Intracerebral Vascular Occlusive Disease In The Diabetic Patients

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ABSTRACT

Diabetic arteriosclerosis is considered as a more serious form of atherosclerosis characterized by its premature onset. The aim of our study is to identify the pattern of intracerebral vascular occlusive disease in the diabetic patients presenting with cerebrovascular disease and the relation of this pattern to the affection of peripheral nervous system. Fifty Egyptian patients recruited from Ain-Shams University Hospitals underwent cross-sectional study. All of them were diabetics presenting with cerebrovascular events. Clinical history and examination, laboratory indices, magnetic resonance angiography, carotid duplex, transcranial Doppler ultrasonography, vibration perception threshold and sensory nerve conduction velocity were done for all patients. The study has shown that intracranial stenosis was prevalent in 54% of our study sample. The accumulation of the components of the metabolic syndrome was the most statistically significant factor affecting the grade of intracranial vessel stenosis (p<0.007). The mean age of this sample was 48 years. This less than average age of stroke in the general population (more than 2/3 of cases are more than 65 yrs). The severity of peripheral nervous affection correlated directly with the duration of diabetes. And no direct correlation was found between peripheral and cerebral vascular affection. (Egypt J. Neurol. Psychiat. Neurosurg., 2008, 45(2): 513-519)

INTRODUCTION

Atherosclerosis is the most frequent complication of diabetes. It affects all major vascular beds. Atherosclerosis causes most morbidity and mortality in patients with diabetes mellitus. Diabetes mellitus markedly increases the risk of myocardial infarction, stroke, amputation, and death¹.

Accelerated atherosclerosis in diabetes due to mechanism unique to diabetes like non-enzymatic glycation of proteins, oxidative modification of lipoproteins, lipoproteins immune complexes, lipoproteins aggregation, disturbances of cell replication and growth factors and propensity to thrombosis are clearly established. Therapeutic implication for the prevention of atherosclerosis in diabetes and hypertension clearly emphasizes the need to achieve tight control of hyperglycemia, hypertension, and hyperlipidemia in addition to avoiding cigarette smoking and developing obesity².

In a recent study based on transcranial Doppler ultrasound, diabetic patients with previous stroke have a high pulsatility index than non-diabetic patients with previous strokes, which indicates a higher increase in intracranial arterial resistance and more severe damage to cerebral blood flow in diabetes mellitus³.

Non-fatal small infarction especially with multiple occurrences is a feature of cerebrovascular disease complicating diabetes mellitus. The atherosclerosis of the cervical and cerebral arteries, especially in the posterior circulation is more severe than in non-diabetic⁴.

Diabetic arteriosclerosis is considered as a more serious form of atherosclerosis characterized by its premature onset. Hyperglycemia is assumed to be the crucial pathophysiological cause of the development of macro- and microangiopathy in diabetes mellitus. Apparently, hyperglycemia has a direct toxic influence on the arterial wall by increased accumulation of irreversible –
glycosylation and provoking endothelial dysfunction. Diabetic macroangiopathy is often viewed as an accelerated and aggravated form of atherosclerosis. Diabetes influences brain ischemia in a number of different ways. Diabetes causes and exacerbates macroangiopathies, increases the severity of ischemia, and increases stroke mortality.

Although the metabolic syndrome unequivocally predisposes to type two diabetes mellitus, many investigators of cardiovascular diseases consider this syndrome to be a multidimensional risk factor for atherosclerotic cardiovascular disease.

Several recent reports show that the metabolic syndrome is associated with greater risk for cardiovascular disease, but once type two diabetes mellitus, cardiovascular risk increases even more.

Although the phenomenon of clustering of metabolic risk factors did not draw conclusions on mechanistic pathogenesis, the criteria thus required no single factor for diagnosis, but instead made the presence of three of five factors the basis for establishing the diagnosis; these were abdominal obesity (also highly correlated with insulin resistance), elevated triglycerides, reduced high density lipoproteins, cholesterol (HDL-C), elevated blood pressure, and elevated fasting glucose (type two diabetes mellitus).

