Familial Hyperlipidemia in Stroke in the Young

B.C. Bansal, M.D., M.A.M.S., F.I.A.M.S.,* A.K. Sood, M.D., † C.B. Bansal, M.D. ‡

SUMMARY Serum cholesterol, low density lipoproteins (LDL), very low density lipoproteins (VLDL) and chylomicron levels were studied in 25 young patients (age 40 years or less) of non-embolic ischemic stroke of unknown aetiology. Fifteen patients were males and 10 were females. The prevalence of hyperlipidemia was found to be 60%. Frederickson's type IIb hyperlipoproteinemia was the commonest (32%) abnormal pattern observed, followed by type IIa (12%), type IV (12%) and type V (4%). Family studies were carried out in all the 25 index patients (15 hyperlipidemic and 10 normolipidemic). Familial hyperlipidemia (i.e. 2 or more hyperlipidemic members in the same family) was found in 9 of the 15 hyperlipidemic index patients and in none of the normolipidemic index patients. The common pattern was found to be that of familial combined hyperlipidemia. The study indicates that screening the family members of hyperlipidemic young patients of non-embolic ischemic stroke may delineate a group of high risk individuals for possible primary prevention before they develop the disease.

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Since cerebral stroke is often crippling, and the impact of treatment on the prognosis is limited, the potential to control the disease lies in its primary prevention. 1-3 This implies reliable and comprehensive information on the factors related to the risk of stroke. Hyperlipidemia has been considered as one of the important risk factors in the causation of atherothrombotic stroke. 4-6 The task of identifying the individuals with high lipid levels in the general population sounds cumbersome. A desirable and feasible alternative approach, however, could be to screen the first degree relatives of hyperlipidemic young patients of atherothrombotic stroke for familial hyperlipidemia, thus delineating a group of high risk individuals for possible primary prevention before they develop the stroke. Since the relative contribution of genetic factors in the causation of any trait may vary among different populations, a pilot study has been carried out to identify the importance of familial hyperlipidemia in patients of ischemic stroke in Haryana (North India).

Material and Methods

Selection of the Index Patients

This study was conducted in the Department of Neurology at Medical College and Hospital, Rohtak (Haryana). Twenty-five patients (15 males and 10 females), of the age of 40 years or less, suffering from cerebral infarction (nonembolic ischemic stroke) of unknown aetiology (based on the criteria of Walker et al, 198110) were taken for the study as index patients. Diagnosis was made on the basis of history, physical...
examination and investigations like CSF examination, carotid angiography and CT scan where necessary. The age of the patients ranged from 9–38 years, with a mean of 24.5 ± 8.75. The following categories of patients were excluded: patients of subarachnoid/intraparenchymal haemorrhage; patients having a known source of embolism; patients of arteritides because of tuberculosis, syphilis and collagen disorders; patients of diabetes mellitus, hypertension and coagulopathies; patients who were pregnant, postpartum or on pills; patients known to have a cause for secondary hyperlipidemia; and patients who were already on lipid lowering diet/drugs.

An equal number of age/sex and socioeconomically matched healthy volunteers were taken as controls. Family studies were carried out in all the 25 index patients. Two hundred and three first degree relatives of these patients (parents, siblings and offspring) were studied. Those family members who were known to have a cause for secondary hyperlipidemia or were on lipid lowering diet/drugs were excluded.

Collection and Analysis of Blood

Blood in all the categories (controls, patients and family members) was drawn after an overnight fast of 22–24 hours before the start of any treatment which might alter the serum lipid levels. The serum was separated on the same day, stored at 4° C overnight and analysed the next day. The following two analyses were done: serum cholesterol by the method of Zlatkis as modified by Zak, 1953; and serum lipoproteins (low density lipoproteins (LDL), very low density lipoproteins (VLDL, and Chylomicrons) by using the Thorp Micronephlometer MKIV (Brewster et al, 1982). A lipid-lipoprotein profile of each patient and family member was categorized according to Fredrickson's classification (Chandra et al, 1983; WHO 1970). The family tree was then analysed for any familial clustering of hyperlipidemia which was considered positive when two or more members (including the index patient) were found to be hyperlipidemic in a family (Das et al, 1983). The student's "t" test (unpaired) and Chi2 (χ2) test was used for statistical considerations wherever applicable.

