Observational longitudinal and genetic study of superficial siderosis

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Summary
Superficial siderosis is a progressive neurological disease caused by iron deposition in the central nervous system from chronic subarachnoid bleeding. Until 2011, there has been no effective treatment for this progressive condition that leads to hearing loss, spasticity, weakness, loss of bowel/bladder function, incoordination, dementia and ultimately death.

Last year, we demonstrated that a lipid soluble iron chelator, deferiprone, can reduce hemosiderin deposition in patients with superficial siderosis by MRI in as little as 3 months. As the only therapy that can improve this condition, chelation with deferiprone is the standard of care for treatment of superficial siderosis. Now that the FDA has approved deferiprone in the United States for thalassemia, we propose documenting the clinical effect of deferiprone over 2 years in superficial siderosis patients. Our goal is to understand how the clinical course of this disease is altered using standard of care chelation therapy with deferiprone.

Patients with superficial siderosis who are taking deferiprone for chelation therapy at doses consistent with the standard of care will be offered enrollment into this observational study. Patients will be treated and monitored locally by participating neurologists who have agreed to help us collect information for this study. We are interested in documenting the clinical effect of deferiprone on hearing, ataxia and myelopathy using standardized scales performed and documenting the effect of deferiprone on hemosiderin deposition in the CNS by MRI, all performed according to standard of care.

Background Information: Superficial Siderosis

First described over 100 years ago, superficial siderosis is a rare neurodegenerative disease caused by iron toxicity in the CNS due to chronic subarachnoid bleeding. Iron from red blood cells in the subarachnoid space is preferentially taken up by the Bergmann glia in the cerebellum, brainstem, spinal cord, eighth cranial nerve and the cerebral cortex; the iron is stored as ferritin within the glial cells. With continued subarachnoid bleeding, the glia are overwhelmed by the ferritin load and die. Their loss exposes neurons to free iron which is toxic to cells because it catalyzes the breakdown of hydrogen peroxide to superoxide, a reactive oxygen species that can cause lipid peroxidation, membrane dysfunction, and neuronal cell death.

Neurological consequences of iron overload depend on the area of the brain exposed to free iron. With chronic subarachnoid bleeding, the blood tends to pool around the brainstem, cerebellum and spinal cord thus leading to the classic triad of hearing loss, ataxia and myelopathy that is seen in more than 50% of patients with superficial siderosis. The eighth cranial nerve courses through the subarachnoid space until it reaches the inner ear exposing it to the toxic blood; in contrast, the other cranial nerves are protected by the peripheral Schwann cells within 1 mm of exiting the brainstem. Compared to the other CNS structures affected in superficial siderosis, the eighth cranial nerve is the most susceptible because it exposes the most surface area to volume. Thus, the most common and often the first symptom patients get is sensorineural hearing loss. This is followed by ataxia due to dysfunction of both the vestibular component of the eighth cranial nerve and neurodegeneration of the cerebellum. Myelopathy develops when the

brainstem and spinal cord are involved. With continued bleeding, other areas of the brain can degenerate leading to a myriad of other symptoms seen in superficial siderosis including urinary problems headaches, anosmia, diplopia, bowel problems, ageusia, cranial nerve palsies, and dementia.

The etiologies of chronic subarachnoid bleeding are (in order of incidence): Idiopathic, Head/back trauma, A/V malformations, Current CNS tumor, Previously resected CNS tumor, CNS post-surgical (non-tumor), Amyloid angiopathy, Brachial plexus/root injury. Currently, there are fewer than 100 patients world-wide with the diagnosis of superficial siderosis. In the United States, there are an estimated 40-50 patients.

The diagnosis of superficial siderosis is definitively made by MRI. FLAIR sequences show characteristic hypointensities around the affected areas of the brain (Figure 1). Hearing tests, measures of ataxia and myelopathy and neurocognitive testing are methods of tracking the progression of disease.