The aim of our study is to identify the pattern of intracerebral vascular occlusive disease in the diabetic patients presenting with cerebrovascular disease.

**PATIENTS AND METHODS**

A total of 50 diabetic patients admitted to Ain Shams University Hospitals and Ain Shams University Specialized Hospital presenting or with a history of cerebral ischemia were recruited to this study between October 2004 and February 2006.

**Inclusion criteria**
1. Both sexes were included
2. Age above 35 years.
3. Patients may have other ischemic risk factors.
4. Patients may be symptomatic for diabetes or not.

**Exclusion criteria**
1. Haemorrhagic transformation of ischaemic infarct before MRA and/or TCD.
2. Patients with organ failure.
4. AF, Rheumatic heart disease or any other definite embolic stroke.
5. Coma or disturbed conscious level.

**All patients were subjected to the following**
1. Full clinical full history and examination
2. Complete blood picture
3. Erythrocyte sedimentation rate
4. Coagulation profile.
5. Fasting and postprandial blood sugar.
6. Liver and kidney functions tests.
7. Lipid profile.
8. Computed tomography (CT) scan of the head without contrast was done for all patients.
10. Magnetic Resonance angiography.
11. Carotid Doppler ultrasonography.

**RESULTS**

The study included 50 patients complaining of different medical risk factors, presenting or with past history of ischemic stroke and diabetes mellitus.

The mean age of the studied sample was 48.5 with a standard deviation of 10. The study included 21 (42%) males and 29 (58%) female patients.

All the studied cases were diabetics, of whom 96% had NIDDM, while only 4% were IDDM. The mean duration of DM was 11.5±9.2 years. Hypertension was the most prevalent risk factor among the studied group as it was present in 90% of cases and 50% were uncontrolled despite combination therapy.

Twenty eight patients (56%) had lacunar infarcts (LI), 13 (26%) had partial anterior circulation infarcts (PACI), 7 (14%) had posterior circulation infarcts (POCI) and only 3 patients had total anterior circulation infarcts (6%).

MRA showed intracranial stenosis in 27 patients (54%). Two patients (4%) had complete occlusions, 7 (14%) had severe stenosis, 16 (32%)
had moderate stenosis and 2 (4%) had only mild stenosis (Table 1).

Interestingly 27 patients had intracranial stenosis by MRA, 16 patients (59%) had anterior circulation affection, 21 patients (77%) had posterior circulation affection. 10 of these 21 patients had combined anterior and posterior circulation affection.

The analysis of the relationship between the different risk factors and the grade of intracranial stenosis showed a positive correlation between the number of positive risk factors and the grade of intracranial stenosis among the studied cases using Pearson test (P<0.007). Yet there was no statistical significant correlation between any of the individual risk factors (hypertension, hyperlipidemia, smoking, hyperurecemia, heart disease, duration of diabetes mellitus) and either the presence or the grade of intracranial stenosis (Table 2).

Carotid duplex showed significant stenosis in only 9 patients. Eleven patients had intracranial stenosis by TCD (Fig. 1).

There was no statistically significant relationship between transcranial Doppler and MRA results using the Chi-Square test however, sensitivity and specificity studies show that TCD had a higher specificity than sensitivity so when the results are negative we need confirmation by MRA i.e. it's better as a good positive test (Table 3 and 4).

Table 1. Grades of intracranial stenosis in MRA.

<table>
<thead>
<tr>
<th>Grades of stenosis</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>No stenosis</td>
<td>23</td>
<td>46.0</td>
</tr>
<tr>
<td>Mild</td>
<td>2</td>
<td>4.0</td>
</tr>
<tr>
<td>Moderate</td>
<td>16</td>
<td>32.0</td>
</tr>
<tr>
<td>Severe</td>
<td>7</td>
<td>14.0</td>
</tr>
<tr>
<td>Occlusion</td>
<td>2</td>
<td>4.0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>50</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>

Table 2. Correlation between the number of risk factors and degree of stenosis.

