LETTER TO THE EDITOR

To The Editor

Salmonella Typhi Bacteremia and Mild Encephalitis with a Reversible Splenial Lesion

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A 29-year-old man presented with 3 days of progressive word-finding difficulty, coordination impairment, and headache in the context of a diarrheal illness. He had no history of prior illnesses, was not on any medications, and had no significant travel history. On exam, he was febrile and tachycardic. Language exam revealed decreased fluency with grammatical errors, verbal paraphasias (e.g. "descended" instead of "distended"), and mild anomia. For example, when asked to name the tip of a pen, the patient responded, "it's what you write with, the stylet, the stylo, the tip." The patient was dysarthric. He had left-sided dysmetria and dysdiadochokinesis without associated weakness, as well as a slightly wide-based gait. There was no ideomotor apraxia. Formal cognitive testing was not completed. On bedside testing, processing of serial sevens was slowed. No meningeal signs were observed. Routine blood investigations revealed hyponatremia (serum sodium 123 mmol/L), thrombocytopenia, and a mild acute kidney injury. CT head was normal. Cerebrospinal fluid studies showed 1×10^6/L WBCs, protein of 0.26 g/L, glucose of 3.4 mmol/L, negative gram stain, and negative viral PCR for herpes simplex virus 1 and 2. Peripheral smear showed no evidence of hemolysis. The patient was initially treated empirically with ceftriaxone, vancomycin, dexamethasone, and acyclovir.

Magnetic resonance imaging (MRI) revealed a homogenously diffusion-restricting ovoid splenial lesion (Figure 1(A), (B), and (D)) and bilateral diffusion restriction in the centrum semiovale (Figure 1(C)). There was no associated gadolinium enhancement. Blood cultures were positive at 41 hours for *Salmonella typhi*. Stool cultures were also positive for *S. typhi*. Transthoracic and transesophageal echocardiograms were negative for vegetations and valvular disease. The patient was maintained on intravenous ceftriaxone, while other empiric treatments were discontinued. Four days after his initial presentation, repeat blood cultures were negative and the patient returned to his neurologic baseline, with intact language and coordination on examination. Repeat MRI on day 7 revealed complete resolution of the splenial lesion (Figure 1(E), (F), and (H)) and diffusion restriction in the centrum semiovale (Figure 1(G)).

Mild encephalitis with a reversible splenial lesion (MERS) is an uncommon clinicoradiologic syndrome. The initial clinical presentation of MERS is nonspecific; common presenting symptoms include headache, seizures, ataxia, and altered level of consciousness. Notably, callosal disconnection syndromes, such as unilateral apraxia, alexia, and agraphia, have not been described in MERS and were not observed in our patient. The characteristic MRI finding is a solitary, ovoid lesion of the splenium of the corpus callosum that demonstrates diffusion restriction and low apparent diffusion coefficient values. Neurologic and radiologic resolution are key to making the diagnosis of MERS.

Numerous pediatric cases of MERS have been described, particularly among Japanese populations, while adult cases are comparatively rare. A 2017 review by Yuan et al. identified 29 cases of adult-onset MERS in the English language scientific literature published between January 2004 and March 2016.[1] Among these patients, the most common clinical manifestations were fever and headache. Cerebrospinal fluid studies may be within normal limits or show mild, transient protein elevation and leukocytosis. Given the nonspecific presentation, patients ultimately diagnosed with MERS are often treated empirically for bacterial meningitis and viral encephalitis, and some undergo treatment with pulse steroids and intravenous immunoglobulins. All cases of MERS have clinicoradiologic resolution by definition, and it is difficult to determine the efficacy of such treatments retrospectively. In the majority of cases, clinical and radiologic resolution occurs within 1–2 weeks of presentation.

Infectious causes of MERS include numerous viral (adenovirus, Chikungunya virus, dengue virus, Epstein–Barr virus, influenza A and B viruses, and rotavirus) and bacterial (*Enterococcus faecalis*, *Staph aureus*, and *Mycoplasma pneumoniae*) pathogens.[1–3] Kobuchi et al. described a case of MERS secondary to *Salmonella enteritidis* in an 8-year-old Japanese patient, but MERS as a manifestation of *S. typhi* infection has not previously been reported to the best of our knowledge.[3]

How diverse pathogens result in a common clinicoradiologic entity is incompletely understood. The homogenous, diffusion-restricting lesion characteristic of MERS is consistent with cytotoxic edema and is similar to lesions seen in familial hemiplegic migraine and venous sinus occlusion.[4] Cytotoxic edema is thought to be the result of an inflammatory cytokine cascade triggered by infection.[5,6] Hyponatremia accompanies many presentations of MERS, including our case, and may contribute to the intracellular edema.[7] The predilection for the splenium is not completely understood, but may be related to a higher density of cytokine and glutamate receptors, density of interhemispheric fibers, and a relative lack of adrenergic tone. Some authors have proposed that MERS be included in the broader category of cytotoxic lesions of the corpus callosum (CLOCCs).[5]

"MERS type II" has been used to describe cases in which reversible splenial lesions are accompanied by more extensive white matter lesions. A 2013 review by Notebaert et al. identified 17 cases of MERS type II, of which only 2 cases were adult patients, and in both cases the causative pathogen was unknown.[6] Patients with a MERS type II radiologic appearances have a mild clinical course, similar to other MERS cases. Kobuchi et al. reported bilateral parietal white matter lesions in a patient who had *S. enteritidis* MERS.[3] Our patient had bilateral diffusion-restricting lesions involving the centrum semiovale as well as the splenium, which could be considered MERS type II. The distinction between MERS and MERS type II is not consistent in the literature. Based on the clinical and etiologic similarities among reported cases, it is likely MERS I and II represent a continuum rather than distinct disease entities.

