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CASE REPORT

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Acute disseminated encephalomyelitis in two Nigerian children with typhoid fever

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Abstract The involvement of central nervous system in children with typhoid fever is common. However, encephalopathy with focal neurological signs, coma and cerebellitis is rare. We report two children from the South-western part of Nigeria with blood culture proven typhoid fever who developed encephalopathy and acute cerebellar syndrome due to acute disseminated encephalomyelitis (ADEM). In this report, we discussed the symptomatology and management of post-Salmonella disseminated encephalomyelitis in children.

Key words: Cerebellar syndrome, Children, Encephalomyelitis, Fever, Typhoid.

Introduction

Typhoid fever still remains a major public health problem, with global annual incidence of about 21 million cases.[1] The greater burden however, occur in the developing countries with annual incidence of 10.2 – 50.3 per 100, 000 population since most of these population neither have adequate portable water nor proper waste disposal methods.[2]

Children typically present with fever, anorexia, headache, abdominal pains, diarrhoea, constipation and myalgia. Central nervous system involvement in typhoid fever which constitutes an important atypical presentation in childhood has a reported incidence ranging from 5 to 35 percent depending on the age group and drug resistance.[3] They usually manifest with neuropsychiatric features such as confusion, encephalopathy, meningism, convulsions and focal neurological deficits.[3]

In children, post-infectious CNS disease is common, and in most cases, they follow viral illness such as chicken pox, mumps, cytomegalovirus, Ebstein-Barr virus, Herpes simplex and measles infection.[4] However, bacterial agents such as *Salmonella, Streptococcus and Campylobacter* have been implicated.[4] Disseminated encephalomyelitis is an inflammatory disease involving multiple sites within the central nervous system. It is characterised by a predemyelinating infection; encephalopathy (seizure, coma and other focal neurological signs) and cerebellitis, manifesting with cerebellar ataxia and tremor.[4] This disease entity as a complication of enteric fever is very rare and only few cases had been reported in India.[5] In Nigeria, none has been reported despite various analysis of neuro-psychiatric manifestations of typhoid fever.[3]

We therefore, report two children from South-western Nigeria with culture proven typhoid fever, encephalopathy, acute cerebellar syndrome and Magnetic Resonance Imaging or histopathologic evidence of ADEM.

Case 1

LJ, a 7 year old girl was admitted into the Children Emergency Room of the Wesley Guild Hospital Unit of Obafemi Awolowo University Teaching Hospitals' Complex, Ilesa on the 3rd October, 2011 with high grade continuous fever of 8 days, headache, constipation, vomiting and abdominal distension of 3 days. She was conscious on admission, but was moderately dehydrated, febrile (temperature was 39.1^0C), dyspneic and tachypneic (respiratory rate was 68 cycles/ minute), tachycardic (heart rate 136 beats / minute) and moderately pale. The blood pressure was however normal, 100/60 mmHg. Her abdomen was grossly distended, she had generalised as well as rebound tenderness, guarding and absent bowel sound. On neurological examination, her higher mental functions and cranial nerves were normal. There were no signs of meningeal irritation or sensory deficit and the muscle power was normal.

The plain abdominal X-rays (Supine) and abdominal ultrasonography revealed features of gut perforation, intestinal obstruction and abscess collection in the peritoneum. Blood culture confirmed *Salmonella typhi*, which was sensitive to Ceftriaxone, Genticin, Ofloxacin and Tarivid. The urine and stool microscopy, culture and

sensitivity were normal. The haematological profile showed moderate anaemia (Packed Cell Volume of 22%); leucopaenia (total white cell count of 2, 200 / mm^3); neutrophilia (69% neutrophils); normal serum electrolytes (sodium = 134 mmol/L; potassium = 3.8mmol/L; Chloride 116 mmol/L; bicarbonate = 21 mmol/L). Although, blood urea was elevated (9.8mmol/ L), creatinine (95µmol/ L) and the liver enzymes were within normal limit. She was commenced on intravenous ceftriaxone and metronidazole. She also had surgery to drain the peritoneal abscess and repair of the ileal perforation within two hours of presentation. The immediate post-operative period was uneventful.

Fifty-two hours after the surgery, she had two episodes of generalised tonic-clonic convulsions and became unconscious (Glasgow Coma Score of 7/15). She had positive signs of meningeal irritation, global hypertonia and hyperreflexia with sustained ankle clonus. Diagnosis of typhoid septicaemia with encephalitis was made. The repeat serum electrolytes, urea, creatinine and random blood sugar were normal. The cerebrospinal fluid analysis showed pleocytosis (WBC > $12/mm^3$) and elevated protein (72g/ dl). It was however sterile (no organism was identified or cultured). She had Magnetic Resonance Imaging (MRI) because of repeated convulsions, deepening coma, focal neurological signs and absent pupillary reflex. This revealed widespread large globular lesions affecting the subcortical white matter. The periventricular structures were however normal. There was also no evidence of intraparenchymal or intraventricular collection (figure 1).

