Arachnoiditis and acute MTX neurotoxicity

Arachnoiditis

Definition

Arachnoiditis literally means "inflammation of the arachnoid," which is the middle of the three meninges. The term more generally refers to neurologic disorders caused by inflammation of a portion of the arachnoid and subarachnoid space, affecting the neural tissue that lies beneath.

Description

Arachnoiditis always involves inflammation in restricted areas, but the entire membrane is never affected. Fibrous tissue growth along the affected section usually occurs, projecting down through the subarachnoid space and encompassing neural tissue of the brain (cerebral arachnoiditis) and/or nerve roots of the spinal cord (spinal arachnoiditis). Nerve damage occurs through restricted blood flow, compression from accumulated fluids, and secondary effects of the inflammatory process itself.

Causes and symptoms

Arachnoiditis in leukaemia patients is most commonly caused by intrathecal injections of DepoCyte®, methotrexate or free cytarabine, but may also be caused by trauma (surgery, injury, or lumbar puncture), infection or blood in the CSF.

Arachnoiditis due to external agents given intrathecally most often occurs in the lumbosacral area. Likewise, spinal arachnoiditis of any type is more common than the cerebral/cranial variety. Intrathecal DepoCyte® may be associated more often with cerebral arachnoiditis than methotrexate or free cytarabine probably due to its better distribution within the CNS.

Symptoms of acute arachnoiditis typically occur within hours after intrathecal injection. It usually responds well to administration of systemic dexamethasone. Subacute chemical arachnoiditis occurs typically after 3rd or 4th methotrexate injection and the symptoms are often more severe including neurological deficits. Since arachnoiditis is a severe and well known complication of DepoCyte®, it shall never be given without steroids, either systemic dexamethasone or intrathecal prednisolon succinate. Symptoms of arachnoiditis after DepoCyte® typically occur within 5 days after intrathecal injection.

Symptoms of cerebral arachnoiditis may include

- severe headaches
- nausea/vomiting
- vision disturbances, especially pronounced in optochiasmatic arachnoiditis
- dizziness
- hydrocephalus if inflammation and tissue growth in specific areas of the cranial arachnoid membrane divert or obstruct normal flow of the CSF

Typical symptoms of spinal arachnoiditis include

- back pain that increases with activity
- pain in one or both legs or feet
- sensory abnormalities of some type, usually involving decreased reflexes
• decreased range of motion of the trunk or legs
• urinary sphincter dysfunction
• in severe cases, partial or complete paralysis of the lower extremities

**Diagnosis**

The most reliable method of establishing the diagnosis of arachnoiditis is MRI scan combined with one or more of the symptoms. Inflammatory cell infiltration in the CSF is present in the acute phase, and CSF protein content is increased. On the other hand, imaging studies may be negative or equivocal early on, and only later be more definitive as inflammation and tissue growth becomes more pronounced.

**Treatment**

Treatment for arachnoiditis is geared toward reducing the inflammation and alleviating pain. Dexamethasone (0.15 mg/kg or 4 mg twice daily) penetrates well to CSF and is the recommended steroid for treatment of arachnoiditis. Non-narcotic and narcotic pain medications may be needed. Surgery to remove fibrous or ossified tissue at the site of the inflammation is used only if more conservative methods do not provide sufficient relief. Hydrocephalus is a very rare and severe complication which may require shunting.

**Prognosis**

Early steroid treatment is important in preventing progression of arachnoiditis. Prognosis in advanced cases is poor, with the neurological symptoms often remaining static or worsening over time.

**Acute CNS complications during MTX treatment**

**Acute encephalopathy**

Acute encephalopathy usually develops within 2 – 9 days after administration of MTX either intrathecally or high-doses intravenously. The mechanism is unknown. Elevated levels of adenosine 1 or homocysteine 2 in CSF have been reported in patients with acute encephalopathy. Age > 10 years seems to be a risk factor 3. This complication has been reported in 0.8 - 8 % of ALL patients after HDMTX treatment 4.

**Symptoms** may include headache, nausea, vomiting, lethargy, seizures, altered mental status, emotional lability, blurred vision, dysphasia or aphasia and hemiparesis. Most typically patients have a stroke-like hemiparesis or bilateral weakness, which may develop over minutes or several hours, and the hemiparesis symptoms may alternate 4. The symptoms are usually transient.

**Diagnosis**

Restricted diffusion of water can be seen in the deep white matter in diffusion weighted imaging (DWI) at anatomic areas associated with motor impairment 5. When that is detected in context of stroke-like waxing and waning clinical symptoms the diagnosis of acute MTX associated encephalopathy can be confidently done. Conventional MRI or CT are usually normal in the acute phase 4.

**Treatment**
Optimal treatment is not well established. Symptoms are usually reversible regardless of treatment used, which makes the documentation of efficacy difficult. Symptoms like seizures should be treated according to local guidelines. Following agents have been tried in the treatment:

- **Folinic acid** has been used in patients with measurable s-MTX concentration. Increased doses of folinic acid have shown to prevent acute encephalopathy after intrathecal MTX and low dose oral MTX treatment.\(^6\)
- **Aminophylline (or theophylline)** displaces adenosine from its receptor sites, and has been reported to induce resolution of symptoms in some cases\(^1\), but the efficacy has not been proven. It can be used in the same doses than used in the treatment of asthma.
- **Dextromethorphan**, a common cough medicine, at doses of 1-2 mg/kg orally has been suggested to reverse the neurotoxic effects of homocysteine\(^7\). It is a neuroprotector and antagonist of NMDA receptor, while homocysteine metabolites are excitatory agonists of the same receptor\(^8\).

**Prognosis**

Symptoms usually resolve within a week. Typically patients do not have residual neurological deficits. Recurrence after resumed administration of MTX has been reported in some cases, but most patients tolerate MTX normally\(^4\).

**Reference List**
