ACUTE DISSEMINATED ENCEPHALOMYELITIS (ADEM)

OVERVIEW

Acute Disseminated Encephalomyelitis (ADEM) is a rare inflammatory demyelinating disease of the central nervous system. ADEM is thought to be an autoimmune disorder in which the body's immune system mistakenly attacks its own brain tissue, triggered by an environmental stimulus in genetically susceptible individuals. More often it is believed to be triggered by a response to an infection or to a vaccination. For this reason, ADEM is sometimes referred to as post-infectious or post-immunization acute disseminated encephalomyelitis.

EPIDEMIOLOGY

According to a study published in 2008, the estimated incidence in California is 0.4 per 100,000 population per year, and there are approximately 3 to 6 ADEM cases seen each year at regional medical centers in the US, UK, and Australia[2]. ADEM is more common in children and adolescents than it is in adults, and there does not seem to be a higher incidence of ADEM among males or females, nor does there seem to be a higher frequency among any particular ethnic group.

Post-infectious In approximately 50-75 percent of ADEM cases, the inflammatory attack is preceded by a viral or bacterial infection. There have been a large number of viruses associated with these infections, including but not limited to: measles, mumps, rubella, varicella zoster, Epstein-Barr, cytomegalovirus, herpes simplex, hepatitis A, influenza, and enterovirus infections. A seasonal distribution has been observed showing that most ADEM cases occur in the winter and spring. The inflammatory attack and neurological symptoms often begin within a couple of weeks after the viral or bacterial illness.

Post-immunization Less than 5 percent of ADEM cases follow immunization[2]. The association between an inflammatory attack following an immunization has been temporal and the direct connection between a vaccination and an immune attack has not been established. Post-vaccinial ADEM has been associated with immunization for: rabies, hepatitis B, influenza, Japanese B encephalitis, diphtheria/pertussis/tetanus, measles, mumps, rubella, pneumococcus, polio, smallpox, and varicella. Currently, the measles, mumps, and rubella vaccinations are most commonly associated with post-vaccinial ADEM. No infectious agent is isolated in most cases. The incidence of ADEM associated with the live measles vaccination is 1 to 2 per million. Neurologic symptoms typically appear 4 to 13 days after a vaccination.

SIGNS AND SYMPTOMS

The neurological signs from the inflammatory attack often begin with fever, headache, and vomiting. Encephalopathy (damage or malfunction of the brain) is a characteristic feature of ADEM and usually develops rapidly. This results in symptoms, such as altered level of consciousness, acute cognitive dysfunction, behavioral changes, and seizures in about a third of those diagnosed. The altered consciousness can range from lethargy to coma.

In addition to encephalopathy, other common neurologic signs of ADEM include: long tract pyramidal signs (decreased voluntary movement), acute hemiparesis (muscle weakness on one side of the body), cerebellar ataxia (decreased muscle coordination), and cranial neuropathies (damage of cranial nerves). ADEM is multifocal; meaning the inflammatory attack can occur in the brain, as well as occur as optic neuritis (ON) and/or transverse myelitis (TM). Thus, a child or adult with ADEM can have the symptoms of ON (i.e., impaired vision and eye pain), and/or all of the symptoms from an inflammatory attack in the spinal cord (TM). The TM symptoms depend on the severity and the level of the attack in the spinal cord. These can include: impaired breathing, bowel and bladder dysfunction, paralysis or muscle weakness, spasticity, paresthesias, or nerve pain. The inflammatory attack can go on for a few days or for a few weeks. The most severe symptoms are ordinarily reached within the first 4 to 7 days, and the first 2 to 4 weeks are the most severe period.

DIAGNOSIS

The diagnosis of ADEM is based on clinical and radiologic characteristics. Unfortunately, there is no specific biologic marker or confirmatory test to specifically identify the disorder, nor is there scientific, randomized, or controlled data on the diagnosis and treatment of ADEM. Decisions about the diagnosis and treatment of this disorder are based primarily on the opinions of experts. Since decisions will be based on clinical judgment, trying to connect to an expert is critically important.