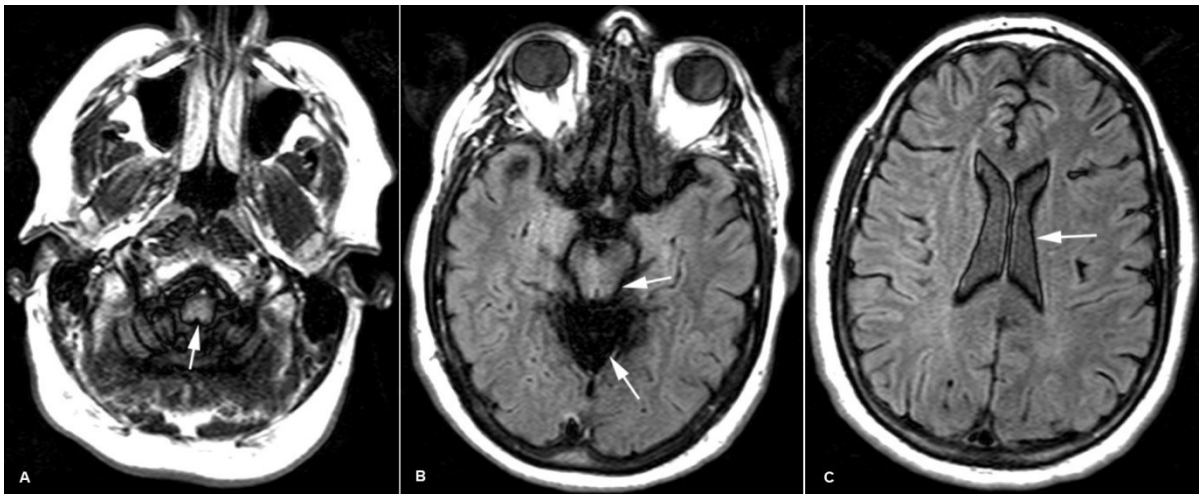

Figure 1. Panel A shows a T2 weighted inversion recovery image shows the brainstem outlined by a rim of hypointensity (arrow) where hemosiderin has deposited. Panel B shows the rim of hypointensity around the cerebellar vermis (arrow) and midbrain (arrow) and Panel C shows a rim of hypointensity around the lateral ventricles (arrow).

Iron chelators, other than deferiprone, used in other iron-overload disorders such as hemochromatosis are not expected to be effective in superficial siderosis because they do not cross the blood brain barrier. Copper chelators used in Wilson's disease can permeate the brainblood barrier, but are unfortunately not effective in superficial siderosis, as they do not bind iron. Surgical intervention is thought to be key to slowing the disease by stanching the leak of blood into the subarachnoid space. However, once the neurodegenerative process has begun, surgical intervention does not prevent the neurodegenerative disease from progressing.

Design

Subjects will be recruited from 2 sources. First, patients from the Johns Hopkins neurology clinic with superficial siderosis who are currently on deferiprone and have indicated a willingness to participate in studies will be called and offered the opportunity to enroll. Second, outside patients not seen at Johns Hopkins can enroll in the study remotely. All reviews of outside patients to confirm diagnosis by clinical and radiological criteria will be done by the PI, Michael Levy.

The inclusion criteria are:

1. Confirmed diagnosis of superficial siderosis by MRI.
2. Must be able to understand and sign the informed consent form.

If the subject meets the above inclusion criteria, he/she will be offered enrollment into the study if he/she is not excluded by the following exclusion criteria:

1. If the patient is unwilling or unable to comply with the requirements of the study.

This is an observational study that only documents the longitudinal history of the disease and effects of chelation therapy.

Patient compliance with deferiprone will be monitored by the treating physician. Weekly or monthly blood tests monitoring for neutrophil count and for liver function tests and ferritin are the responsibility of the treating physician. In addition to monitoring test results, we will request of patients a blood sample for DNA testing. The specific genotype we are interested in relates to recent research on the importance of haptoglobin isoforms, as described below.

