Young Females and Cerebral Venous Thrombosis

Corresponding Author:
Dr. Ilirjana Zekja,
Neurologist, Service of Neurology- University Hospital Center 'Mother Theresa', Tirana - Albania

Submitting Author:
Dr. Gentian Vyshka,
Lecturer, Biomedical and Experimental Department, Faculty of Medicine, University of Tirana, Rr Dibres 371 - Albania

Other Authors:
Dr. Silvana Mijo,
Neurologist, Service of Neurology- University Hospital Center Mother Theresa, Tirana - Albania
Dr. Serla Grabova,
Neurologist, Service of Neurology- University Hospital Center Mother Theresa, Tirana - Albania
Dr. Aldi Shehu,
PhD, Swissmed sh.p.k, Tirana - Albania

Article ID: WMC004294
Article Type: Review articles
Submitted on: 21-Jun-2013, 05:14:08 PM GMT  Published on: 22-Jun-2013, 04:27:05 AM GMT
Article URL: http://www.webmedcentral.com/article_view/4294
Subject Categories: NEUROLOGY
Keywords: Venous thrombosis, risk factors, thrombophilia, antiphospholipid syndrome, brain imaging, anti-coagulation.

How to cite the article: Zekja I, Mijo S, Grabova S, Shehu A, Vyshka G. Young Females and Cerebral Venous Thrombosis. WebmedCentral NEUROLOGY 2013;4(6):WMC004294

Copyright: This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC-BY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Source(s) of Funding:
No funding for the article.

Competing Interests:
No competing interests to declare.
Abstract

Cerebral venous thrombosis (CVT), is an under diagnosed condition for acute or slowly progressive neurological deficit. CVT has a wide spectrum of signs and symptoms, which may evolve suddenly or over the weeks. It is clinically challenging and mimics neurological conditions, such as: meningitis, encephalopathy, benign intracranial hypertension, and stroke. We have seen 12 female patients of CVT, during 2011 – 2012. The mean age was 29.75 years (25 – 40 years old). Of the 12 females, 8 were postpartum, 2 were pregnant, one was on oral contraceptives and in one Antiphospholipid antibodies were positive.

CVT cases are now being diagnosed more frequently. Newer imaging procedures have led to easier recognition of CVT, offering the opportunity for early therapeutic measures. Headache is the most frequent symptom in patients with CVT, present in about 80% of cases. Sixth cranial nerve palsy usually manifests as false localizing sign. Patients may have seizures that can be recurrent. CVT, an important cause of stroke in puerperium is frequently observed in Albania.

Introduction

Cerebral venous thrombosis, including thrombosis of cerebral veins and major dural sinuses, is an uncommon disorder in the general population. However, it has a higher frequency among patients younger than 40 years of age, patients with thrombophilia, and women who are pregnant or receiving hormonal contraceptive therapy. Annual incidence is estimated to be 3 to 4 cases per million. (Stam J. N Engl J Med, 2005). The incidence of cerebral venous thrombosis increases to 12 cases per 100 000 deliveries in pregnant women (Lanska DJ, Kryscio RJ Stroke2000). Cerebral venous thrombosis occurs 3 times as frequently in women (Coutinho JM, Ferro JM, Canhao P, Stam J, Bousser MG, Barinagarrementeria F. Stroke. 2004). Inherited thrombophilias associated with cerebral venous thrombosis include deficiencies of antithrombin, protein C, protein S, factor V Leiden mutation, and the prothrombin gene mutation 20210. Antiphospholipid antibodies and hyperhomocysteinemia are acquired prothrombotic states associated with cerebral venous thrombosis.

TABLE 1:

<table>
<thead>
<tr>
<th>Risk Factors for Cerebral Venous Thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombophilia</td>
</tr>
<tr>
<td>Deficiencies of antithrombin, protein C, and protein S</td>
</tr>
<tr>
<td>Factor V Leiden mutation</td>
</tr>
<tr>
<td>Prothrombin gene mutation 20210</td>
</tr>
<tr>
<td>Antiphospholipid antibodies</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
</tr>
<tr>
<td>Women's health concerns</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
<tr>
<td>Postpartum state</td>
</tr>
<tr>
<td>Hormonal contraceptive or replacement therapy</td>
</tr>
<tr>
<td>Infection</td>
</tr>
<tr>
<td>Localized infections such as otitis, mastoiditis, sinusitis</td>
</tr>
<tr>
<td>Meningitis</td>
</tr>
<tr>
<td>Systemic infectious disorders</td>
</tr>
<tr>
<td>Chronic inflammatory diseases</td>
</tr>
<tr>
<td>Vasculitides</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>Cancer</td>
</tr>
<tr>
<td>Hematologic disorders</td>
</tr>
<tr>
<td>Polycythemia</td>
</tr>
<tr>
<td>Essential thrombocytosis</td>
</tr>
<tr>
<td>Paroxysmal nocturnal hemoglobinuria</td>
</tr>
<tr>
<td>Trauma</td>
</tr>
<tr>
<td>Head trauma</td>
</tr>
<tr>
<td>Local injury to cerebral sinuses or veins</td>
</tr>
<tr>
<td>Jugular venous cannulation</td>
</tr>
<tr>
<td>Neurosurgical procedures</td>
</tr>
<tr>
<td>Lumbar puncture</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
</tr>
</tbody>
</table>

