L-Asparaginase Therapy with Concomitant Cranial Venous Thrombosis: Can MRI Help Avoiding Stroke

ALAA M. ELORABY, M.D.
The Department of Radiology, National Cancer Institute, Cairo University.

ABSTRACT

Purpose: To prospectively use MRI in the early detection of intracranial sino-venous thrombosis during the L-asparaginase induction therapy of acute leukemia thus preventing the evolution of brain venous infarct.

Materials and Methods: The study population consisted of seventy patients receiving L-asparaginase induction therapy for acute leukemia in the National Cancer Institute of Cairo University presenting with clinical neurological signs suggestive of aseptic intracranial venous thrombosis. All the patients were studied by 1.5 Tesla magnet using conventional MRI pulse sequences and MR venographic studies. The imaging findings were processed as regards the detection of venous thrombosis, its signal criteria and the evaluation of any companion brain parenchymal ischemic insults.

Results: Eleven patients were diagnosed with dural venous sinus thrombosis with subsequent specific signal pattern of the thrombus that could be linked to the duration of thrombosis. The MR venographic studies detected the thrombosis in nine cases out of eleven. Ten cases scored brain parenchymal signal abnormality that could indicate infarction, eight of them were hemorrhagic in nature.

Conclusion: L-asparaginase therapy is accompanied by high risk of venous thrombosis that could involve the intra-cranial sino-venous structures. MRI could be used effectively in the early diagnosis of such serious, curable complication using a combination of conventional spin echo pulse sequences and MR venographic studies. Hemorrhagic venous infarcts should draw the attention to underlying established venous thrombosis.

Key Words: Asparaginase – Venous thrombosis-MRI.

INTRODUCTION

L-asparaginase (asparaginase), a bacterial enzyme that depletes serum asparagine, is a standard component in most treatment protocols for acute lymphoblastic leukemia (ALL), both in children and in adults. ALL cells are unable to produce asparagine, and are dependent on plasma levels of this amino acid for protein synthesis. Plasma asparagine depletion results in inhibition of protein synthesis, which leads to inhibition of RNA and DNA synthesis with a subsequent apoptotic cell death of the leukemic cells [1].

A major limitation of E coli asparaginase is development of hyper-sensitivity, reported in 15% to 73% of both adults and children. It has been suggested that allergies and other side effects from E coli asparaginase were more frequent and severe in adults than in children [2].

Among the malignant hematologic disorders, the incidence of thrombosis is higher in patients with acute leukemia. Significant morbidity and high mortality in acute leukemia due to complications of bleeding and infection frequently overshadow thromboembolic events. Case-controlled studies of patients with cancer revealed a fourfold increase in thromboembolic occurrence in acute leukemia, with about the same rate in acute myelogenous leukemia (AML) and in acute lymphocytic leukemia (ALL). Among patients with acute leukemia, thrombosis has the highest incidence in acute promyelocytic leukemia (APL) [3].

Among those agents used to treat acute leukemia, L-asparaginase has adverse effects that cause both bleeding and thrombosis. This drug has a profound effect on hepatic synthesis of coagulation and fibrinolytic factors, this results in a decrease in plasma levels of fibrinogen, factors VII, IX, X and XI, histidine-rich
glycoprotein, α-2 macroglobulin, and α-2 antiplasmin, producing an increased bleeding risk. The incidence of bleeding complications is low. One reason for this low frequency is the concurrent impaired synthesis of naturally occurring anticoagulant proteins, including antithrombin, protein C and protein S, and plasminogen. L-Asparaginase is used in many treatment protocols for acute lymphoblastic leukemia, with various combinations of prednisone, daunorubicin, vincristine, cytarabine, cyclophosphamide, methotrexate and thioguanine [4].

The improvements in imaging techniques and increased awareness among the clinicians and radiologists have however led to the diagnosis of patients having cerebral venous thrombosis being considered more often, as the clinical course and the radiological findings are both highly variable, diagnosis remains difficult. Magnetic resonance imaging (MRI) has assumed the central role in the diagnosis and follow-up of these patients [5].

Magnetic resonance has been used in the diagnosis of cerebral venous thrombosis for approximately two decades and is the modality of choice when such a diagnosis is considered clinically, magnetic resonance in combination with magnetic resonance venography is the single most sensitive diagnostic technique [6].

Study objective:
This study was carried out with a multifaceted objective composed of shining light on the risk of dural sino-venous thrombosis during the use of L-asparaginase therapy, the role of magnetic resonance imaging in detecting Sinovenous intra-cranial thrombosis and then how to use such a diagnostic tool in order to help in the rapid and confident diagnosis of the potential venous thrombosis and the ultimate goal of preventing a venous stroke in evolution.

