Adiponectin Level in Cerebral Venous Thrombosis: A Possible Role

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ABSTRACT

Background and Aim of Study: Cerebral venous thrombosis (CVT) is an underdiagnosed cause of stroke with a relatively high mortality, if not discovered and treated early. A significant number of patients with CVT has no clear aetiology. Thus, CVT risk factors represent a tempting area of study. Adiponectin is an endogenous antithrombotic factor that has an independent negative association with intracranial atherosclerosis. Atherosclerosis and venous thromboembolism proved to share common risk factors. Through a controlled study, we investigated the possible relationship between plasma adiponectin level and CVT.

Subjects and Methods: Using clinical, cranial imaging (magnetic resonance imaging (MRI), and phase-contrast magnetic resonance venography (MRV)), and laboratory data, and out of 50 patients with newly diagnosed CVT, only 20 patients (14 females, and 6 males) with neither clear aetiology for CVT nor detectable risk factors for ischaemia were included in the study, together with an age and sex matching control group of 20 healthy subjects. For both patients and control subjects, plasma adiponectin level was assessed by an enzyme-linked immunosorbent assay(ELISA).

Results: All patients (100%) had direct evidence(s) of CVT on cranial phase-contrast MRV. Cranial MRI showed venous infarction in 11 patients(55%), and haemorrhagic infarction in 5 patients(25%).Headache was found in 16 patients(80%), focal neurological deficits in 9(45%), vomiting in 8(40%), seizures in 5(25%), and impaired level of consciousness in 3(15%).Mean plasma adiponectin level was found to be significantly lower in patients with CVT versus healthy control subjects (mean value ± SD 6.44±1.22 μg/ml versus 11.33±2.90 μg/ml, P<0.001).The estimated risk of CVT associated with low mean plasma level of adiponectin was expressed as odds ratio(OR) and its 95% confidence interval(CI), and showed significant association [OR, 76; 95% CI, 6.6 to 2081; P<0.001]. A significant negative correlation was found between mean plasma level of adiponectin and both of patients’ age (P<0.05), and body mass index(BMI) (P<0.05). No significant difference in mean plasma level of adiponectin was found with sex difference, nor inbetween patients with or without venous infarction. Conclusion: Our results demonstrate a significant association of low plasma adiponectin level and CVT, suggesting hypoadiponectinaemia as a risk factor for CVT. (Egypt J. Neurol. Psychiat. Neurosurg., 2009, 46(1): 111-118)

INTRODUCTION

CVT is an underdiagnosed cause of stroke due to its variable and nonspecific clinical presentation, and the relative lack of proper noninvasive cerebral imaging tools, which cause delay in diagnosis¹.

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 factors².

CVT incidence has much increased during the past few decades, and it is not any more a rare disorder, yet, there is a paucity of well designed large scale epidemiologic studies focusing on CVT from regions where it is relatively frequent (South Asia, Middle East), and often a hypercoagulable state, or a genetic prothrombotic condition is present³.

The causes and risk factors for CVT encompass numerous conditions, yet, the proportion with unknown aetiology remains about 25%⁴.

Adiponectin is a protein secreted by adipose cells that improves insulin sensitivity and possesses antiatherogenic properties, and its level was found to be independently negatively associated with intracranial atherosclerosis⁵.
An association between venous thromboembolism and atherosclerosis has been reported.

It is possible that adiponectin deficiency may contribute indirectly to the aetiology of venous thromboembolism.

Digging for possible un-investigated risk factors in patients with CVT of no clear aetiology, may lead to earlier diagnosis and treatment of such a pretty fatal underdiagnosed disorder that usually present unspecifically. Our work aims to study the possible role of adiponectin in the development of CVT.

SUBJECTS AND METHODS

This study has been carried out in the departments of Neurology, Radiology, and Clinical Pathology, Zagazig University Hospitals. Out of 50 patients who had an MRI- and MRV-confirmed diagnosis of CVT on the clinical suspicion of an acute cerebrovascular accident, only 20 patients with no clear aetiology were included in the study. Patients comprised 14 females (70%), and 6 males (30%) with mean age in years±SD 31.75±9.49 (Table 1). As an inclusion criterion, all patients had direct cranial MRV evidence(s) of CVT in the form of visualized cerebral venous thrombus or filling defect(s). Indirect cranial MRI evidence(s) of CVT was considered as venous infarction, with or without haemorrhagic changes. To rule out known causes of CVT, the following were used as criteria of exclusion of patients: smoking, hypertension, dyslipidemia, diabetes mellitus, dehydration, history of recent head/neck trauma, invasive central nervous system procedure, pregnancy, puerperium, history or clinical manifestations suggesting infection, inflammatory bowel disease, collagen-vascular disease, thrombophilia, liver failure, nephrotic syndrome, neoplastic disease, current intake of corticosteroids, hormonal contraception, epsilon-aminocaproic acid, L-asparaginase, and Heparin.

20 age/sex matching healthy subjects were included in the study as control. They comprised 13 females (65%), and 7 males(35%) with mean age in years±SD 30.05±9.58 (Table 1).