Risk Factors

At least 1 risk factor can be identified in >85% of patients with cerebral venous thrombosis (Table 1).
An additional precipitating factor is often present in patients with thrombophilia who develop cerebral venous thrombosis. Pregnancy, postpartum state, and hormonal contraceptive therapy are the most frequent risk factors in women with cerebral venous thrombosis. Localized infections, such as otitis, mastoiditis, sinusitis, and meningitis and systemic infectious disorders, are also associated with cerebral venous thrombosis. Additional risk factors include chronic inflammatory diseases, such as vasculitides and inflammatory bowel disease, nephrotic syndrome, and malignancy and hematologic disorders, such as polycythemia, essential thrombocytosis, and paroxysmal nocturnal hemoglobinuria. Cerebral venous thrombosis may result from head trauma, local injury to cerebral sinuses or veins, jugular venous cannulation, neurosurgical procedures, and, rarely, lumbar puncture. (Stam J. N Engl J Med, 2005).

Pathophysiology

Two major pathophysiological mechanisms contribute to the clinical presentation of cerebral venous thrombosis (Stam J. N Engl J Med, 2005). First, thrombosis of cerebral veins or sinuses can result in increased venular and capillary pressure. As local venous pressure continues to raise, decreased cerebral perfusion results in ischemic injury and cytotoxic edema, disruption of the blood-brain barrier leads to vasogenic edema, and venous and capillary rupture culminates in parenchymal hemorrhage.

Obstruction of cerebral sinuses may also result in decreased cerebrospinal fluid absorption. Cerebrospinal fluid is normally absorbed through arachnoid granulations into the superior sagittal sinus. Thrombosis of cerebral sinuses increases venous pressure, impairs cerebrospinal fluid absorption, and ultimately leads to increased intracranial pressure. Consequently, increased intracranial pressure worsens venular and capillary hypertension and contributes to parenchymal hemorrhage and vasogenic and cytotoxic edema.

Review

Clinical Presentation

The clinical presentation of cerebral venous thrombosis can be highly variable. Onset of symptoms and signs may be acute, subacute, or chronic. Four major syndromes have been described: isolated intracranial hypertension, focal neurological abnormalities, seizures, and encephalopathy. These syndromes may present in combination or isolation depending on the extent and location of cerebral venous thrombosis (Figure 1).

Figure 1: Major clinical syndromes according to location of cerebral venous thrombosis.

Intracranial hypertension resulting from cerebral venous thrombosis most frequently presents as headache. Headache is the presenting complaint in up to 90% of patients with cerebral venous thrombosis, and is described as subacute in onset 64% of the time. However, some patients report acute onset of severe headache mimicking subarachnoid hemorrhage. Headache can be localized or generalized and may worsen with Valsalva maneuvers or position change. (Agostoni E Neurol Sci. 2004). Other findings of intracranial hypertention include papilledema and visual complaints. Headache caused by cerebral venous thrombosis is often initially diagnosed as a migraine. Focal neurological deficits are noted in 44% of patients with cerebral venous thrombosis. (Tanislav C, Siekmann R, Sieweke N, Allendorfer J, Pabst W, Kaps M, Stolz E BMC Neurol. 2011). Motor weakness including hemiparesis is the most common focal finding, and may be present in up to 40% of patients. Fluent aphasia may result from left transverse sinus thrombosis. Sensory deficits are less frequent. Focal or generalized seizures, including status epilepticus, are observed in 30% to 40% of patients with cerebral venous thrombosis. (Tanislav C, Siekmann R, Sieweke N, Allendorfer J, Pabst W, Kaps M, Stolz E BMC Neurol. 2011). Because seizures occur less often in other types of stroke, cerebral venous thrombosis should be considered in patients with seizures and other focal findings consistent with stroke. Seizures are encountered more frequently with thrombosis of the sagittal sinuses and cortical veins. (Ferro JM, Canhao P, Bousser MG, Stam J, Barinagarrementeria F. Stroke. 2008).

Encephalopathy can result from thrombosis of the straight sinus and its branches or from severe cases of cerebral venous thrombosis with extensive cerebral edema, large venous infarcts, or parenchymal hemorrhages that lead to herniation. (Stam J. N Engl J Med. 2005). Elderly patients with cerebral venous thrombosis are more likely to present with mental status changes than younger patients. (Ferro JM, Canhao P, Bousser MG, Stam J, Barinagarrementeria F. Stroke. 2005).