MATERIAL AND METHODS
This was a prospective study based upon suspecting and establishing sino venous thrombosis criteria during L-asparaginase therapy using conventional MRI.

Seventy patients from the National Cancer Institute (Cairo University) fulfilled the inclusion criteria of this work as follows:
- Both pediatric and adult age groups were included.
- No sex predilection.
- All were inpatients in the hospital receiving treatment for acute leukemia with L-asparaginase drug constituting essential part of the therapy.
- Patients with previous history of cranial irradiation or intracranial infectious septic conditions were excluded.
- All members of the study pool received initial, pre therapy, full neurological evaluation to exclude any patients with prior neurological deficits.
- Cranial MRI studies were performed routinely when the full clinical dose of the L-asparaginase drug levels had been reached and upon the appearance of any neurological symptoms that could indicate cerebral dysfunction or a stroke in evolution.
- MRI studies were performed with 1.5 Tesla super-conductive General Electric magnet and Toshiba 0.5 Tesla magnet in the Radiology Department of the National Cancer Institute of Cairo University and in the Nile Diagnostic Center, Cairo, before and after intravenous contrast administration.
- The study protocol and imaging parameters were as follows:
  T1, T2, FLAIR (fluid attenuation inversion recovery), and MR venography pulse sequences were obtained in multiplanar diversity to obtain axial, coronal and sagittal images.
  T1 images before and after intravenous contrast injections were obtained.
  The study parameters were standardized with fixed slice thickness, slice gap, number of excitations (NEX) and matrix as in Table (1).

Table (1): The technical parameters used in the different pulse sequences throughout the conventional magnetic resonance imaging

<table>
<thead>
<tr>
<th>Pulse sequence</th>
<th>TR</th>
<th>TE</th>
<th>IT</th>
<th>NEX</th>
<th>Slice thickness</th>
<th>Slice gap</th>
<th>Matrix size</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>480</td>
<td>15</td>
<td>1</td>
<td>1</td>
<td>6.5mms</td>
<td>1mm</td>
<td>256x192</td>
</tr>
<tr>
<td>T2</td>
<td>4000</td>
<td>104</td>
<td></td>
<td>1</td>
<td>6.5mms</td>
<td>1mm</td>
<td>256x192</td>
</tr>
<tr>
<td>Flair</td>
<td>7152</td>
<td>148</td>
<td>1787</td>
<td>1</td>
<td>6.5mms</td>
<td>1mm</td>
<td>256x192</td>
</tr>
</tbody>
</table>
The MRI venography study was performed using the time of flight acquisition sequences with the following imaging parameters:

**Patient position:** Supine.
**Scan type:** 2-D gradient echo.
**Imaging plane (orientation):** Sagittal.

Central slice or volume center Slices were centered to the midline on the transverse localizer image.

**Echo time (TE):** 9 msec.
**Repeat time (TR):** 30 msec.
**Flip angle (FA):** 50º.
**Field of view:** (FOVx, FOVy) 210mm, 210mm.
**Resolution:** (Δx, Δy) 0.82mm, 0.82mm.
**Number of data points collected:** (Nx, Ny) 256, 256.
**Slice thickness (Δz):** 3mm.
**Number of slices:** 64.
**Slice gap:** 1mm.
**Number of acquisitions:** (Nacq) 1.

No swap read and phases encoding.

Sslice location angle was selected as sagittal to coronal -12º (to reduce in-plane saturation) off transverse scout image.

Saturation band was angled off sagittal scout image 60mm thick.

Slice series ascending.

Scan time 6min, 43sec.

The MRI images were interpreted using the following guidelines:

- Detection of any intra-axial, brain parenchymal signal abnormality with special attention as regards the presence of blood degradation products.
- Evaluation of the flow signal pattern of the sino-venous structures in the various pulse sequences with reference to the normal flow void pattern.
- Interpretation of the venographic study as regards the flow pattern, collateral circulation and any companion anatomical abnormality.

The imaging data obtained was processed to obtain MRI diagnostic signal pattern regarding the appearance of sino venous thrombosis in different MRI imaging pulse sequences with subsequent conclusion of proper protocol design of the study to obtain maximal impact upon the clinical course of the patients thus avoiding a devastating stroke.

**RESULTS**

In 70 leukemic patients under induction L-asparaginase therapy who underwent cranial MRI, eleven patients had loss of the normal characteristic flow void signal in major dural venous sinuses which was replaced by wide array of signals in the different pulse sequences scoring about 16% of the study sample.

When comparing the conventional MRI images to the acquired MR venographic images nine cases showed complete occlusion of the sinus under investigation scoring about 85% of cases.

