International Journal of Infectious Diseases 124 (2022) 164–167

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Autoimmune glial fibrillary acidic protein astrocytopathy masquerading as tuberculosis of the central nervous system: a case series

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ARTICLE INFO

Article history:
Received 2 July 2022
Revised 6 September 2022
Accepted 19 September 2022

Keywords:
Tuberculosis
Meningoencephalitis
Autoimmune glial fibrillary acidic protein astrocytopathy
Steroids

ABSTRACT

We describe the case history of three patients with meningoencephalitis who were initially treated for presumed tuberculous meningoencephalitis before being diagnosed with autoimmune glial fibrillary acidic protein (GFAP) astrocytopathy. We highlight the overlapping clinical features between autoimmune GFAP astrocytopathy and tuberculous meningoencephalitis and the challenges in early diagnosis, as both entities respond to an initial course of steroids accompanying antituberculous medications. Early evaluation of GFAP-immunoglobulin G in the cerebrospinal fluid of patients who present with aseptic meningoencephalitis could reveal autoimmune GFAP astrocytopathy, which responds favorably to immunotherapy.

Introduction

Tuberculosis (TB) is a devastating cause of meningoencephalitis (Wilkinson *et al.*, 2017). Because early recognition and treatment are central to a favorable outcome, antituberculous medications are often initiated before mycobacterial culture results become available, especially in countries where TB is endemic (Wilkinson *et al.*, 2017). We describe the case history of three patients with autoimmune glial fibrillary acidic protein (GFAP) astrocytopathy who were initially treated for tuberculous meningoencephalitis.

Case 1

A man aged 56 years presented with fever (38.5°C), confusion, headache, and hiccups. He had nuchal rigidity and intention tremors. Cerebrospinal fluid (CSF) examination revealed lymphocytic pleocytosis (151 × 10^9/µl white blood cells [WBC]), elevated protein (1.5 g/l; normal, 0.10-0.40 g/l), and reduced glucose (2.9 mmol/l, serum glucose 6.3 mmol/l), prompting the initiation of intravenous antibiotics and acyclovir. Brain magnetic resonance imaging (MRI) demonstrated diffuse leptomeningeal enhancement, especially in areas surrounding the brainstem and cerebellum (Figure 1a-c). He remained febrile despite treatment. A repeat lumbar puncture performed a week after hospitalization revealed an opening pressure of 18 cm H_20, with worsening CSF indexes (WBC 234 × 10^9/µl, protein 1.17 g/l, and glucose 3 mmol/l). Results of his other investigations are summarized in Supplementary Table 1. Despite initial treatment, he developed further confusion and drowsiness, which prompted a switch in antimicrobial treatment to antituberculous medications and dexamethasone. Two weeks later, he made significant improvements in his consciousness and mentation. A repeat MRI brain showed significant reduction in leptomeningeal enhancement (Figure 1a-c), and a repeat lumbar puncture revealed improvement in CSF indexes (WBC 50 × 10^9/µl, protein 0.58 g/dl, and glucose 3.2 mmol/l). Eight weeks after initiation of anti-TB treatment, his headaches, tremors, and confusion recurred, coinciding with dexamethasone cessation. At this point, he complained of visual blurring and was found to have bilateral fundal disc swelling. MRI brain showed a linear and perivascular pattern of enhancement radiating from the periventricular region (Figure 1d, e). Subsequent CSF analysis revealed GFAP antibody positivity. He received intravenous methyl-

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https://doi.org/10.1016/j.ijid.2022.09.029