MRIs of the brain and spinal cord are done every 12-24 months according to standard of care with emphasis on the T2*-weighted and gradient echo imaging to assess the degree of hemosiderin deposition in the CNS. We will request copies of the MRIs on CD for analysis.

Genetic study of haptoglobins.

The body has a high affinity system designed to scavenge extracellular hemoglobin before it causes iron deposition and toxicity; this system relies on the binding of extracellular hemoglobin by haptoglobin, and clearance of the resultant hemoglobin-haptoglobin complex by CD163 expressed on the surface of monocyte-lineage cells[3]. There are two isoforms of haptoglobin protein chain: Type I and Type II, with Type I being more efficient than Type II in clearing hemoglobin[4] and less pro-inflammatory[5]. Haptoglobin is present in reduced amounts in the central nervous system compared to the blood[6], so the difference in scavenging capacity between haptoglobin isoforms may be more consequential.

One blood sample (up to 12ml, or one tablespoon) will be collected for the specific purpose of this protocol, using plastic Becton Dickinson Vacutainer® K_2EDTA tubes (either 1 x 10ml or 2 x

6ml), which will be immediately frozen upright at -80°C. Surplus material from other available biological samples, or samples collected during procedures undertaken for other and clinical reasons, may be used for the purposes of this project. Clinical data will be collected. All data will be link-anonymized or fully anonymized.
In Dr. Ian Galea's laboratory in Southampton, UK: DNA and plasma will be extracted from whole blood using an in-house protocol. The molecular components of hemoglobin scavenging will be studied in DNA, blood, spinal fluid or other biological samples.The molecular data will be correlated with the clinical data to determine whether aspects of hemoglobin scavenging pathways relate to clinical, radiological or other features of superficial siderosis.

Discontinuation of study.

Subjects may elect to discontinue participation in the observational study at any time for any reason.

Outcome Measure

Outcome measures for this study are focused on documenting longitudinal history and clinical efficacy of chelation therapy. We will use the clinical examinations employed for standard of care that are based on the most common neurologic deficits in superficial siderosis patients: hearing loss, ataxia and myelopathy.

Hearing is assessed by common audiogram testing. This test graphically depicts the frequency and severity of hearing loss in both ears. It is objective and reproducible. Objectivity and reproducibility are also optimized in the two clinical examinations to assess ataxia and myelopathy, two very common features of superficial siderosis.

MRIs of the brain and spinal cord are done every 12-18 months according to the standard of care with emphasis on the T2*-weighted and gradient echo imaging to assess the degree of hemosiderin deposition in the CNS.

Statistical analysis.

1. Clinical efficacy is defined as an improvement in the SARA scale (ataxia) or Ashworth scale (motor spasticity) scores. The baseline score will be compared to the post-study score for each patient. A paired t-test will be used to determine statistical significance in the average difference.
2. Audiograms will provide an objective measure of change in hearing after treatment with deferiprone. A basic audiogram plots the hearing levels in decibels against the frequency in Hertz. An improvement in hearing would manifest as a downward shift in the threshold hearing level at any particular frequency. The baseline audiogram will be compared to the post-study audiogram for each patient. A paired t-test will be used to

determine statistical significance in the average difference in the threshold hearing level at any particular frequency.

3. MRIs will be objectively analyzed for changes in iron deposition. The technology and methodology are emerging and may be useful in this condition.

Direct Access to Source Data/Documents

The IRB will have access to source data and documents by request from Dr Levy or lead nurse researcher, Maureen Mealy.

De-identified clinical data will be shared with Dr. Galea's group (Southampton, UK) to correlate with DNA studies. No other boards, committees or individuals will have direct access to source data and documents.

Quality Control and Quality Assurance

No issues.

Data Handling and Recordkeeping

All data will be kept confidential on a computer separate from hospital or clinic computers. The computer will remain in the possession of Dr Levy or Maureen Mealy at all times. It will be password protected on startup to ensure confidentiality if lost or stolen.