Results

Lipid-lipoprotein Profile of the Patients

For this purpose, patients were divided into three groups: Group A, 25 patients as a whole; Group B, 15 male patients; Group C, 10 female patients. Patients in each group were compared with an identical number of age/sex and socio-economically matched controls. Group B, in addition, was also compared with group C. The rise in the levels of serum cholesterol and LDL

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Comparison of Serum Lipids-lipoproteins in Different Groups of Patients and Corresponding Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group A</td>
</tr>
<tr>
<td>C</td>
<td>P</td>
</tr>
<tr>
<td>Serum cholesterol (mg%)</td>
<td>140-250</td>
</tr>
<tr>
<td>Mean</td>
<td>186.96</td>
</tr>
<tr>
<td>SD</td>
<td>25.02</td>
</tr>
<tr>
<td>t value</td>
<td>3.66</td>
</tr>
<tr>
<td>p value</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL (gms/L)</td>
<td>2.9-5.8</td>
</tr>
<tr>
<td>Mean</td>
<td>4.06</td>
</tr>
<tr>
<td>SD</td>
<td>0.60</td>
</tr>
<tr>
<td>t value</td>
<td>5.9</td>
</tr>
<tr>
<td>p value</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VLDL (gms/L)</td>
<td>1.0-3.0</td>
</tr>
<tr>
<td>Mean</td>
<td>1.94</td>
</tr>
<tr>
<td>SD</td>
<td>0.49</td>
</tr>
<tr>
<td>t value</td>
<td>4.52</td>
</tr>
<tr>
<td>p value</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chylomicrons (gm/dl)</td>
<td>0.10-0.30</td>
</tr>
<tr>
<td>Mean</td>
<td>0.20</td>
</tr>
<tr>
<td>SD</td>
<td>0.04</td>
</tr>
<tr>
<td>t value</td>
<td>1.0</td>
</tr>
<tr>
<td>p value</td>
<td>&gt;0.1</td>
</tr>
</tbody>
</table>

C = Control; P = Patients.
was found to be statistically significant in all the three groups. VLDL levels were significantly high in group A and C. In group B, however, the rise was not statistically significant. There was no significant difference in the levels of chylomicrons in any of the groups. There was no difference when group B was compared with group C (table 1). Mean + 2 SD of the controls for each lipid-lipoprotein particle was taken as a cut-off point between normal and abnormal. Twelve percent of the controls and 60% of the patients were found to be hyperlipidemic. The difference was statistically significant \( (p < 0.001) \). Fredrickson's type Iib hyperlipoproteinemia was the commonest abnormal pattern observed (32%) to be followed by type IIa (12%), type IV (12%) and V (4%) (table 2).

Family Studies
Serum lipid lipoprotein levels of relatives were considered abnormal if it exceeded the 95th percentile of the controls. Among the 76 relatives of ten normolipidemic index patients, only 2 (2.6%) were hyperlipidemic; whereas, amongst 127 relatives of fifteen hyperlipidemic index patients 40 (41.5%) were hyperlipidemic. The difference was statistically significant \( (p < 0.001) \). It was observed that out of 10 families of normolipidemic index patients, only 2 had sporadic hyperlipidemia and none had familial hyperlipidemia. In 15 families of hyperlipidemic index patients, 6 had sporadic hyperlipidemia and 9 had familial hyperlipidemia (2 familial hypercholesterolemia and 7 familial combined hyperlipidemia). Fredrickson's lipoprotein pattern in the patients and their relatives in the nine affected families is shown in figure 1. It was observed that all three generations were affected; members of both sexes were equally affected and out of the total of 81 family members in the nine affected families 40 (49.4%) were hyperlipidemic. These observations are compatible with the hypothesis of autosomal dominant inheritance.

Discussion
The results of this study indicate that hyperlipidemia is a significant risk factor in the aetiopathology of nonembolic ischemic stroke in young patients. A vast literature is available on the relation of serum lipids and stroke supporting and denying these results. Furthermore, hyperlipidemia in such patients has a significant familial clustering and the observations suggest an autosomal dominant type of inheritance.

Danniels et al, 1982 and Glueck et al, 1982 have observed significant familial hyperlipidemia in paediatric patients of stroke, and reported two generation parent/child clustering of elevated triglycerides or depressed C-HDL levels, and laid emphasis on familial aggregation of low C-HDL (high density lipoprotein cholesterol) levels; but they have not suggested the mode of inheritance. Similar studies, however, have been carried out in atherosclerotic ischemic heart disease subjects by Das et al, 1983, the results of which are in agreement with this study.

We speculate and intend to hypothesize that, as in the patients of atherosclerotic IHD, hyperlipidemia in young patients of non-embolic ischemic stroke may be...
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References


of genetic origin, autosomal dominant type. The study gives an impetus for further work on this line which ultimately might prove useful in the prevention of atherosclerotic stroke.
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Stroke. 1986;17:1142-1145
doi: 10.1161/01.STR.17.6.1142

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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