An ADEM diagnosis is considered when individuals develop multifocal neurologic abnormalities with confusion, excessive irritability, or altered level of consciousness (encephalopathy), especially if the onset of symptoms occurs within 1 to 2 weeks after a viral/bacterial infection or a vaccination. Physicians must rule out that there is a direct infection of the central nervous system as opposed to an infection that subsequently triggered the immune system to cause the attack. Should a direct infection be suspected, one is often placed on an antibiotic and/or acyclovir (an antiviral drug) to fight the infection.

Laboratory studies include a complete blood count and cultures, and serologic studies are performed on blood and cerebrospinal fluid to detect bacterial and viral organisms. Additionally, viral cultures are obtained from nasopharynx and stool.

A lumbar puncture is also performed. This test is useful because evidence of inflammation is common in cerebrospinal fluid (CSF), with pleocytosis (increased white blood cell count) and/or increased protein concentration. While this is common, sometimes the CSF can be normal. Additionally, although oligoclonal bands are nonspecific and are more often associated with Multiple Sclerosis (MS), they are sometimes also present in ADEM.

An MRI of the brain and spine is important to establish a diagnosis of ADEM. Abnormalities are best defined by T2-weighted images, FLAIR sequences, and contrast-enhanced MRI with gadolinium. Abnormalities on MRI usually vary in location. Lesions associated with ADEM tend to be bilateral, but can also be asymmetric and are typically poorly marginated. Multiple lesions in the deep and subcortical white matter are common, which is characteristic of demyelination (gray matter lesions sometimes accompany white matter lesions, especially among children). While the number varies, multiple brain lesions are usually present. ADEM lesions are typically large (though smaller ones have also been seen) with diameters ranging from <5 mm to 5 cm. Additionally, brainstem and spinal cord abnormalities on MRI are common in ADEM. In the spinal cord, there are typically large confluent intramedullary lesions that extend over multiple segments of the cord.

It is possible that the MRI may be normal early in the course of the disorder and may have to be repeated. Some physicians recommend repeating MRIs on follow-up to ensure there are no new lesions, which could change the diagnosis from ADEM to multiphasic ADEM (see below) or MS.

In a situation where nonspecific cerebrospinal fluid abnormalities and MRI evidence of white matter lesions are present, it is important that other inflammatory demyelinating disorders be considered. These include: MS, ON, TM, and Neuromyelitis optica (NMO).

Diagnostic Criteria An important paper was recently published by the International Pediatric Multiple Sclerosis Study Group, which proposed diagnostic criteria for ADEM in children.[1] The criteria are important for the purpose of arriving at better decisions about treatments and are meant to facilitate research on ADEM. The major criteria include:

1. A first clinical attack of central nervous system demyelinating disease with acute or subacute onset, polysymptomatic neurologic features, and encephalopathy
2. Brain MRI showing focal or multifocal lesions, predominantly involving the white matter, without evidence of previous white matter changes

3. Encephalopathy as a presenting symptom, with the onset of encephalopathy corresponding with the occurrence of the disease state (encephalopathy is defined to include behavioral changes, such as lethargy or irritability, or severe changes in the level of consciousness such as coma)

These features help distinguish ADEM from other clinically isolated syndromes, which have a greater risk for recurrence and subsequent diagnosis of MS.

The authors of the publication define three different categories of ADEM:

1. Monophasic ADEM is a one-time episode that can develop over a period for as long as three months. Any new or changing symptoms within this three month period is considered as one event. Symptoms that might occur during an oral steroid taper or within one month of the completion of the taper are also classified as one single episode. Recurrent and multiphasic ADEM episodes must occur more than three months after the initial event and more than one month after the completion of steroids.

2. Recurrent ADEM is defined as a subsequent attack that involves the same symptoms that occurred during the initial attack. The MRI findings tend to be similar to the initial attack, and there are no lesions, but there could be an enlargement of the lesions from the original episode.

3. Multiphasic ADEM is defined as an attack that involves new areas of the central nervous system from the initial or previous attacks. There must be signs of encephalopathy, but symptoms and neuroimaging findings are in different areas from the initial attack. There might be new lesions evident on MRI and there might also be evidence of partial or complete resolution of the lesions associated with the first episode.

