significance as an important differential in individuals manifesting with neuroinflammatory changes on imaging.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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