

Acute Hemorrhagic Leukoencephalitis in a Patient with Sickle Cell Disease: A Case Report

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Citation

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Abstract

Acute hemorrhagic leukoencephalitis (AHLE), otherwise known as Hurst's Disease, is a rare, rapidly progressive and usually fatal demyelinating condition affecting the central nervous system. It is usually preceded by an upper respiratory tract infection and is thought by many authors to be a hyperacute form of post infectious encephalomyelitis. It was recently found to be linked to Epstein-Barr virus infection. We report what we think is the first case of AHLE occurring in a child with homozygous sickle cell disease. As with our case, this is usually a fatal condition; however, there have been few recent reports of survival following aggressive, high dose corticosteroid therapy. It is therefore important to recognize this disease early so appropriate treatment can be instituted.

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INTRODUCTION

Acute hemorrhagic leukoencephalitis (AHLE) is a rare, fulminant, demyelinating condition of the central nervous system (CNS) which is usually fatal. The condition was first described by Weston Hurst [1] in 1941 and later by Adams [2] in 1949. Since these first descriptions, there has been less than 100 adult [3,4,5,6,7,8] and 10 pediatric [9,10] cases of AHLE reported in the literature. So far, only 4 children with the condition have survived and of these only one has definitive pathological confirmation of the diagnosis.

It is widely hypothesized that because AHLE shares many clinical features with acute disseminated encephalomyelitis (ADEM), the two are part of a spectrum of diseases rather than two distinct entities. Both conditions are commonly preceded by upper respiratory tract infections, infection with Herpes simplex virus (HSV), Epstein-Barr virus (EBV), influenza virus, rubella, measles, mumps or by vaccination. We report a fatal case of pediatric AHLE in a sickler who was diagnosed with infectious mononucleosis some 4 years previously. To our knowledge, this is the first reported case of AHLE occurring in a person with sickle cell disease.

CASE REPORT

This 10 year old girl with sickle cell disease (Hb SS) presented with a one week history of a "flu-like" illness

which resolved. One day prior to presentation she developed severe headache associated with fever and one episode of vomiting. She was treated with acetaminophen but was found unresponsive some eight hours later.

On examination, she was unresponsive with a Glasgow Coma Score of 10/15 (eye response-5; verbal response-1; motor response -4) with fluctuations in consciousness noted during examination. She was also febrile with a temperature of 100.4 F. There was generalized hypotonia and hyporeflexia associated with marked neck stiffness. Kernig's and Brudzinsky's signs were negative. There was no obvious hemiparesis. Her pupils were small and sluggishly reactive to light. Fundoscopy revealed a normal appearing optic disc on the right while the left was not properly visualized. Laboratory results at the time revealed a polymorphonuclear leukocytosis. A lumbar puncture was not performed.

A computed tomography (CT) scan of the brain was done which revealed bilateral frontal lobe white matter changes which were thought to be due to either cerebritis or an infiltrative disease such as lymphoma or a high grade glioma. There was evidence of marked cerebral edema with early coning. (Figure 1).

Figure 1

Figure 1: Non-contrast CT scan showing asymmetric expansion of frontal lobe white matter and the genu of the corpus callosum with bowing of the anterior falx cerebri to the right. Frontal lobe sulcal effacement is also evident.



