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Neuroimaging Highlight

Atypical Imaging Findings in Anti-GQ1b Brainstem Encephalitis

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Brainstem encephalitis is a rare neurological entity with different etiologies.[1] When associated with ophthalmoplegia, ataxia, disturbance of awareness, in the setting of a positive antiganglioside (GQ1b) antibody serology, a diagnosis of Bickerstaff's brainstem encephalitis (BBE), a postinfectious autoimmune condition, can be made.[1–3] A large majority of the patients have a monophasic course with generally good outcomes.[4]

We report the case of a 63-year-old male with a history of tongue cancer, treated with surgery and adjuvant radiotherapy in 2012, who presented with progressive headache, diplopia, and gait unsteadiness in 2 days. The patient denied any recent illness. Neurological examination was noticeable for ataxic gait, complex bilateral ophthalmoplegia, vertical gaze-evoked nystagmus, dysarthria, and dysphagia. Mild drowsiness was apparent. Brain MRI revealed extensive T2 hypertense brainstem lesions, some with ring enhancement post-gadolinium (Figure 1A–D). Cerebrospinal fluid (CSF) investigation documented normal opening pressure [15 cm H20 (5–20 cm H20)], mild pleocytosis [10 cells/μL, predominant lymphocytic (<5 cells/μL)], elevated protein [81 mg/dL (15-45 mg/dL)], normal glucose levels [69 mg/dl, 69% (60%–80% from blood glucose)], and a slight cerebral barrier dysfunction disorder with IgG index of 0.72 (0.3 to 0.7). Cytological examination of CSF was normal. Serum and/or CSF antibodies (Joaquim Chaves, Lisbon) were negative (Anti- Hu, -Ri, -Yo, -CV2/CRMP5, -amphiphysin, -Ta/Ma2, -Ma1, -SOX1, -GAD65, -NMDAR, -AMPA, -GABAA, - GABAB, -LGI1, -CASPR2, -GlyR, -mGluR1, -MOG, and AQP4). CSF and blood cultures were negative for bacteriological agents including Listeria and mycobacterium tuberculosis. PCR multiplex for the neurotropic virus (HSV1, HSV2, VZV, EBV, CMV, HHV6, HHV7, Enteroviruses, Parvovirus, Adenoviruses) and serology for *B. burgdorferi*, *M. pneumoniae*, and *C. Jejuni* were also negative. Thoracic–abdominopelvic CT and PET scan did not reveal any relevant changes. Laboratory results were relevant for strong positive antiganglioside (GQ1b) antibodies (detected by EUROIMMUN immunoblot assay). Other antiganglioside antibodies (-Sulfatides, -GM1, -GM2, -GM3, - GM4, GD1a, -GD1b, -GT1b, -GD2, -GD3, -GT1a, -GT1b) were negative. The patient was treated with intravenous immunoglobulins for 5 days, leading to a near-complete clinical recovery. A subsequent MRI (4 weeks later) showed marked imaging appearances improvement, with contrast enhancement resolution. Nevertheless, multiple microbleeds were still visible (Figure 1E–H).

This case highlights an atypical radiological presentation of GQ1b brainstem encephalitis. MRI findings in BBE are generally nonspecific and are detected in only approximately 30% of the cases.[5] They include extensive high-signal intensity lesions on T2-weighted imaging, concerning the midbrain and pons, and sometimes the thalamus and basal ganglia.[5,6] One single report to date described additional involvement of the spinal cord.[7] These abnormalities usually reduce or disappear completely, after several months, even though, they might remain for longer periods, according to some reports.[6] Post-gadolinium enhancement is also usually not detected, with some authors arguing this can be present along with other autoimmunological diseases.[8] Furthermore, Roos et al.[9] described a case, in which strong focal enhancement in the brainstem was detected. Additionally, in our patient, there were T2* hypointensities present in the follow-up MRI consistent with microhemorrhages. This is also not common in GQ1b brainstem encephalitis, being reported previously in only two patients with Listeria rhombencephalitis with additional GQ1b antibody positivity.[10,11] The underlying mechanism of intracerebral microhemorrhages remains unknown but some have argued that it can be related to an autoimmune response associated, with vascular and endothelial cell activation, triggering the release of procoagulant factors and proinflammatory cytokines.[11] Although in our case report CSF investigations for Listeria were negative, we hypothesized that probably another nondetected infectious triggered an anti-GQ1b autoimmune response. These findings raise questions about the pathophysiology of microhemorrhages, namely whether they represent a sign of an underlying auto-immune response involving dysregulation of coagulation pathways and endothelial cell activation. However, this topic remains unclear and requires further investigation.

