CASE REPORT

Atypical Presentation of Acute Encephalomyelitis Associated with Hyperosmolar Hyperglycemic State in a 63 Year Old Female

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CASE PRESENTATION

A 63-year-old independently living retired woman was admitted to hospital with decreased level of consciousness (LOC) and confusion. She had been well until the previous morning when she experienced onset of flu-like symptoms, nausea, vomiting and lethargy; the sudden change in consciousness prompted the patient’s family to call the emergency medical services (EMS). This episode was preceded by an upper respiratory tract infection two weeks prior to admission. Past medical history was significant for type 2 diabetes mellitus. Her medications included insulin glargine, metformin and glyburide although she had been non-adherent with these medications for four days prior to presentation. She had no known sick contacts, and no history of recent travel.

On arrival to hospital, she was febrile at 38.2°C and her heart rate and blood pressure were within normal limits. Initial neurological examination revealed a Glasgow Coma Scale (GCS) of 9; she opened her eyes to tactile stimulus, made incomprehensible sounds and localized to pain. She had nuchal rigidity, right gaze preference, sluggish right pupillary light reflex, left sided neglect, with normal passive movement of all four limbs. The remainder of the physical exam was noncontributory.

Initial laboratory values were as follows (with lab normal values in parentheses): serum glucose 41.4 mmol/L (3.8-11.9 mmol/l), serum osmolality 334 mmol/kg (280-300 mmol/kg), venous blood gas with pH 7.30 (7.32-7.42) and bicarbonate 18 mmol/L (22-30 mmol/L), white blood cell (WBC) 20.7 x 10^9/L, predominantly neutrophilic (18.6 x 10^9/L), creatinine 115 μmol/L (64-111 μmol/L), urea 11.1 mmol/L, lactate 4.2 mmol/L (0.5-2.2 mmol/L), hemoglobin A1C 12.5% (4.0-6.0%), ESR 37 mm/h (0-15 mm/h) and CRP 25.4 mg/L (<10 mg/L). All other serum investigations were within normal limits including: ketones, electrolytes, calcium, phosphate, magnesium, albumin, liver and thyroid function tests, serum B12, anti-nuclear antibody, rheumatoid factor, and anti-neutrophil cytoplasmic antibody. Cerebrospinal fluid (CSF) showed WBC of 5/μL, glucose 18.8 mmol/L, protein 1.0g/L with absent oligoclonal banding. Infectious work-up was negative on chest x-ray, urinalysis, abdominal computed tomography (CT), blood cultures and CSF (gram stain and culture, herpes simplex virus and West Nile virus). CT head on arrival revealed a small wedge-shaped focus of low attenuation in the right mid temporal lobe, which was subsequently visualized with T2 weighted and FLAIR sequences on magnetic resonance imaging (MRI) (Figure 1) with no evidence of infarction on diffusion-weighted images.

She was successfully managed with intravenous fluids and insulin for hyperglycemia. Empiric anti-infective agents (ampicillin, ceftriaxone, vancomycin, fluconazole and acyclovir) and high dose steroids were initiated for presumed meningitis/encephalitis and continued until infection was ruled out. Due to persistently decreased LOC, she underwent electroencephalography (EEG) the morning after admission, which revealed generalized slowing with frequent sharp waves in the frontocentral regions. Few hours later, she became less responsive (GCS 8) consistent with a post-ictal state, prompting initiation of phenytoin.

By the third day of admission, the patient’s GCS normalized. Despite correction of hyperglycemia and hyperosmolality and no focus for infection, she continued to display moderate confusion, was not oriented to place and time, displayed poor attention and memory, and had no recollection of the preceding week’s events. Left lower limb weakness was noted (motor strength: 4/5), but a full neurological examination revealed no other deficits.
INTRODUCTION

Acute disseminated encephalomyelitis (ADEM) is a monophasic immunological disease of the central nervous system. It has an incidence of 0.4 to 0.8 per 100,000, with the predominant age of onset being in childhood. Pathological features of ADEM include perivascular inflammation and edema followed by CNS demyelination. The pathogenesis of ADEM is unknown. Animal models indicate that both primary autoimmune and secondary immune responses to an environmental or infectious stimulus may contribute to the development of auto-antigens, inflammation and subsequent demyelination.

ADEM typically develops one month following a viral infection, with upper respiratory tract infections being most frequently linked to its occurrences. ADEM has been described, less commonly, following personal history of childhood exanthematous disease or immunization with but not limited to the measles, mumps or rubella vaccine. In half of adults presenting with the disease, preceding infection or vaccination is not found. There have also been published reports of ADEM secondary to malignancy, toxins, drugs including sulphonamides and the correction of hypercortisolism after the surgical management of Cushing’s disease. There have been no reported cases of ADEM precipitated by or occurring concomitantly with hyperosmolar hyperglycemic state.

Neurologic deficits in ADEM can have an abrupt onset or evolve over several days. Clinical presentation depends on the CNS region involved. Most common signs include: obtundation and depressed LOC, unilateral long tract signs (85%), acute hemiparesis (76%), ataxia (59%), and meningismus (26-31%) caused by inflammation of the subarachnoid space. In children, persistent fever, headache and seizures occur more frequently, while in adults motor and sensory deficits predominate.