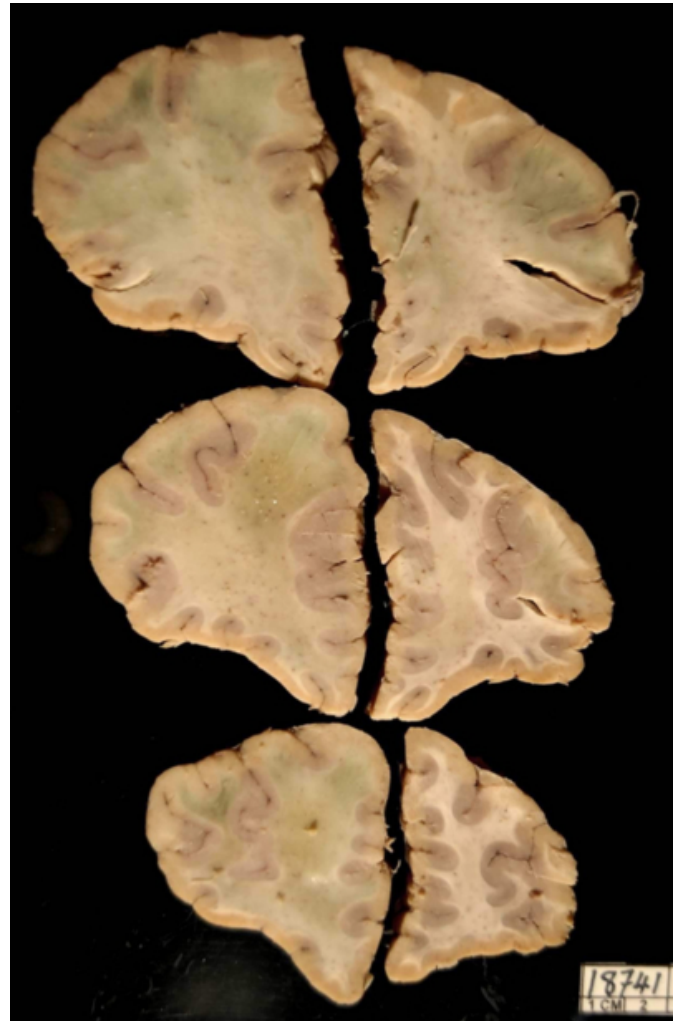
The patient was admitted to the Intensive Care Unit with a working diagnosis of viral meningoencephalitis and aggressive therapy was instituted. However despite this, she died within 24 hours of presentation.

In her past medical history, she had had several admissions previously for acute chest syndrome, dactylitis and the most recent in 2002 at the age of 6 years old for infectious mononucleosis. At this time, she had a positive Monospot test. One month later, Epstein Barr Virus viral capsid antigen (EBV-VCA) IgM and IgG were reactive.

At autopsy, the brain weighed 1250gm. Sectioning revealed expansion of the frontal lobe white matter, more marked on the left (fig. 2).

Figure 2

Figure 2: Sections of frontal lobe exhibiting asymmetric expansion of white matter and multiple punctuate hemorrhages more marked on the left. Icterus is also present.



Histology of these areas showed a marked acute inflammatory cell infiltrate within the white matter with accentuation around all types of blood vessels. This was associated with fibrin deposition and hemorrhage around many of the vessels with surrounding demyelination (Fig. 3, 4). Viral inclusion bodies were not identified. There was no evidence of neoplasia, thrombosis, granulomas, fungi or parasites.

Figure 3

Figure 3: The image on the left illustrates acute white matter inflammation with accentuation around blood vessels whilst the right shows fibrinoid degeneration of blood vessel walls with surrounding hemorrhage. (H&E).

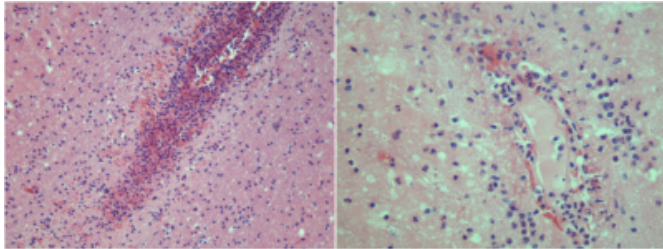
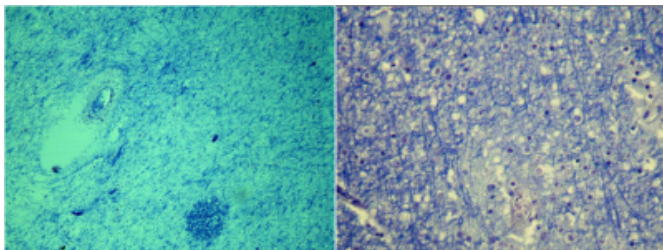


Figure 4

Figure 4: The image on the left illustrates perivascular demyelination while the right shows areas with more widespread demyelination (LFB).