Diagnosis

Cerebral venous thrombosis should be considered in
patients 50 years of age who present with acute, subacute, or chronic headache with unusual features, signs of intracranial hypertension, and focal neurological abnormalities in the absence of vascular risk factors, new seizure disorder, or hemorrhagic infarcts especially if multiple or in nonarterial vascular territories. Because of variability in clinical presentation, delays in diagnosis are common.

**Laboratory Testing**


**Imaging**

The American Heart Association (AHA)/American Stroke Association (ASA) 2011 Scientific Statement on diagnosis and management of cerebral venous thrombosis recommends imaging of the cerebral venous system in patients with suspected cerebral venous thrombosis. (Saposnik G, Barinagarrementeria F, Brown RD Jr, Bushnell CD, Cucchiara B, Cushman M, deVeber G, Ferro JM, Tsai FY. Stroke. 2011) Head CT is the most frequently performed imaging study for evaluation of patients with new headache, focal neurological abnormalities, seizure, or change in mental status. Although noncontrast head CT may detect alternative diagnoses or demonstrate venous infarcts or hemorrhages, it has poor sensitivity and shows direct signs of cerebral venous thrombosis in only one third of patients. (Saposnik G, Barinagarrementeria F, Brown RD Jr, Bushnell CD, Cucchiara B, Cushman M, deVeber G, Ferro JM, Tsai FY. Stroke. 2011). Signs of cerebral venous thrombosis on CT include hyperdensity in the area of a sinus or cortical vein (cord sign) and filling defects, especially in the superior sagittal sinus (empty A sign), in contrast-enhanced studies. (Saposnik G, Barinagarrementeria F, Brown RD Jr, Bushnell CD, Cucchiara B, Cushman M, deVeber G, Ferro JM, Tsai FY. Stroke. 2011).

Magnetic resonance imaging of the head is the most sensitive study for detection of cerebral venous thrombosis in the acute, subacute, and chronic phases (Bousser MG, Ferro JM, Lancet Neurol 2007). Acutely, cerebral venous thrombosis appears isointense to brain tissue on T1-weighted images and hypointense on T2-weighted images (Saposnik G, Barinagarrementeria F, Brown RD Jr, Bushnell CD, Cucchiara B, Cushman M, deVeber G, Ferro JM, Tsai FY. Stroke. 2011). In the subacute phase, thrombus appears hyperintense in both T1- and T2-weighted images. In chronic stages, the thrombus can be heterogeneous with variable intensity relative to surrounding brain tissue. On T2-weighted images, thrombus may be directly visualized in cerebral veins and dural sinuses and appears as a hypointense area. Parenchymal lesions associated with cerebral venous thrombosis such as infarction and hemorrhage are often better visualized by MR.

Cerebral intra-arterial angiography with venous phase imaging and direct cerebral venography are invasive diagnostic techniques that are reserved for instances when the clinical suspicion of cerebral venous thrombosis is high but MR or CT is inconclusive or if an endovascular procedure is being considered. (Saposnik G, Barinagarrementeria F, Brown RD Jr, Bushnell CD, Cucchiara B, Cushman M, deVeber G, Ferro JM, Tsai FY. Stroke. 2011).

**Thrombophilia Testing**

Because of the high frequency of thrombophilias among patients who develop cerebral venous thrombosis, screening for hypercoagulable conditions should be performed. (Saposnik G, Barinagarrementeria F, Brown RD Jr, Bushnell CD, Cucchiara B, Cushman M, deVeber G, Ferro JM, Tsai FY. Stroke. 2011). Thrombophilia testing should include evaluation for the factor V Leiden mutation, prothrombin gene mutation 20210, lupus anticoagulant, anticardiolipin antibodies, hyperhomocysteinemia, and deficiencies of protein C, S, and antithrombin. Protein C, S, and antithrombin levels may be abnormal in the setting of acute thrombosis, anticoagulation, oral contraceptives, or pregnancy.

**Discussion**

The primary cause of death during the acute phase of cerebral venous thrombosis is transtentorial herniation, most frequently from large venous hemorrhage. (Dentali F, Gianni M, Crowther MA, Ageno W. Blood. 2006), (Canhao P, Ferro JM, Lindgren AG, Bousser MG, Stam J, Barinagarrementeria F. Stroke. 2005) Although the majority of patients have a complete or partial recovery, 10% are found to have permanent neurological deficits by 12 months of follow-up.
Recanalization occurs within the first few months after cerebral venous thrombosis, and is limited thereafter. Recurrence of cerebral venous thrombosis is rare (2.8%). However, patients with cerebral venous thrombosis have an increased incidence of venous thromboembolism, including deep vein thrombosis and pulmonary embolism, the majority of which occur within the first year. (Miranda B, Ferro JM, Canhao P, Stam J, Bousser MG, Barinagarrementeria F, Scoditti U. Stroke. 2010).