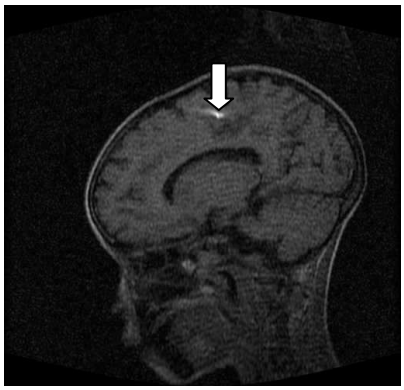

Fig 1: A saggital T1 weighted MRI scan of the brain
The arrow shows an hyperintense lesions affecting the subcortical white matter. The periventricular structures were normal and there was no evidence of intraparenchymal or intraventricular collection.

She regained consciousness 22 hours later but subsequently developed bilateral cerebellar signs such as tremor, ataxia, nystagmus and dysdiadocokinesia. Also, she had bowel and urinary incontinence, expressive and receptive aphasia as well as visual impairment.

Based on the post-infectious encephalopathy, cerebellitis and the MRI findings, diagnosis of acute disseminated encephalomyelitis was made. She was commenced on intravenous dexamethasone and later oral prednisolone. Eleven days after admission, she was no longer having cerebellar signs and also not aphasic or visually impaired. She was subsequently discharged on oral Prednisolone 5 weeks after admission. She was yet to be seen at follow-up clinic at the time of writing this report.

Case 2

AS, a 12 year old boy was admitted to the Children Emergency Room of the Ekiti State University Teaching Hospital, Ado-Ekiti, Ekiti State, Nigeria on 15th August, 2011 with continuous fever of two weeks, vomiting, diarrhoea, and abdominal pain of four days. On examination, he was conscious but irritable and acutely ill-looking. He had a temperature of 39.4^0C, was dyspneic and tachypneic (respiratory rate 72 cycles per minute). He was also lethargic, moderately dehydrated and pale. He had a normal blood pressure of 95/60mmHg but was tachycardic with heart rate of 128 beats/ minute and in sinus rhythm. Heart sounds and intensity were normal with no murmur. The lung fields were also clear on auscultation. His abdomen was however tense with generalized tenderness and guarding on palpation. There was no rebound tenderness and the bowel sounds were hyperactive. The spleen and liver were not palpably enlarged and there was no other mass noted. Neurological examination was normal at presentation.

Initial laboratory findings revealed the following: Moderate anaemia with Packed Cell Volume (PCV) of 25%; leucopaenia with total white cell count of 2,800/ mm^3, and normal platelet count of 132, 000/ mm^3. Although he was acidotic with serum bicarbonate of 17 mmol/ L, other serum electrolytes and glucose were normal. Sodium was 135mmol/l, potassium was 3.2mmol/ L, chloride was 108mmol/ L and random blood sugar was 4.8 mmol/ L. In addition, the serum total protein and albumin were normal: 77 g/l and 36 g/l respectively. However, the liver enzymes were elevated (Alkaline Phosphate, = 131U/L; Aspartate aminotransferase, = 300U/L; Alanine Aminotransferase, = 73U/L) and serum total bilirubin (245µmol/ l).

Abdominal ultrasonography showed minimal fluid collection in the peritoneum and the plain (erect and supine) abdominal X-rays showed slightly enlarged large bowel loops but no air under the diaphragm. Diagnosis of enteric fever (typhoid septicaemia) was made based on her clinical presentation and laboratory findings. He was managed with intravenous Ceftriaxone and metronidazole. On the fourth day of admission, the blood culture done at presentation confirmed *Salmonella typhi* which was sensitive to Ofloxacin, Ceftriaxone, Ciprofloxacin, Imipem and Amikacin but resistant to Genticin, Cotrimoxazole and Cefuroxime. However, the urine and the stool were sterile. Ceftriaxone was therefore continued due to steady progress in the clinical state.
By the 9th day of admission, his condition deteriorated. Initially, he had fine tremor, tachycardia, tachypnoea and temperature of 40.3^0C. Later, he had several epi-

sodes of generalised tonic-clonic convulsions, became deeply unconscious (Glasgow Coma Score of 4), his pupils became unreactive to light, had global hypertonia and hyperreflexia with sustained ankle clonus, hypertension and bradycardia. Due to the suspected raised intracranial pressure, he was giving hyperventillation and IV 10% mannitol, however, he died about 2 hours after the onset of convulsion. Lumbar puncture could not be done before his demise due to the severe cardiopulmonary instability and suspected intracranial hypertension. Also, CT scan or MRI was not done because of financial constraint.