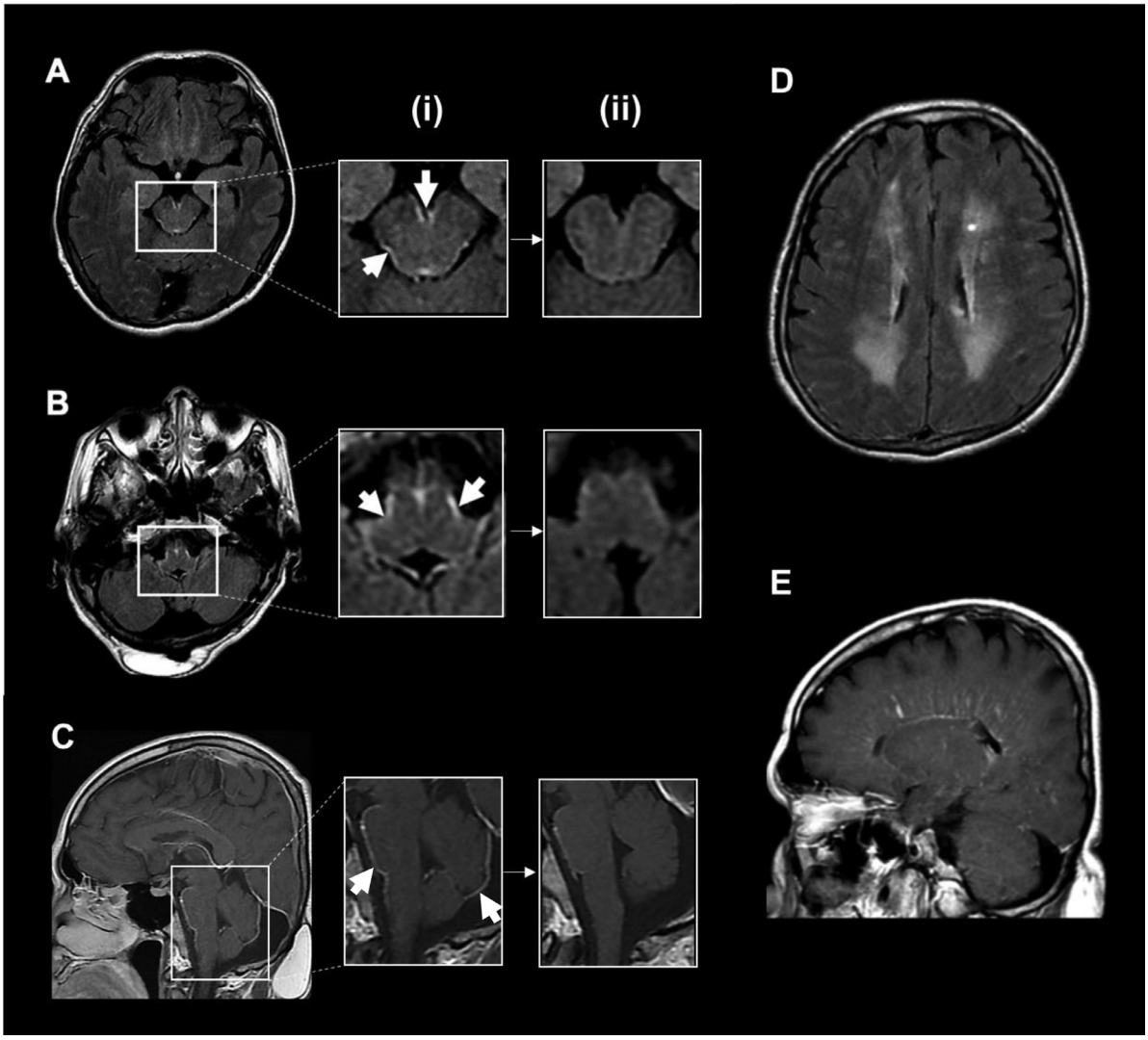

Figure 1. MRI brain scans. MRI postcontrast axial fluid attenuated inversion recovery scans reveal leptomeningeal enhancement of the pons (a) and medulla (b), whereas sagittal T1-weighted scans reveal diffuse leptomeningeal uptake of gadolinium in the pons, medulla, and cerebellum (c), as highlighted by the bold arrows in images a (i), b (i), and c (i). A 2-week treatment with dexamethasone and antituberculous medications resulted in improvement and resolution in leptomeningeal enhancement as shown in images a (ii), b (ii), and c (ii). After steroid discontinuation, he developed further clinical deterioration. A repeat MRI of the brain revealed new findings of diffuse periventricular and deep white matter hyperintensities on axial fluid attenuated inversion recovery images (d), as well as linear, perivascular pattern of enhancement radiating from the periventricular region on gadolinium-enhanced sagittal T1-weighted images (e). Abbreviation: MRI, magnetic resonance imaging.