Management

Acute phase therapy for cerebral venous thrombosis focuses on anticoagulation, management of sequelae such as seizures, increased intracranial pressure, and venous infarction, and prevention of cerebral herniation (Stam J, N Engl J Med. 2005). Management of seizures and increased intracranial pressure in patients with cerebral venous thrombosis requires a team approach that includes consultation with neurology and neurosurgery.

Anticoagulation

The rationale for anticoagulation is to prevent thrombus propagation, recanalize occluded sinuses and cerebral veins, and prevent complications of deep vein thrombosis and pulmonary embolism. Anticoagulation has been controversial for treatment of cerebral venous thrombosis because of the tendency for venous infarcts to become hemorrhagic even before anticoagulants have been administered (Stam J, N Engl J Med. 2005).

Anticoagulation has posed a particular concern in cerebral venous thrombosis patients presenting with hemorrhagic infarction. In two randomized, controlled trials, no new cerebral hemorrhages or extension of hemorrhages present before therapy were observed. (de Bruijn SF, Stam J. Stroke. 1999), (Einhaupl KM, Villringer A, Meister W, Mehraein S, Garner C, Pellkofer M, Haberl RL, Pfister HW, Schmiedek P. Lancet. 1991). This observation supports the hypothesis that improvement in venous outflow obstruction with anticoagulation, decreases venular and capillary pressure and reduces the risk of further hemorrhage.

On the basis of data from randomized, controlled trials and observational studies, anticoagulation is recommended as safe and effective for treatment of cerebral venous thrombosis with or without intracranial hemorrhage on presentation. Immediate anticoagulation is administered with either intravenous unfractionated heparin or with subcutaneously administered low–molecular weight heparin as a bridge to oral anticoagulation with a vitamin K antagonist.

Conclusions

The AHA/ASA 2011 Scientific Statement recommends anticoagulation with an oral vitamin K antagonist and keeping international normalized ratio 2.0 to 3.0 for 3 to 6 months in patients with provoked cerebral venous thrombosis and 6 to 12 months in those with unprovoked cerebral venous thrombosis (Saposnik G, Barinagarrementeria F, Brown RD Jr. Bushnell CD, Cucchiara B, Cushman M, deVeber G, Ferro JM, Tsai FY. Stroke. 2011). Patients with recurrent cerebral venous thrombosis, deep vein thrombosis, or pulmonary embolism complicating cerebral venous thrombosis or initial cerebral venous thrombosis in the setting of severe thrombophilia (homozgyosity for prothrombin gene mutation 20210 or factor V Leiden; combined thrombophilias; deficiencies of antithrombin, protein C, or protein S; or antiphospholipid antibodies) should be considered for indefinite duration anticoagulation with a target international normalized ratio of 2.0 to 3.0.

Women who have suffered cerebral venous thrombosis in the setting of hormonal contraceptive therapy should seek alternative non–estrogen-based methods for contraception. The progestin-only pill, levonorgestrel intrauterine device, and copper intrauterine device are reasonable alternatives. Women with a history of cerebral venous thrombosis while receiving hormonal contraceptive therapy, during pregnancy, or during the postpartum period have an increased risk of recurrence during subsequent pregnancies. Prophylactic anticoagulation with low–molecular weight heparin during future pregnancies and the postpartum period is often recommended. (Saposnik G, Barinagarrementeria F, Brown RD Jr. Bushnell CD, Cucchiara B, Cushman M, deVeber G, Ferro JM, Tsai FY. Stroke. 2011).

References

Illustrations

Illustration 1

Figure 1: Major clinical syndromes according to location of cerebral venous thrombosis.
Disclaimer

This article has been downloaded from WebmedCentral. With our unique author driven post publication peer review, contents posted on this web portal do not undergo any prepublication peer or editorial review. It is completely the responsibility of the authors to ensure not only scientific and ethical standards of the manuscript but also its grammatical accuracy. Authors must ensure that they obtain all the necessary permissions before submitting any information that requires obtaining a consent or approval from a third party. Authors should also ensure not to submit any information which they do not have the copyright of or of which they have transferred the copyrights to a third party.

Contents on WebmedCentral are purely for biomedical researchers and scientists. They are not meant to cater to the needs of an individual patient. The web portal or any content(s) therein is neither designed to support, nor replace, the relationship that exists between a patient/site visitor and his/her physician. Your use of the WebmedCentral site and its contents is entirely at your own risk. We do not take any responsibility for any harm that you may suffer or inflict on a third person by following the contents of this website.