The superior sagittal sinus was the most common sinus to be affected scoring about 70% of the isolated thrombosed sinuses followed by the cavernous sinus scoring about 20% while the transverse sinus scored about 10% of cases.

In the remaining two cases with conventional MRI signal abnormality complete sinus block could not be demonstrated on MR venography. The abnormal signals within the major dural sinus of these patients were attributed to slow flow within the sinus or partial luminal thrombosis.

<table>
<thead>
<tr>
<th>Time since initial complaint</th>
<th>T1 Images pattern</th>
<th>T2 Images pattern</th>
<th>Signal pattern explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than a week</td>
<td>Iso intense</td>
<td>Hypo intense</td>
<td>Presence of deoxyhaemoglobin</td>
</tr>
<tr>
<td>Less than two weeks</td>
<td>Hyper intense</td>
<td>Hyper intense</td>
<td>Presence of methaemoglobin</td>
</tr>
<tr>
<td>More than two weeks</td>
<td>Void</td>
<td>Void</td>
<td>Restored lumen</td>
</tr>
</tbody>
</table>

Table (2): The change of signal pattern of thrombosis and its causative factors in correspondence with the time since the initial complaint.
MRI findings demonstrated intra-axial signal abnormality in ten cases of the total study pool matching the diagnosis of infarction not following the strict territorial supply of any arterial trunk denoting venous nature.

Eight of the ten cases revealed blood degradation signal within the areas of infarction denoting parenchymal hemorrhage with variable degrees of perifocal edema in the same area.

All the non-hemorrhagic infarcted areas portrayed standard MRI images signal criteria of hypo intense T1 pattern changing to hyper intense T2 and FLAIR signal with faint contrast uptake of heterogeneous nature.

The use of intravenous contrast was of some value in assessing the lumen of different sinuses with delineation of the thrombus as filling defect within the enhancing lumen, also comparing the appearance of the cavernous sinuses was of diagnostic aid in early detection of cavernous sinuses abnormality that could be seen as sinus enhancement asymmetry.

Of special interest was the observation that fifteen patients were presenting with severe clinical symptoms but turned out to be of normal brain parenchymal signal. They all presented with headache of long duration and six of them also had papilledema and raised CSF pressure, but when they were treated for dural sinus thrombosis there was dramatic improvement in the symptoms.

No statistical analysis was performed because of the small size of the study population with positive MRI findings and the increased probability of error.
Fig. (2-A): T1 image showing hyper intense thrombus within the superior sagittal sinus with straight sinus extension of the thrombosis.

Fig. (2-B): T1 Image post contrast with the thrombus within the superior sagittal sinus seen as irregular, moderately hypo intense signal.

Fig. (3-A): T1 image of a thrombosed left cavernous sinus showing internal thrombus of moderate signal intensity and loss of flow signal of the left internal carotid artery.

Fig. (3-B): T2 image of the same patient with the thrombosed cavernous sinus showing relatively lower signal intensity compared to the T1 image denoting acute natur.

Fig. (3-C): The post contrast T1 image revealing enlarged left cavernous sinus, intrasinus filling defect and loss of the normal flow signal of the left internal carotid artery.

Fig. (4-A): T1 images with bilateral transverse sinuses sub acute thrombosis seen as bright intra sinus signal.

Fig. (4-B): T2 image of the same case with the bright signal of sub acute thrombosis seen within the transverse sinuses.
DISCUSSION

Alterations in haemostasis have been well documented in patients with acute lymphoblastic leukemia (ALL). These thrombotic events are typically seen during the period of induction therapy consisting of L-asparaginase, which is an essential drug in the treatment of ALL. Both laboratory and clinical evidences supported the occurrence of thrombosis as a complication of L-asparaginase therapy, but the role of other predisposing factors such as co-existing congenital thrombophilic condition remain elusive [7,8].

All of the members of this study were in the induction treatment phase of acute leukemia with 50 patients were acute lymphatic leukemia patients and 20 patients were of the acute myeloid type.

L-asparaginase compounds constituted a cornerstone of the treatment protocol in addition to other chemotherapeutic agents.

Although the clinical presentation of cranial venous thrombosis is highly variable, the diagnosis should be considered in young and middle-aged patients with recent unusual headache or with stroke-like symptoms in the absence of the usual vascular risk factors, in patients with intracranial hypertension, and in patients with CT evidence of hemorrhagic infarcts, especially if the infarcts are multiple and not confined to the arterial vascular territories. The average delay from the onset of symptoms to the diagnosis is seven days [9].