<table>
<thead>
<tr>
<th>Number of risk factors</th>
<th>Grade of stenosis</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal mild moderate severe occlusion</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1 0 0 0 0</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>0 0 3 1 0</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>0 1 5 3 1</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>0 0 5 2 1</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>0 0 2 0 0</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>0 0 0 1 0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>1 1 15 7 2</td>
<td>26</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
<th>df</th>
<th>Asymp. Sig. (2-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson Chi-Square</td>
<td>33.351 (a)</td>
<td>16</td>
<td>0.007</td>
</tr>
</tbody>
</table>
**Fig. (1):** Description of the results of the TCD among the studied cases.

**Table 3.** Relationship between TCD results versus MRA among the studied cases.

<table>
<thead>
<tr>
<th>MRA</th>
<th>TCD</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>NO</td>
<td>18 (46.2 %)</td>
<td>3(27.3 %)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>21 (53.8 %)</td>
<td>8(72.7 %)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>X²=1.3 P&gt;0.05</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 4.** Sensitivity and specificity, of TCD in relation to MRA.

<table>
<thead>
<tr>
<th>Validity of TCD in relation to MRA</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>30%</td>
</tr>
<tr>
<td>Specificity</td>
<td>85.7%</td>
</tr>
<tr>
<td>PPV</td>
<td>72%</td>
</tr>
<tr>
<td>NPV</td>
<td>46%</td>
</tr>
</tbody>
</table>

PPV= positive predictive value  
NPV= negative predictive value
DISCUSSION

Diabetes is a major risk factor for cerebrovascular morbidity. This condition increases the risk of developing cerebrovascular, coronary, and peripheral arterial disease up to 4-folds.\textsuperscript{11} The risk of stroke attributable to history of both diabetes and hypertension was found to be substantially greater than for either conditions alone and diabetes alone had a higher relative risk of stroke than hypertension alone\textsuperscript{12}.

Our results have shown that the mean age of study group was 48±10 years. This is less than average age of stroke in the general population (more than 2/3 of cases are more than 65yrs). This correlates with the meta-analysis by Abdulghani in (1994)\textsuperscript{13}, which reported that risk factors of stroke in young persons below the age of 40 year pointed towards the prevalence of cardiac diseases (44%), followed by hypertension (21%), and diabetes mellitus (7%).

Analysis of Risk factors in our study have shown that as the number of risk factors (hypertension, diabetes hyperurecemia, hyperlipidemia, smoking) increases, the grade of intracranial stenosis increases (P<0.007). This correlates with a study conducted in the Chinese University of Hong Kong, including 2.165 type 2 diabetic patients which conclude that there was positive correlation between the number of risk factors including age, female sex, age at onset of diabetes, duration of diabetes.\textsuperscript{14}

Our study has also shown that the incidence of intracranial stenosis in diabetic patients is more than extracranial stenosis. Nine patients (20% of sample) with extracranial stenosis as evidenced by carotid duplex study, while 27 patients (54% of sample) of the patients, has intracranial stenosis, as evidenced by MRA study. This correlates with a study conducted in Korea between January 1996 and December 1997 including 1436 patients admitted to a hospital and underwent transfemoral, intra-arterial four –vessel cerebral angiography. In this study lesions were located in the intracranial area in 52% and in the extracranial area in 48%. Also in patients with stenosis in only one site, 66% were located in the intracranial area, and 35% were in the extracranial area\textsuperscript{15}. Diabetes was also associated with intracranial stenosis, but not extracranial stenosis, in a study on 510 patients with asymptomatic disease\textsuperscript{16}.

In general, previous studies in our stroke unit have shown that intracranial stenosis more prevalent in Egyptian patients with cerebral infarctions\textsuperscript{16,17}. On a similar note, Zakieldine in 2002 found that intracranial atherosclerotic disease was dominant and prevalent among Egyptian patients with cerebrovascular stroke. These results were mentioned before by Kissela et al.\textsuperscript{18} and Abdulghani\textsuperscript{19}.

Regarding the evaluation tools of our study, TCD was done to all patients, and our results have shown that it is a good screening test, with a sensitivity of 87% and specificity of 30%.