DISCUSSION

Only two diseases of white matter result in a monophasic illness characterized by rapidly progressive, widespread demyelination: acute hemorrhagic leukoencephalitis (AHLE) and acute disseminated encephalomyelitis (ADEM). AHLE and ADEM are thought to represent the extremes of a spectrum of diseases rather than two distinct entities [11]. Most patients with ADEM will recover but AHLE progresses rapidly from confusion to stupor to coma; death usually occurs an average of six days after the onset of symptoms. Both are commonly preceded by upper respiratory tract infections or by HSV, EBV, rubella, measles, mumps, influenza virus infection or vaccination. This association has been observed in most cases of AHLE described so far; however, an active search for such causes has been unrevealing as it was in our patient.

In the case presented here, there was a history of an upper respiratory tract infection approximately one week prior to presentation. Interestingly as well, our patient who was known to be a sickler (HB SS disease), was diagnosed with infectious mononucleosis some four years previously. Also, a blood sample taken at the time of last presentation was positive for Herpes simplex I (HSV I) IgG using the Herpes

Select Elisa kit. However, cultures of both lung and brain tissue obtained at autopsy were sterile.

The pathogenesis of both AHLE and ADEM is not fully understood, but an immune-mediated process is strongly suspected. The pathological changes in both these conditions are quite similar – they range from perivascular edema, lymphocytic infiltrates and endothelial proliferation in ADEM to vessel wall necrosis, fibrinoid degeneration, infiltrates of neutrophils and sometimes eosinophils as well as perivascular hemorrhage in AHLE [12]. Identical lesions occur in arterioles and capillaries as well as venules, as occurred in our case. Perivascular demyelination is thought to occur sometime after the vascular insult.

It must also be stressed that any patient with sickle cell anemia, but more so a child, who presents with symptoms and signs of a central nervous system disorder, must be urgently and thoroughly investigated as there are many well known neurological complications. Cerebrovascular accidents (CVAs) are leading causes of neurologic morbidity and mortality in sickle cell anemia, and as many as 12% of these patients experience a stroke by age 21 years [13]. These CVAs maybe ischemic or hemorrhagic. Other common central nervous system pathologies associated with hemoglobinopathies include subarachnoid hemorrhage and meningitis. More recently, acute encephalopathy with parvovirus B19 infection in a child with thalassemia was reported in the literature [14].

Usually, CT scans and magnetic resonance imaging (MRI) are quite accurate in diagnosing and differentiating these lesions. In the case presented here, a CT scan done at the time of presentation revealed asymmetric white matter changes within the frontal lobe which was thought to be consistent with either marked edema or with an infiltrative disease (Fig. 1). Differentials offered by radiology at the time included cerebritis, lymphoma or a high grade glioma. Clinically, viral meningoencephalitis was the working diagnosis and appropriate therapy was instituted. This case emphasizes the point that although there are common neurological complications associated with sickle cell disease, these patients are also subject to all other possible neurological diseases and a diagnosis should only be made after proper clinical and imaging examinations are carried out.

This is, as far as we know, the first reported case of AHLE occurring in a sickler; whether the underlying hemoglobinopathy predisposes to this rare condition is yet to

be seen as more literature emerges about this form of leukoencephalopathy.

So far, there have been only four recorded nonfatal pediatric cases of AHLE reported in the literature with only one having pathological confirmation while all the others were diagnosed on clinical and radiographic grounds; in all cases, high dose corticosteroid therapy was used [11]. It is therefore thought and recommended by some that once a viral cause for white matter disease has been excluded, then it may be of value to administer corticosteroids early in a patient who is deteriorating acutely. Prospective investigation of the effects of anti-inflammatory therapy in conditions such as AHLE and ADEM is thus needed.

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