The most sensitive examination technique is MRI in combination with magnetic resonance venography, T1-weighted and T2-weighted MRI will show a hyper intense signal from the thrombosed sinuses. The characteristics of the signal depend on the age of the thrombus and are isointense on T1-weighted images during the first five days and after one month [10].

The combination of an abnormal signal in a sinus and a corresponding absence of the flow signal on magnetic resonance venography confirm the diagnosis of thrombosis, but expert radiologic judgment is required to avoid diagnostic and technical pitfalls [11].

In this work, the MRI studies were performed according to the clinical assumption of neurological deficit or according to a previous cranial CT study with positive findings raising the question of an ongoing process of venous thrombosis, so the attempt of categorizing a signal pattern of thrombus within a sino venous structure according to the elapsing time period was accurate as much as possible.

Demonstration of the thrombus in the dural sinus or vein is pathognomonic of cerebral venous thrombosis. The signal from the thrombus within the dural sinus or cortical vein is variable however by the time most patients are scanned the thrombus shows hyper-intense

Fig. (5-A): Enhanced T1 image with thrombosed superior sagittal sinus and the right transverse sinus accompanied by right parietal cortical hemorrhagic infarct.

Fig. (5-B): MR venographic sequence of the same patient with loss of the flow signal of the occluded sinuses.
In our work the phase of hyper acute thrombosis was not strongly pronounced as the thrombus formation is directly related to the concentration of the L-asparaginase dose used with the critical time for the development of concomitant venous thrombosis is two weeks leading to intraluminal hyper intensity in the T1 and T2 images.

Signal abnormality which replaces the normal signal void from the sinus is a more reliable sign of thrombosis as very slow flowing blood may occasionally give rise to high signal on spin echo T1-weighted images even in the absence of any thrombus. Additionally the thrombus may be iso-intense on T1-weighted images in the first 5 days. The loss of the normal flow void on spin echo T2 images is a sensitive parameter for evaluation of thrombosis. Care should however be taken to ensure that the image being evaluated is a spin echo T2 (TR >1500ms, TE >75ms) sequence as gradient echo images which use short TR are prone to the same pitfall [11].

Abnormal signal replacing the hypo intense signal void of flowing blood could be recognized on a combination of T1, T2-weighted and FLAIR images. Sub acute thrombus (5 days to 2 weeks old) is hyper intense on both T1 and T2-weighted images, and is more readily detected than acute thrombus (less than 5 days old), which is iso intense on T1-weighted image and hypo intense on T2-weighted images, thus mimicking the normal flow void [13].

In the present study the images interpretation of luminal thrombosis depended upon T1 and T2 spin echo sequences only with no gradient echo pulse sequences acquisitions. Thrombus on MRV is seen either as loss of high flow signal from the sinus, in cases of complete occlusion of the sinus or frayed and patchy flow signal in the presence of non occlusive thrombus. The demonstration of thrombus in cortical veins is very difficult due to the high degree of anatomic variations [14].

The parenchymal changes secondary to venous thrombosis are of two types. Changes secondary to intracranial hypertension and focal changes of edema and infarction. Changes secondary to intracranial hypertension are non-specific, with generalized cerebral edema and effacement of basal cisterns and sulci. The size of ventricles is variable but is usually enlarged. Focal changes occur in approximately 50% of cases. The location of the parenchymal changes may not correspond to the site of the sinus involved; however the lesions do correspond to cortical or deep venous involvement [15].

We scored ten cases with brain parenchymal signal abnormality all were of supratentorial configuration exhibiting hypo intense T1 signal, hyper intense T2 pattern with mild contrast uptake, all of the cases were accompanied by signs of cerebral venous thrombosis including positive venographic study. The FLAIR sequences helped in detecting subtle parenchymal edema with relatively more pronounced image contrast compared to the T2 pulse sequences.

The appearances of infarcted lesions are dependent on their age and the presence of hemorrhagic component. Non hemorrhagic infarcts are progressively hyper-intense on T2 and hypo-intense on T1 weighted images. Hemorrhagic infarcts follow the pattern of other cerebral hematomas [16].

Eight of our ten cases with the radiological diagnosis of venous infarct exhibited a signal pattern indicative of extravasated blood degradation products all of them portrayed bright T1 and T2 signals denoting the sub acute nature of the local hematoma.

In conclusion, the dural sino venous thrombosis represents a major clinical set back during the L-asparaginase induction therapy of acute leukemia, its early detection can lead to good prognosis with adequate control of the neoplastic disease. MRI is an essential diagnostic tool in this clinical situation, using standard T1 and T2 spin echo sequences in combination with MR venography can diagnose sinus luminal thrombosis in early phases with subsequent initiation of anti thrombotic therapy thus preventing a deletrious venous infarct that carries major risk of bleeding.

REFERENCES