prednisolone (1 g/day for 5 days), followed by oral prednisolone (1 mg/kg/day) and mycophenolate mofetil (2 g/day); oral prednisolone was gradually tapered over 3 months. He was continued on oral mycophenolate mofetil for 2 years and did not experience a disease relapse.

Case 2

A man aged 43 years from India presented with fever (40.2°C), confusion, hiccups, and neck stiffness. CSF opening pressure was 29 cm H_20, with lymphocytic pleocytosis (287 WBC $\times$ 10^9/µl), elevated protein (2.37 g/dl), and low glucose (1.8 mmol/l, serum glucose 4.7 mmol/l) (Supplementary Table 1). MRI brain showed diffuse leptomeningeal enhancement. He developed generalized seizures and decreased consciousness and underwent endotracheal intubation for airway protection. Antituberculous medications and dexamethasone were initiated and he was successfully extubated a week later. Three weeks after commencement of antituberculous medications and dexamethasone, he developed persistent fever and weakness involving both lower limbs. MRI of the spine showed patchy and longitudinally extensive T2 hyperintensity changes involving the cervical and thoracic segments of the spinal cord. No tuberculomas were observed in his MRI brain scans. His clinical deterioration and neuroradiological findings were initially ascribed to tuberculous paradoxical reaction because he had previously responded to antituberculous medications, and increasing the dose of dexamethasone led to clinical improvement. GFAP antibodies were subsequently reported to be positive in CSF, whereas repeated mycobacterial cultures remained negative.

Case 3

A woman aged 59 years presented with fever (38.7°C), headache, confusion, and vomiting. She had dysmetria and myoclonus. MRI brain revealed diffuse leptomeningeal enhancement. CSF opening pressure was 21.2 cm H_20, showing lymphocytic pleocytosis (WBC 505 $\times$ 10^9/µl), elevated protein (1.19 g/dl), and low glucose (2.2 mmol/l; serum glucose 5.4 mmol/l) (Supplementary Table 1). After the initiation of antituberculous medications and dexamethasone, her symptoms and CSF indexes improved. A re-

peat MRI of the brain 2 weeks into treatment revealed resolution of leptomeningeal enhancement. Autoimmune antibody test subsequently revealed GFAP positivity in the CSF. Oral dexamethasone was switched to prednisolone, and antituberculous medications were discontinued. She was continued on oral prednisolone for 3 months and remained disease-free for the subsequent 6 months.

Discussion

Elucidating an autoimmune etiology in patients with meningoencephalitis can be challenging because autoimmune GFAP astrocytopathy may be clinically indistinguishable from the infectious causes of meningoencephalitis (Flanagan *et al.*, 2017; Gravier-Dumonceau *et al.*, 2022; Héraud *et al.*, 2022; Kimura *et al.*, 2019; Li *et al.*, 2021; Salvador *et al.*, 2021; Thwaites *et al.*, 2013; Wang *et al.*, 2020; Wilkinson *et al.*, 2017). Although the presence of CSF lymphocytic pleocytosis, increased protein, hypoglycorrhachia, and diffuse leptomeningeal enhancement on neuroimaging are suggestive of tuberculous meningoencephalitis, such findings could be similarly observed in patients with autoimmune GFAP astrocytopathy (Iorio *et al.*, 2018; Ip *et al.*, 2020; Kimura *et al.*, 2019; Wang *et al.*, 2020). Because a delay in treatment carries a poor prognosis, antituberculous medications and steroids are often initiated before mycobacterial culture results become available, guided mostly by clinical suspicion (Poplin *et al.*, 2020; Thwaites *et al.*, 2013; Wilkinson *et al.*, 2017).