Clinical and Anthropometric Methods:

All patients and control were subjected to detailed history taking, and thorough clinical neurological and general examination, and assessment of body mass index(BMI). The latter was expressed as weight in kilograms divided by the square of height in meters(kgm/m²).

Radiological Methods:

All patients had cranial MRI and MRV. Scans were performed with 0.5-T radiofrequency MRI imager(GE Medical System Signa Contour).

Laboratory Methods:

All patients had laboratory assessment of protein C, protein S, antithrombin III, complete blood count, fasting blood sugar, lipid profile, liver function tests, and complete urine analysis. In all patients and control, plasma adiponectin level was assessed using human adiponectin (ACRP30) enzyme-linked immunosorbent assay (ELISA) kit.

RESULTS

Patients presented with a variable combinations of neurological findings (Table 2). Acute severe generalized headache with no to poor response to conventional analgesics was found in 16 patients (80%), focal neurological deficits in 9 (45%) [two with hemiparesis, three with paraparesis, and four with lower limb monoparesis], vomiting in 8 (40%), seizures in 5(25%) [three with generalized tonic-clonic, one with simple partial motor, and one with secondary generalized tonic-clonic], and impaired level of consciousness in 3 (15%).

All patients had one or more site(s) of cerebral venous loss of flow signal on MRV(Figs. 1 and 2). Additional MRI venous infarction was seen in 11 patients(55%), and haemorrhagic venous infarction (Fig. 3) in 5 (25%) (Table 3). MRV showed loss of cerebral venous flow signal in one sinus in 6 patients(30%), and in more than one sinus -in variable combinations- in 14 (70%) (Table 4). Loss of flow signal of superior sagittal sinus (Fig. 1) was seen in 15 patients (75%), of transverse sinus (Fig. 2) in 8 (40%), of sinus rectus in 4 (20%), and of sigmoid sinus (Fig. 2) in 2 (10%) (Table 2).
Mean plasma level of adiponectin was found to be significantly lower in patients versus healthy control (mean value ± SD 6.44±1.22 μg/ml versus 11.33±2.9 μg/ml, P<0.001) (Table 1). The estimated risk of CVT associated with low mean plasma level of adiponectin expressed as odds ratio (OR) and its 95% confidence interval (CI) showed significant association (OR 76; 95% CI 6.6 to 2081; P<0.001)(Table 5).

A significant negative correlation was found between mean plasma level of adiponectin and patients' age (P<0.05), as well as patients' BMI (P<0.05) (Table 6).

No significant difference in mean plasma level of adiponectin was found inbetween patients with or without venous infarction (Table 3), inbetween patients with one or more sinus thrombosis (Table 4), nor with sex difference in patients and control (Table 7).

Table 1. Age, sex, body mass index (BMI), and mean plasma level of adiponectin (μg/ml) ± SD in patients and control.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Patients</th>
<th>T</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (in years±SD)</td>
<td>30.05 ± 9.58</td>
<td>31.75 ± 9.49</td>
<td>0.561</td>
<td>NS</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>35% (n=7)</td>
<td>30% (n=6)</td>
<td>Z = 1.11</td>
<td>NS</td>
</tr>
<tr>
<td>female</td>
<td>65% (n=13)</td>
<td>70% (n=14)</td>
<td>Z = 0.337</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>25.69 ± 3.08</td>
<td>26.96 ± 4.36</td>
<td>1.201</td>
<td>NS</td>
</tr>
<tr>
<td>Adiponectin (μg/ml)</td>
<td>11.33 ± 2.903</td>
<td>6.44 ± 1.227</td>
<td>6.955</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Table 2. Neurological findings, and site of cerebral venous sinus thrombosis in patients at presentation.

<table>
<thead>
<tr>
<th>Neurological finding</th>
<th>Number of patients (%)</th>
<th>Site of thrombosis</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>16 (80%)</td>
<td>Superior sagittal sinus</td>
<td>15 (75%)</td>
</tr>
<tr>
<td>Focal neurological deficit</td>
<td>9 (45%)</td>
<td>Transverse sinus</td>
<td>8 (40%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8 (40%)</td>
<td>Sinus rectus</td>
<td>4 (20%)</td>
</tr>
<tr>
<td>Seizures</td>
<td>5 (25%)</td>
<td>Sigmoid sinus</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>Impaired level of consciousness</td>
<td>3 (15%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Mean plasma level of adiponectin (μg/ml) ± SD in patients with and without parenchymal changes.

<table>
<thead>
<tr>
<th>Number of patients with isolated cerebral venous thrombosis</th>
<th>Number of patients with cerebral venous sinus thrombosis + venous infarction</th>
<th>Number of patients with cerebral venous sinus thrombosis + venous haemorrhagic infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 (20%)</td>
<td>11 (55%)</td>
<td>5 (25%)</td>
</tr>
<tr>
<td>6.75±1.59</td>
<td>6.30±1.21</td>
<td>6.50±1.06</td>
</tr>
</tbody>
</table>

Table 4. Mean plasma level of adiponectin (μg/ml) ± SD in patients with one or more sinus thrombosis.
### Table 5. Odds ratio for risk of cerebral venous thrombosis associated with low mean plasma level of adiponectin.

