Cerebral Thromboembolism Among Young Women and Men in Denmark 1977–1982

OJVINID LIDEGAARD, M.D., MORTEN SOE, M.S., AND MADS VARIS NIS ANDERSEN, M.S.

SUMMARY In the period 1977–1982, the Danish National Patient Register recorded 1000 cases of cerebral thromboembolic attacks among women 15–44 years of age, and 971 cases among men of the same age. Cerebral infarction accounted for 70% of cases and transient ischemic attacks (TIA) for the remaining 30%.

By analysing this material we found an average age-adjusted incidence rate of cerebral thromboembolism of 14.4/100,000 among men and 15.5/100,000 among women. The Incidence rates rose rapidly with increasing age. Women aged 15–34 had significantly higher incidence rates of brain infarction and TIA compared to those of men of the same age. This was reversed in the age group 35–44.

The magnitude of the ratio between the female and the male mean incidence rates by increasing age corresponded exactly to the age distribution of the use of oral contraceptives in Denmark. The relative risk for developing cerebral thromboembolism among users of oral contraceptives was estimated to be 3.2–6.5.

The mortality in male patients with brain infarction was 3.3% and in females 1.7%. The mean duration of stay in hospital was 8.8 days for TIA and about 26 days for cerebral infarction. Sixteen percent of men and 13.6% of women had hypertension during their stay.

IN DENMARK, cerebral thromboembolic attacks in people of 15–44 years of age account for about 4% of all cerebral thromboembolism. Nevertheless, it has been a major subject of debate for almost 20 years due to the suspected etiological connection to oral contraceptive use.

Many methodological difficulties are attached to epidemiological studies of strokes. How is data gathered, which clinical and paraclinical parameters are used, where is the investigation undertaken and how is the collected material analysed. Differences in these factors explain the mainly quantitative divergences found in different studies.

Studies of cerebral thromboembolism in the young is impeded by the low incidence rate of stroke whether thrombotic or hemorrhagic, and thus demands extensive retrospective studies. This probably explains the paucity of reports concerning the morbidity of stroke among young people.

Contrary to older age groups, young people attacked by stroke undergo extensive clinical and paraclinical investigations, including angiographic and computer tomographic examinations. Therefore, a differentiation between thrombotic and hemorrhagic strokes among young people is reliable, and this allowed us to consider only the thromboembolic attacks.

The aim of the present study has been to quantify the occurrence of cerebral thromboembolism in young women and men. In order to obtain a large and unbiased group of patients, we have analysed all cases of cerebral thromboembolism in people 15–44 years of age in Denmark during a 6 year period. For the present report, cerebral thromboembolism included cerebral thrombosis, cerebral embolism and transient cerebral ischemic attack (TIA). Also the unspecified group

(USG) — apoplexia cerebri — was included in this study, since thrombotic cases constitute at least 90% of this group.¹

No customarily used expression includes all these cerebral thromboembolic attacks. For this purpose we introduced the term CTA for all cerebral thromboembolic attacks.

Material and Methods

Since 1977, all cases of cerebrovascular diseases in Denmark have been centrally recorded in the National Patient Register (NPR). This study was based upon an extract from NPR, comprising the period 1977–1982 inclusive, and the diagnoses of cerebral thrombosis (ICD 433), cerebral embolism (434), TIA (435) and the unspecified group (436). For each hospitalization the age of the patient was recorded, the year of the attack, the duration of stay in hospital, diagnostic category, type of hospital department, the presence of hypertension during the stay and whether the patient survived.

Since a stroke-patient usually is treated primarily at the local hospital, and then referred to a central hospital, each patient is often reported to the NPR more than once during the treatment for the same attack. For this reason, a patient hospitalized more than once in any one year in the present study, was recorded as having had only one attack. On the other hand a patient hospitalized in different years under the same diagnosis was recorded as having had two attacks, despite the fact that occasionally, both admissions were due to the same attack.