TCD was found to be less reliable than MRA in detecting intracranial stenosis and cannot be used alone to confirm its presence.\textsuperscript{18} Similar findings were found in other studies on Egyptian patients\textsuperscript{18}. MRA is reproducible, has little inter-rater variability and affords sensitivity and specificity up to 100% and 96% respectively\textsuperscript{19}. This provides support for using MRA as the main tool to detect intracranial stenosis in our study.

Although atherosclerosis is a generalized disease process that affects large as well as medium-diameter arteries throughout the arterial tree, our study has shown that out of 27 patients (who had intracranial stenosis), 16 patients (32% of the sample, 59% of the patients with stenosis) had anterior circulation affection and 21 (42% of the sample, 77.7% of the patients with stenosis) patients included 10 patients (20% of sample, 37% of patients with stenosis) with both circulation affected. This predilection to posterior circulation affection in diabetics was not however scrutinized by other researchers so far. This issue is of particular interest regarding the diagnosis prognosis and prevention plans for such a group of patients.

Analysis of risk factors in our study have shown that as a number of risk factors (hypertension, diabetes mellitus, hyperurecemia, hyperlipidemia, smoking) increase, the grade of intracranial stenosis increase.

The prevalence of vascular disease was markedly increased in the presence of the metabolic syndrome. Those with both the metabolic syndrome and the diabetes mellitus has the highest prevalence of vascular disease followed by those with the metabolic syndrome without diabetes mellitus\textsuperscript{5}. Metabolic syndrome is present in about half of the individuals with symptomatic intracranial atherosclerotic disease and is associated with a substantially higher risk of major vascular events\textsuperscript{5}. When type two DM is present, concomitant metabolic risk factors must not be overlooked because of strong evidence that intervention on them can substantially reduce risk for atherosclerotic cerebrovascular disease.\textsuperscript{10}
In conclusion, diabetes affects both intracranial and extracranial vasculature and it is identifiable risk factors for cerebrovascular ischemic events. Diabetes is a disorder with underlying multiple atherogenic risk factors that accumulate to result in concomitant burden on the intracerebral blood vessels. Regarding the distribution of intracranial stenotic lesion it was found that the majority of cases have both anterior and posterior circulation affection with marginal predilection towards posterior circulation. However compared to TCD, MRA has shown greater accuracy in detecting intracranial stenotic lesion.

Finally the management of diabetes has to be multidimensional and control of all constituents of the metabolic syndrome seems mandatory.

REFERENCES

الملحص العربي

تم إجراء هذه الدراسة على 50 مريضاً محسنًا بمستشفى جامعة عين شمس ومستشفى عين شمس التخصصي في دراسة عرضية تم فيها انعقاد جميع المرضى من المصابين بالسمنة، وطارأت عليهم أعراض الجلطة الدماغية الحادة، حيث خضعت كافة العوامل للتحليل والدراسة متضمنة التاريخ المرضي، والمؤشرات العملية، وصور الرنين المغناطيسي، والموجات فوق الصوتية على الشرايين السباتية والموجات فوق الصوتية على الشرايين الدماغية وحده استنارة الإحساس بالدشنة وسرعة توصيل الأعصاب الحسية، وذلك لجميع المرضى في الدراسة.

أشرفت هذه الدراسة عن وجود اختلافات بالشرايين الدماغية بنسبة تصل 54% من عينه البحث، كما تبين أن تراكم مكونات المتلازمة الأيضية هو أهم العوامل من حيث دلائله الإحساسية، كمثير على درجة تسبيح الأوعية الدماغية.

ومع ذلك، نشأت علاقة هامة فيما بين النتائج المبسطة بالشرايين الدماغية والموجات فوق الصوتية للشرايين الدماغية، مما يجعل الفحص الأخير ذو حاسة في حالات متزامنة وعمر ممر الإشارة يتطلب أيضاً زيادة عدد الإصابات بمتلازمة الأيضية، بينما تظهر ثمة علاقة مباشرة فيما بين الفحص في الأعصاب الهرمية من ناحية الأولية والأوعية الدماغية من ناحية أخرى.

كما وجدنا أن معدل إصابة شرابين المخ داخل الدماغ أكثر من خارج الدماغ كما أن الدورة القلبية كانت أكثر من الدورة الأمامية.