A wide differential diagnosis was considered, given the atypical imaging findings in this patient, including an infectious etiology

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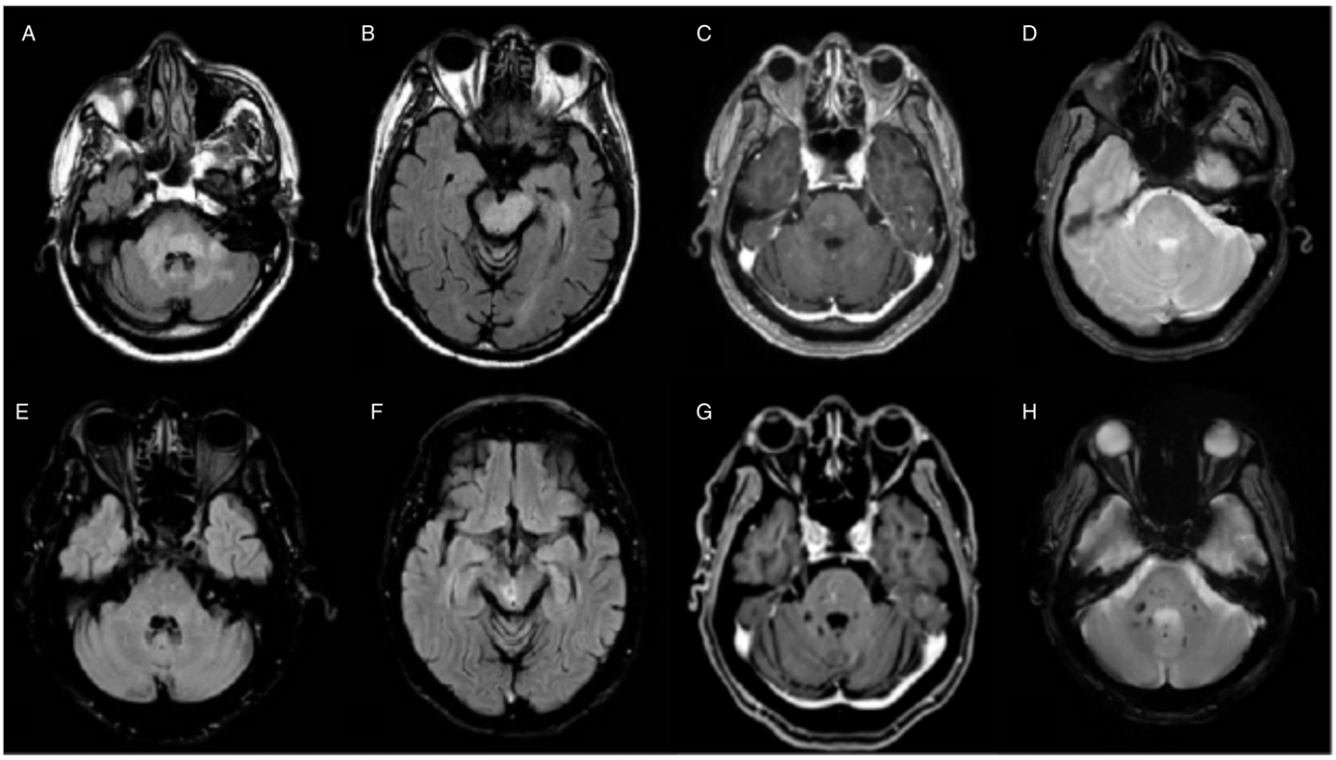

Figure 1: (A–D) Extensive involvement of the brainstem by T2 hyperintense (A, B) and ring-enhancing lesions post-gadolinium (C), with some microbleeds (D). E–H: Marked improvement of the lesion burden both on T2 FLAIR (E, F) as well as of the ring-enhancing lesions (G), though with the persistence of brainstem and cerebellar microbleeds as shown by T2* hypointensities (H). Please note some inherent differences in contrast windowing and slice thickness and orientation due to images acquired in scanners of different vendors under different conditions.

(a viral or bacterial disease), an autoimmune process (Behcet's disease, neurosarcoidosis, or other vasculitis entities), brain tumor, and paraneoplastic encephalomyelitis.[1,3] However, the absence of systemic symptoms, negative autoimmune, viral, and bacterial screenings, made these differential diagnoses unlikely. Radiation necrosis was considered but ultimately ruled out given the fact the brainstem/posterior fossa was outside of the radiation field.[12] In our case, even though the MRI showed extensive signal changes and post-gadolinium enhancement, a near-complete clinical recovery happened, favoring the final diagnosis of BBE, especially when considering positive anti-GQ1b antibodies. To our knowledge, an imaging appearance with ring-enhancing lesions with microbleeds has not been previously reported in the literature, thus widening the spectrum of possible BBE-imaging phenotypes. This case also highlights that anti-GQ1b screening should be part of the work-up for brainstem encephalitis.

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Conflicts of Interest. The authors have no conflicts of interest to declare.

Statement of Authorship. GC, FS, JR: Case concept and design, acquisition, interpretation of data, and manuscript writing. MP, MVB: Case concept and design, acquisition, interpretation of data, and critical revision of the manuscript for intellectual content.

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