Length of stay in hospital was calculated as the sum of stays for each patient in one year. Each TIA however was recorded independently. If diagnoses from departments treating a patient differed, a priority was given to the more specialized department. Thus one admission at the local hospital under the unspecified diagnosis, and another in the same year at the central hospital under the diagnosis of cerebral thrombosis, figured as one stay of cerebral thrombosis.
TABLE 1  The Incidence of Cerebral Thrombosis (TC), Cerebral Embolism (EC), Transitory Ischemic Attack (TIA) and Cerebral Apoplexia (AC) among Danish Women Aged 15—44 Years during the Period 1977—1982

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<tbody>
<tr>
<td>TC</td>
<td>62</td>
<td>61</td>
<td>69</td>
<td>66</td>
<td>69</td>
<td>69</td>
<td>396</td>
</tr>
<tr>
<td>EC</td>
<td>11</td>
<td>9</td>
<td>10</td>
<td>19</td>
<td>12</td>
<td>16</td>
<td>77</td>
</tr>
<tr>
<td>TIA</td>
<td>48</td>
<td>71</td>
<td>42</td>
<td>53</td>
<td>39</td>
<td>60</td>
<td>313</td>
</tr>
<tr>
<td>AC</td>
<td>33</td>
<td>39</td>
<td>22</td>
<td>33</td>
<td>44</td>
<td>43</td>
<td>214</td>
</tr>
<tr>
<td>Total</td>
<td>154</td>
<td>180</td>
<td>143</td>
<td>171</td>
<td>164</td>
<td>188</td>
<td>1000</td>
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This was done to achieve as reliable figures as possible. For this reason our incidence rates were expected to be significantly lower than those of other studies, where the incidence rates were based on all admissions.

For incidence rates the 95% confidence limits were calculated, and for comparing incidence rates, the $\chi^2$-test was applied.

Results

The total number of cerebral thromboembolic attacks through the period of six years were 1000 among the women and 971 among the men (tables 1 and 2). These 1971 attacks were distributed over 2711 admissions. From statistics of the Danish population between 15 and 44 years of age through the period 1977—1982, the age adjusted incidence rates were calculated (fig. 1, table 3).

A total increase in the incidence rate of cerebral thromboembolic attacks of 70% among men ($p < 0.001$) and of 13% among women (not significant) from 1977—1982 was found. Through the whole period we found an average annual incidence rate of CTA of 14.4/100.000 among men and of 15.5/100.000 among women. Cerebral infarction (thrombotic and embolic infarction of brain and the unspecified group) accounted for about 70%, TIA for the last 30% (fig. 2). No major differences in these percentages by age or sex were seen.

The average annual CTA-incidence rate in both sexes showed a rapid increase with increasing age. This was the case for cerebral infarction as well as for TIA (figs. 3 and 4). However the CTA-incidence rate was significantly higher among women between 15 and 34 years of age as compared to that of men ($p < 0.001$) (fig. 3). The reverse pattern was seen in the age group 35—44 years ($p < 0.001$). These sex-differences existed for cerebral infarction alone and for TIA alone (fig. 4).

Among 692 men and 687 women with cerebral infarction, 23 men and 12 women died, corresponding to a mortality of 3.3% among the male patients and 1.7% among the female patients. This difference was not significant (0.05 < $p < 0.1$).

Hypertension was detected in 16.0% of the men and in 13.6% of the women.

The average duration of stay in hospital was 26 days among patients with brain infarction and 8.8 days among the TIA patients (fig. 5). An increase in length of hospitalization with increasing age was seen. Furthermore sex-differences were disclosed: women aged 15—24 years had longer duration of stay compared to that of men of same age. In the age group 25—44 the reverse was seen.