DIAGNOSIS

Diagnosis of ADEM is based on clinical grounds, taking into account patient history, neurologic and neuroimaging findings along with CSF analysis. The clinical differential diagnosis in adults includes multiple sclerosis (MS), infectious meningitis, encephalitis, metabolic-related encephalopathy from electrolyte disturbances, hyperglycemia, renal, liver, adrenal or thyroid dysfunction and diffuse hypoxemia, related to infarction or following seizure.

While not pathognomonic, cardinal features of ADEM include a history of preceding infection followed by the return of fever and systemic symptoms, altered LOC, multifocal neurologic dysfunction, seizures, or movement disorders. Suggestive features on CSF analysis include lymphocytic pleocytosis and elevated protein levels. Oligoclonal banding may be transiently present.

Neuroimaging plays a key role in the diagnosis of ADEM but so far no standardized MRI criteria have been identified that are specific to ADEM. Typical MRI findings are
multiple, bilateral, symmetric, large lesions in subcortical and central white matter in cerebral hemisphere, cerebellum, brainstem or spinal cord with relative sparing of the periventricular area. Abnormalities are more likely to be seen on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images. The radiographic differential diagnosis for hyper-intense lesions includes MS, ischemic demyelination from anoxia, vasculitis or infarction, infectious and toxin-related demyelination. In ADEM, MRI changes occur early, usually when the neurological signs and symptoms appear. Lesions of MS differ in appearance and location, they tend to be sharp, well demarcated, asymmetrical and found in the periventricular, juxtacortical, infratentorial, or spinal cord regions. Additionally, it is widely accepted that follow-up MRI scans can help establish or confirm the diagnosis of ADEM; the appearance of new lesions would be strongly suggestive of MS, permanence of lesions would support infarction while lesions in ADEM are expected to resolve or remain stable in appearance. Lesions secondary to hyperglycemia are characteristically bilateral, well-circumscribed, hyper-intense on T1 weighted images and located in the caudate nucleus.

A diagnostic brain biopsy is generally discouraged due to its invasive nature and limited histopathological classification guidelines to unequivocally establish a diagnosis. It may be considered in cases where a CNS malignancy is suspected. Histological findings in ADEM include perivascular infiltration with macrophages and T-cells. Differentiating features from MS include restricted demyelination to perivascular area, without confluent demyelination.

**MANAGEMENT**

First line treatment for ADEM is high dose intravenous corticosteroids, with the goal of halting the inflammatory reaction within the CNS and expediting clinical recovery. Plasmapheresis may be effective for ADEM that fails to respond to high-dose corticosteroid treatment. Beneficial effects have also been reported with intravenous immunoglobulin (IVIG) treatment. Complete neurological recovery occurs in 70% of the cases, typically over one to six months. The most common neurologic sequelae following ADEM are focal motor deficits.

**BACK TO THE CASE**

The patient demonstrated continued but delayed recovery as most patients with hyperglycemia and osmolality have a fairly rapid return to normal LOC and cognition with correction of the glucose and osmolality disturbances. During hospitalization, the patient’s Folstein Mini-Mental Status Exam went from indeterminate (day 1) to 24 (day 5) and finally to 30 (day 8). The patient also had demonstrable improvement in power in her left lower limb (5/5) throughout the stay. Repeat EEG (day 5) revealed improved generalized slowing and frequent sharp waves with no visible epileptiform activity. Repeat MRI (Figure 2; day 8) demonstrated near complete resolution of the right temporal lobe lesion with no associated areas of enhancement. Phenytoin was discontinued due to the normalization of EEG brain activity, and improvement noted on MRI. The patient was transferred to a rehabilitation ward on day 14 with eventual return home. There were no persistent neurological deficits.

**Figure 2:** A) MRI brain (axial section) on day eight of admission that demonstrates near-resolution of the hyper-intense right mid-temporal lobe mass previously seen on day two MRI. B) MRI brain (coronal section) on day eight that also reveals the near complete resolution of the right mid-temporal lobe mass.
The rapid regression of the right temporal lobe lesion, together with the near resolution of symptoms suggested that continuing corticosteroid or starting IVIG therapy would have limited benefit here. The temporal relationship between the acute encephalopathy, polysymptomatic neurologic deficits and MRI changes are in keeping with ADEM. However, given the presentation of HHS, seizure activity, and history of poor glycemic control, this combination may have contributed to the pathogenesis. There are a variety of hypotheses for hyperglycemia-induced MRI changes; one is the deposition of myelin breakdown products, which can theoretically serve as a trigger for inflammation and lead to demyelination.

This report represents a very atypical case of acute encephalomyelitis. Firstly, the presentation at age 63 is certainly unusual, as most cases of ADEM present in the pediatric population. Secondly, the lesion seen on MRI was singular as opposed to the more common multi-focal disseminated pattern seen. It is unclear if this represents a more attenuated and focally limited case of acute encephalomyelitis or calls into question the diagnosis of encephalomyelitis to begin with. Alternative diagnoses, such as myelinolysis due to the osmotic disturbances or ischemic infarction from cerebrovascular disease or anoxia from prolonged seizure would have more likely resulted in a persistent MRI lesion with residual neurological deficits. To the authors’ knowledge there have been no previously reported cases of acute encephalomyelitis in association with a hyperglycemic emergency. Moreover, given the atypical presentation in this case, establishing whether or not severe glycemic disturbances could be a precipitant for encephalomyelitis would require corroboration from additional case reports. Nonetheless, the prolonged but transient neurological symptoms and MRI findings would suggest the strong possibility of ADEM in the face of a definitive HHS.

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REFERENCES