The International Pediatric MS Study Group authors also provide an excellent comparison across a number of variables for making the differential diagnosis between ADEM and MS. ADEM more frequently occurs among younger age groups (<10 years) and there does not seem to be a higher incidence between boys or girls. MS occurs more frequently in adolescents and the incidence is higher for girls than for boys. A prior flu-like illness is typically the case in ADEM, while it is variable for MS. Encephalopathy is required to arrive at a diagnosis of ADEM while it is rare in the early stages of MS. Seizures are variable in ADEM and rare in MS. A single event in ADEM can fluctuate over the course of three months, while in MS a discrete event is separated by at least four weeks. Large lesions involving gray and white matter are frequently evident from MRI in ADEM and rare in MS. MRI frequently shows enhancement in both ADEM and MS. Over time, lesions typically

appear to resolve in ADEM, while in MS, there is typically development of new lesions. CSF pleocytosis (presence of a greater number of cells than normal) is variable in ADEM and extremely rare in MS (white blood cell count almost always <50). Finally, the presence of oligoclonal bands in the spinal fluid is variable in ADEM and frequently found in MS.

ACUTE TREATMENT

All of the treatments for ADEM are based largely on opinions from respected authorities based on clinical experience, descriptive studies or reports of expert committees. Standard treatments recommended in acute ADEM are not confirmed from randomized, placebo-controlled trials.[4]

Since patients with ADEM usually present with fever, meningeal signs, acute encephalopathy, and evidence of inflammation in blood and CSF, it is important to first consider a treatment with antibiotics and/or acyclovir until an infectious cause is ruled out. A high dose of intravenous corticosteroids, for 3-5 days is the primary and most common first treatment of ADEM and the corticosteroids can be used concurrently with antibiotics and acyclovir. Plasma Exchange (PLEX) is recommended if there is no response to corticosteroids. Intravenous immunoglobulin (IVIG) is recommended if there is no response to PLEX.

The strength of evidence for the recommendation of corticosteroids and PLEX are graded as moderate. The strength of evidence for a recommendation of IVIG is poor. It should be noted that no studies have compared IVIG treatment with corticosteroids or plasma exchange, and there is debate over whether PLEX or IVIG should be used first when corticosteroids fail to work.

PROGNOSIS AND MANAGEMENT

The prognosis for most children with ADEM is good. The recovery is usually a slow process lasting from four to six weeks and the majority of children with ADEM make a full recovery. Between 60 to 90 percent are left with no neurological deficits. Those children who do have residual symptoms are reported to have symptoms from transverse myelitis (the spinal cord inflammatory attack), recurrent headaches, and behavioral problems. The location of lesions and the extent of inflammatory lesions do not appear to have any predictive value in regard to outcome. Typically, follow-up MRIs show complete or partial resolution of abnormalities in the majority of ADEM cases.

Long-term clinical follow-up and sequential imaging by MRI are normally required to confirm a diagnosis of ADEM. Should there be a development of a relapse with new lesions, it is not compatible with a diagnosis of monophasic ADEM, and depending on the clinical

and imaging features, it likely suggests the correct diagnosis being either multiphasic ADEM or MS. Though there is no consensus, some physicians recommend that children receive follow-up MRIs for a period of up to five years to ensure that there is no new inflammatory activity after the initial ADEM attack; i.e., to confirm that the diagnosis is not MS.

Please be sure to read the symptom management strategies presented in the transverse myelitis article as these strategies will be the same for the symptoms that are present from an inflammatory attack in the spinal cord from ADEM.

REFERENCES

1. Krupp LB, Banwell B, Tenembaum S, et al. Consensus definitions proposed for pediatric multiple sclerosis and related disorders. *Neurology*. 2007; 68:S7-S12.

2. Lotze TE, Chadwick DJ. Acute disseminated encephalomyelitis in children: Pathogenesis, clinical features, and diagnosis. *UpToDate.* 2009.

3. Lotze TE, Chadwick DJ. Acute disseminated encephalomyelitis in children: Prognosis and treatment. *UpToDate.* 2009.

4. Tunkel AR, Glasser CA, Bloch KC, et al. The Management of Encephalitis: Clinical Practice Guidelines by the Infectious Diseases Society of America. *Clinical Infectious Diseases.* 2008; 47:303-327.