His autopsy revealed congestion of the terminal 10 – 15cm of the ileum. The mesenteric lymph nodes were enlarged, but there was no area of ulceration or haemorrhage. On histology, there was thinning of the mucosa of the terminal ileum, effacement of its villi and loss of mucosa glands. The submucosa was infiltrated by numerous lymphocytes. The mesenteric lymph nodes as well as the vessels of the submucosa were also congested, in keeping with typhoid ileitis. Grossly, there was slight oedema of the brain, but no area of haemorrhage or necrosis. However, on histology, there was a widespread demyelination of the brain, especially around the microglial cells and the small vessels of the pons, midbrain and cerebellum. The impression was therefore acute disseminated encephalomyelitis in a child with typhoid septicaemia.

Discussion

Characteristically, acute disseminated encephalomyelitis which is a form of post infectious encephalopathy result from viral infections. However, the present case reports like few others [5,6] show that it can also be caused by bacterial infections such as typhoid fever.

Although, there are many postulations on the pathogenesis of CNS involvement in typhoid fever; the exact pathogenesis is still unclear.[4,] Some of the factors implicated include hyperpyrexia, hypovitaminosis, metabolic derangements such as hypoglycaemia, hyponatremia, hypernatremia and hypocalcemia.[7,8] Others are toxaemia, cerebral oedema, secondary neuronal changes and non-specific inflammatory changes in the vessels of the brain. These non-specific inflammatory changes include capillary thrombosis, haemorrhage, oedema, and perivascular infilteration associated with widespread demyelination.[4] Both patients had widespread demyelination of the brain. This was confirmed in the first patient by MRI scan of the brain and in the second by histopathology.

Typhoid encephalitis has been regarded as a very unusual complication[3] and it is usually a late feature of typhoid fever, as shown by our patients. In addition, the first patient had tremor, choreoathethoid movement, ataxia and dysdiadocokinesia. These features are seen in patients with cerebellitis or basal ganglia lesion. Although they (except tremors) were absent in the second child possibly because of the short duration of stay following convulsion, he had histopathologic features of cerebellitis.

Typically, patients with ADEM present with encephalopathy and cerebellar ataxia.[4,7] It has been reported that the neurological presentation in ADEM vary from an acute explosive onset, with a maximum neurological deficit attained within 1 day, to more indolent progression with maximum deficit of 31 days.[4] In several reports, most children with ADEM (up to 90 percent) had polysymptomatic encephalopathy and cerebellar dysfunction.[4,7] They may also present with facial weakness, dysarthria, dysphagia, ophthalmoplegia, visual impairment arising from optic neuritis; acute flaccid paraparesis and urinary dysfunction resulting from myelitis.[4,7] Our first patient had most of these features. Also, cerebrospinal fluid of this patient showed a mild pleocytosis, slight protein increase and sterile cultures, which agrees with most reports on post-typhoid encephalomyelitis.[4-6]

There are few reports on the brain MRI findings in children with ADEM, particularly in the developing nations. These findings include areas of hyperintense lesions in the subcortical regions of the brain stem and the cerebellum.[4] According to Ahmed *et al*,[9] they are thought to be due to cytotoxic and or diffuse vasogenic cerebral oedema. Other MRI findings in typhoid encephalopathy include bilateral symmetrical hypodensity with slight hypertrophy of the gyri and diffuse cerebral oedema without any focal lesion. [6]

In patients with ADEM, intravenous methylprednisone or dexamethasone, followed by oral Prednisolone have been reported to be effective, usually leading to improved recovery and less disability.[4,10] The first patient who had steroid improved steadily with no obvious neurologic sequelae at discharge. Other treatment modalities include immunomodulatory therapies such as the use of immunoglobulins and plasmapharesis. The survival rates of patients with ADEM is usually high, especially if they are able to overcome the initial acute complications such as intracranial hypertension and metabolic derangement.[4,10] Sadly, our second patient who deteriorated on the 9th day apparently because of these initial complications, died before the diagnosis of ADEM was made histopathologically. In undiagnosed and or untreated patients, the mortality rate may be as high as 20 percent, and the risk of permanent neurological deficits 10 – 30 percent.[7]

Typhoid fever is associated with several neurological complications including post-infectious demyelination as the underlying pathological process. This is usually reversible but occasionally may be irreversibly lethal if left untreated. Since clinical diagnosis of ADEM may not be clear initially and in the absence of brain MRI scan, paediatricians, particularly those who work in resource-poor countries, should consider this diagnosis in children with typhoid encephalopathy associated with

cerebellar dysfunction. Also, more work needs to be done in this area to determine the burden of this disease and factors predictive of its mortality.

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Authors' contributions

Adegoke SA: Conceived the study, did literature search on the subject, managed the patients and did the manuscript writing, editing and review.

Ayoola OO: Involved in the management of the patients, manuscript editing and review.

Oseni SBA: Involved in the management of the patients and manuscript review.

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