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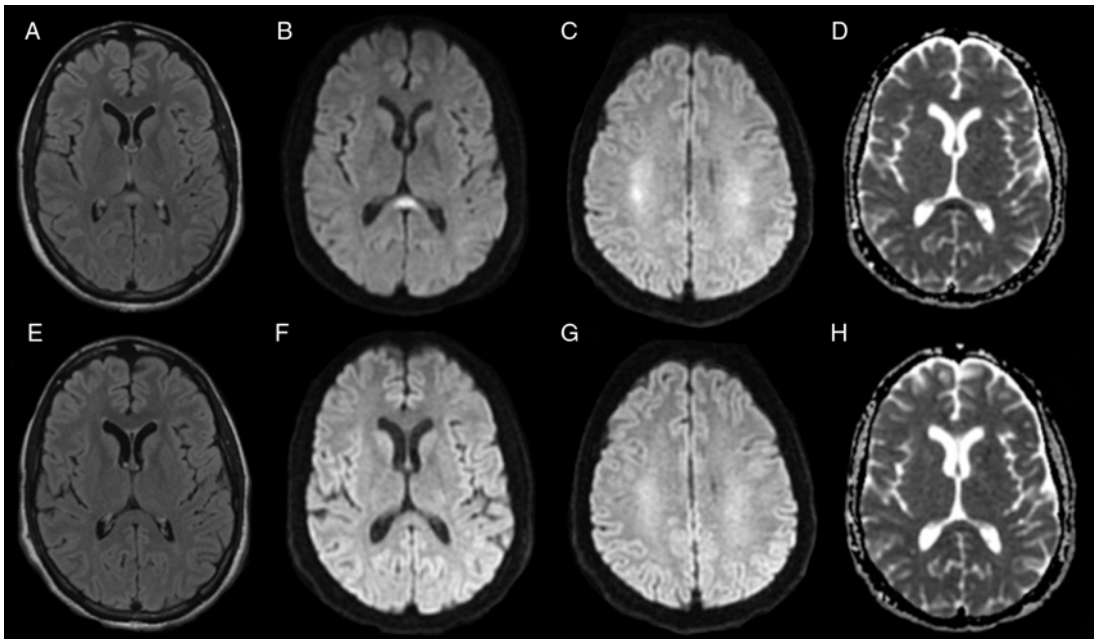

Figure 1: *Axial MRI sequences from day 1 (A–D) and day 7 (E–H) following presentation. (A) T2 fluid attenuation inversion recovery (FLAIR) sequence shows hyperintensity of the splenium of the corpus callosum. (B) Diffusion-weighted imaging (DWI) sequence shows hyperintensity of the splenium, and (C) bilateral centrum semiovale. (D) Corresponding low apparent diffusion coefficient values. (E–H) corresponding T2 FLAIR, DWI, and apparent diffusion coefficient sequences on day 7 following presentation which show resolution of diffusion restriction in the splenium and centrum semiovale.*

Reported noninfectious causes of reversible splenial lesions include antiepileptic drug withdrawal, high-altitude cerebral edema, hemolytic uremic syndrome, hypoglycemia, hyponatremia, and systemic lupus erythematosus flares.[5] Acute disseminated encephalomyelitis (ADEM), posterior reversible encephalopathy syndrome (PRES), extrapontine myelinolysis, pericallosal artery infarction, and Marchiafava–Bignami disease are further diagnostic considerations when confronted with a splenial lesion. Marchiafava–Bignami disease is characterized by focal demyelination of the corpus callosum and typically occurs in malnourished patients with alcohol use disorder. In contrast to lesions characteristic of MERS, lesions in ADEM are typically enhancing, asymmetric, and may resolve slowly over weeks or months.

Central nervous system manifestations of *Salmonella* include encephalopathy, meningitis, and focal infections (brain abscess, subdural empyema, and epidural abscess).[8] Focal infections carry a significant mortality rate, and necessitate a prolonged course of antibiotic therapy and consideration of surgical intervention, unlike the relatively mild course of MERS.

S. typhi bacteremia causing MERS has not been previously described. Our case highlights MERS as a distinct, uncommon clinicoradiologic syndrome in adults, associated with a broad array of pathogens.

Disclosures

Drs. McKenzie, Sugarman, Peng, Bond, Teleg, Minty, and Cooke report no disclosures or conflicts of interest associated with this manuscript.

Statement of Authorship

EDM was involved in manuscript drafting and critical revision of the manuscript. JS, JP, CB, ET, and EM were involved in critical revision of the manuscript. LJS was involved in study supervision and critical revision of the manuscript.

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