Patients with autoimmune GFAP astrocytopathy could respond to steroids that accompany antituberculous treatment and be erroneously diagnosed with tuberculous meningoencephalitis. Kimura and colleagues reported that nine of 14 patients with autoimmune GFAP astrocytopathy were initially treated with anti-TB medications (Kimura *et al.*, 2019), whereas only one of 22 patients from an Italian series of autoimmune GFAP astrocytopathy was initially treated for tuberculous meningitis (Iorio *et al.*, 2018). Findings from these studies highlight differences in the treatment approach to meningoencephalitis, depending on the endemicity of TB (Ip *et al.*, 2020; Wang *et al.*, 2020). Although information on the epidemiology of autoimmune GFAP astrocytopathy is sparsely available, existing data suggest that the disease is likely underrecognized given its recent discovery and poorer recognition among clinicians. A large cohort analysis in Indonesia highlighted that close to 60% of patients who were clinically diagnosed and treated for tuberculous meningitis lacked mycobacterial culture confirmation of TB (Chaidir *et al.*, 2018). It is unclear what proportion of patients who were culture-negative could harbor GFAP antibody positivity, which would support a diagnosis of autoimmune GFAP astrocytopathy. Whether GFAP antibodies could be also present in culture-confirmed tuberculous meningoencephalitis remains uncertain. Although oligoclonal bands are not routinely tested in these clinical settings, future studies should examine their value of measuring oligoclonal bands to identify patients who may require a more detailed analysis of neural autoimmune antibodies. The optimal duration of immunotherapy in patients with autoimmune GFAP astrocytopathy who present with meningoencephalitis should also be examined in future studies.

Despite overlapping features, several clinical clues may differentiate between autoimmune GFAP astrocytopathy and tuberculous meningoencephalitis. Optic disc edema is observed in 30% of GFAP astrocytopathy from papillitis arising from inflammatory vasculopathy (Chen *et al.*, 2018; Flanagan *et al.*, 2017). Unlike papilledema from raised intracranial pressure, CSF opening pressure in papillitis from autoimmune GFAP astrocytopathy is typically normal or minimally elevated (Chen *et al.*, 2018). Brainstem or movement disorders are reported in up to two-thirds of autoimmune GFAP astrocytopathy cases. Our patients had intention tremors, hiccups, and myoclonus, which could also prompt early GFAP-immunoglobulin G evaluation (Gravier-Dumonceau *et al.*, 2022). Diffuse MRI leptomeningeal enhancement is common in both clinical entities. However, basal enhancement is more pronounced in TB (Salvador *et al.*, 2021), whereas perivascular enhancement radiating from periventricular regions is encountered in 30-50% of autoimmune GFAP astrocytopathy (Flanagan *et al.*, 2017; Gravier-Dumonceau *et al.*, 2022). Spinal cord involvement may occur in autoimmune GFAP astrocytopathy, manifesting as longitudinally extensive myelitis on MRI (Flanagan *et al.*, 2017; Gravier-Dumonceau *et al.*, 2022). Finally, after an initial antituberculous treatment response, disease recrudescence with steroid taper, which could be construed as tuberculous paradoxical reaction, should also prompt consideration of autoimmune GFAP astrocytopathy. Because autoimmune GFAP astrocytopathy responds favorably to immunosuppressants, early evaluation with CSF GFAP-immunoglobulin G should be considered in patients with suspected tuberculous meningoencephalitis with atypical features.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Ethical approval

Written informed consent was obtained from all patients.

Declaration of competing interest

The authors have no competing interests to declare.

CRediT authorship contribution statement

Amy ML Quek: Writing – original draft, Writing – review & editing. **David Tang:** Writing – original draft, Writing – review & editing. **Amanda Chin:** Writing – original draft, Writing – review & editing. **Kay WP Ng:** Writing – review & editing. **Hazel Lin:** Writing – review & editing. **Raymond CS Seet:** Writing – original draft, Writing – review & editing.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.09.029.

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