Case of the Week

You are a pediatrics resident who is doing a neurology rotation. Your first patient is a four-month-old girl. Her parents have taken her to their pediatrician twice in the past week. The infant is mostly healthy, aside from some difficulty feeding. She has been especially fussy lately, and her mom thinks that she feels ‘floppier’ than usual. She did not have a fever. At first the pediatrician assumed the baby had a slight illness, and she sent the family home. Later in the week, however, the baby had a short episode where her extremities became very rigid. Concerned about the possibility of meningitis, the pediatrician sent the family to the ED.

At the ED they perform blood cultures and a lumbar puncture, and the infant was started on broad-spectrum antibiotics. The vital signs, blood cultures and LP were normal, however, and a neurology consult suggested that she is suffering from seizures.

Are her symptoms the result of an infectious process or something else?

Construct a broad differential.

You and the neurology team conduct and EEG, which confirms seizure activity. In fact, the seizure activity has increased in the last few days. You order an MRI.

The above MRI scans show what we might expect to see in this case. A) is an axial T2-weighted image and B) is a T2-FLAIR. In both images there is hyperintensity within bilateral periventricular white matter. The abnormal signal is more prominent caudally in the parieto-occipital region.
The MRI provided good clues to the diagnosis, and it was confirmed by an assay run on a blood sample. What was your differential after looking at the MRI? What type of assay did they run on the blood?

After receiving the diagnosis, the family opts for palliative care. Sadly, the infant’s symptoms progress, with vision and hearing loss, muscle rigidity, seizures, and failure to thrive. She dies at the age of 12 months. An autopsy is performed.

This is an example of normal brain by H&E stain. Notice some of the triangular neurons at the top of the image. These are pyramidal neurons. There are also astrocytes and glial cells, all sitting in the pink background of neuropil.

The image above shows a cluster of large cells within a background of neuropil, neurons, and glial cells. This is pathognomonic.

What is the diagnosis?
The infant died of a lysosomal storage disorder/sphingolipidosis called Krabbe disease (globoid cell leukodystrophy). The infantile form of Krabbe disease is progressive and ultimately fatal. It is caused by a recessively inherited defect in galactocerebrosidase (GALC). Without the proper functioning of GALC, galactosylceramide and other sphingolipids build up in the brain to toxic levels. One sphingolipid in particular, psychosine, is toxic to oligodendrocytes. Glial cells within the brain react to the damage and produce inflammatory cytokines. The inflammation and damage lead to progressive demyelination. Most patients with the infantile form die by the age of two.

The last image shows the globoid cells that lend the disease their name. They are multinucleated macrophage-type cells that sequester unusable galactocerebroside and enlarge.

A definitive diagnosis can be made by measuring the level of activity of GALC in leukocytes isolated from blood. A diagnosis can be made if GALC activity is less than 5% of normal. Unfortunately, residual GALC activity is not predictive of clinical phenotype.

There is no treatment for the disease once symptoms are present. However, there are reports of successful treatment by hematopoietic stem cell transplantation, but only if it is performed before the onset of symptoms.

References:

Kanekar and Gustas, Metabolic disorders of the Brain, Part 1. Seminars in ultrasound, CT and MRI.


Up to Date, http://www.uptodate.com/contents/krabbe-disease?source=search_result&search=krabbe+disease&selectedTitle=1~12