<table>
<thead>
<tr>
<th>Adiponectin μg/ml</th>
<th>Control</th>
<th>Patients</th>
<th>Odds ratio</th>
<th>CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 8.43*</td>
<td>4</td>
<td>19</td>
<td>76</td>
<td>6.6-2081</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt; 8.43</td>
<td>16</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

* Cut off point = mean plasma level of adiponectin of control -1SD

### Table 6. Correlation between mean plasma level of adiponectin and age and BMI of patients.

<table>
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<tbody>
<tr>
<td>Age (years)</td>
<td>-0.475</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>-0.507</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

### Table 7. Mean plasma level of adiponectin(μg/ml)±SD and sex difference in patients and control

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
<th>T</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>12.20 ± 2.75</td>
<td>10.86 ± 2.97</td>
<td>1.01</td>
<td>NS</td>
</tr>
<tr>
<td>Patients</td>
<td>6.63 ± 1.33</td>
<td>6.35 ± 1.21</td>
<td>1.643</td>
<td>NS</td>
</tr>
</tbody>
</table>
Fig. (1): Cranial sagittal MRV of a 25-year-old man with headache shows loss of flow signal in superior sagittal sinus (arrow).
Fig. (2): Cranial axial MRV of a 30-year-old female patient with headache showing absent flow in the right transverse sinus, sigmoid sinus, and internal jugular vein (arrow).

Fig. (3): Cranial axial MRI T2-weighted image of a 35-year-old female patient with headache showing left temporal lobe haemorrhagic venous infarction (arrow).

DISCUSSION

MRV gives similar results to conventional angiography, with an additional asset of being noninvasive. So, we used visualized cerebral venous thrombus or filling defect(s) on MRV as direct confirmatory evidences for CVT, and as inclusion criteria in the study.

Our patients showed higher percentage of female sex, and a relative young adult age, as described by other studies. Also, our workup to exclude ischaemic risk factors can contribute to the relative young age of our patients. Until the mid-1970s, men and women were equally affected. More recently, there has been a significant female predominance among young adults with cerebral venous thrombosis.

The overall assessment of neurological findings in our patient at presentation proved nonspecific, where severe headache was the most frequent one. Other studies showed that the most frequent and least specific symptom of cerebral venous sinus thrombosis is severe headache that increases gradually over a couple of days, but it can also start in a split second, mimicking a subarachnoid hemorrhage. Significant headache prevails in the picture, likely due to the considerable increase of intracranial pressure, and the enormous cerebral oedema characterizing CVT. Basically, ischaemia damages the energy-dependent cellular membrane pumps leading to intracellular swelling (cytotoxic oedema), and disrupts the blood-brain barrier leading to leakage of plasma into the interstitial space (vasogenic oedema).

MRV findings of our patients showed in a descending order of frequency thrombosis of superior sagittal sinus, transverse sinus, sinus rectus, then sigmoid sinus. The same order was found in a recent study.
Our study showed a significantly lower mean plasma level of adiponectin in patients than in control, and this low level was found to be significantly associated with the risk of CVT when expressed as odds ratio. Our trial to exclude most of the known ischaemic risk factors in patients, may have given more likelihood and chance for other - not as much investigated- risk factors like adiponectin to be in play. Adiponectin levels have been considered as a predictor of atherosclerosis development and cardiovascular disease. Also, an independent negative association of adiponectin levels and Common carotid artery intima-media thickness has been found. Adiponectin was proven experimentally, as well, to be an endogenous antithrombotic factor. In addition, reduced plasma adiponectin concentrations are considered to be a risk factor of cardiovascular, cerebrovascular and metabolic disorders. Finally, adiponectin suppresses various mechanisms contributing to atherogenesis, including the expression of adhesion molecules in endothelial cells, proliferation of smooth muscle cells, transformation of macrophages to foam cells, and secretion of tumor necrosis factor-α from macrophages.

So, the significantly low level of adiponectin found in patients of our study may have a role in the aetiology of CVT.

Our study showed a significant negative correlation between adiponectin level and both of age and BMI which is in agreement with other studies. A decrease in the metabolic function of the adipocyte as it ages or hypertrophies may be an explanation.

In conclusion, our results bring to light a bit new player in the process of cerebral venous atherogenesis, a disorder whose incidence has much increased over the past few decades, yet not very well studied. Also, low adiponectin level may help to discern some of the enigma of CVT in patients who have no clear risk factors for ischaemia, and represent as high as 25% of cases. With larger future studies, low adiponectin level may prove to be an important risk factor for cerebral ischaemia. A risk factor that carries along with jeopardy a therapeutic potential by being modified, where a significant elevation of adiponectin level on weight reduction has been reported, in addition to the described successful therapeutic up regulation of adiponectin receptors, and increase in its synthesis, and secretion.

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