TABLE 2  The Incidence of Cerebral Thrombosis (TC), Cerebral Embolism (EC), Transitory Ischemic Attack (TIA) and Cerebral Apoplexia (AC) among Danish Men Aged 15—44 Years during the Period 1977—1982

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<tr>
<td>TC</td>
<td>41</td>
<td>54</td>
<td>64</td>
<td>62</td>
<td>55</td>
<td>76</td>
<td>352</td>
</tr>
<tr>
<td>EC</td>
<td>8</td>
<td>11</td>
<td>10</td>
<td>15</td>
<td>23</td>
<td>21</td>
<td>88</td>
</tr>
<tr>
<td>TIA</td>
<td>36</td>
<td>43</td>
<td>46</td>
<td>44</td>
<td>60</td>
<td>50</td>
<td>279</td>
</tr>
<tr>
<td>AC</td>
<td>30</td>
<td>50</td>
<td>36</td>
<td>32</td>
<td>39</td>
<td>65</td>
<td>252</td>
</tr>
<tr>
<td>Total</td>
<td>115</td>
<td>158</td>
<td>156</td>
<td>153</td>
<td>177</td>
<td>212</td>
<td>971</td>
</tr>
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</table>

FIGURE 1.  The average annual incidence rate of cerebral thromboembolism among women and men aged 15—44 in Denmark 1977—1982. 95% CL are indicated.
Seventy-five percent of hospitalizations occurred in neurological departments, the rest mainly in medical departments. There were no major differences in the pattern of visitation by year, diagnostic category or sex. A minor decrease in neurological admissions, as compared to admissions to other departments, with increasing age occurred.

**Discussion**

The difference between the number of attacks (1971) and the number of admissions (2711) indicates that the incidence rates in the present study may be expected to be about 25% lower than corresponding results in other studies, where the incidence rates were calculated from the total number of admissions.

The incidence rates of brain infarction for the whole age group, 15–44 years, correspond to the occurrence in western Europe and the USA. However, Sweden has been reported to have lower incidence rates. The increase in the incidence rate of brain infarction and TIA among men from 1977–1982 is surprising, because other studies have demonstrated a decrease in the incidence rates of cerebrovascular diseases among older people through the last decade. This development is unexplained.

The male group showed an approximately exponential increase in incidence rate with increasing age. In contrast, women in the age group 15–34 years had additional attacks, giving an upward convex curve from the exponential rise (fig. 3), resulting in an incidence rate higher than in the males of the same age.

Most previous epidemiological studies on stroke have been too small to subdivide the age group 15–44, and therefore no significant sex differences have been established. However, a few reports showing sex differences in cerebral infarction among young adults exist, but they are contradictory. In older age groups the higher incidence rate of CTA, whether brain infarction or TIA, among men as compared to women is well documented but unexplained.

Many predisposing factors to stroke in the young have been identified. The relative high incidence rate of cerebral infarction among women aged 15–34, compared to that of men of the same age, may be influenced by oral contraceptive use, pregnancies and the puerperal period among young fertile women.

In Denmark the use of OC in different age groups has been investigated in 1983 (fig. 6). The percentage of pregnant women according to age is shown in the same figure. In figure 7 the incidence rate of CTA among women relative to that of men is plotted against age. A remarkable coincidence is found of a high inci-

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**Figure 2.** The average age adjusted incidence rates of cerebral thromboembolic attacks (CTA) among men and women aged 15–44 years by diagnostic category. TIB = Thrombotic infarction of brain, EIB = Embolic infarction of brain, TIA = Transitory ischemic attack, and USG = Unspecified group (apoplexia cerebri).

<table>
<thead>
<tr>
<th></th>
<th>TIB</th>
<th>EIB</th>
<th>TIA</th>
<th>USG</th>
<th>CTA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>5.2</td>
<td>1.3</td>
<td>4.1</td>
<td>3.7</td>
<td>14.5</td>
</tr>
<tr>
<td>Women</td>
<td>6.2</td>
<td>1.2</td>
<td>4.8</td>
<td>3.3</td>
<td>15.5</td>
</tr>
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</table>

**Figure 3.** The mean annual incidence rates of cerebral thromboembolic attacks among men and women in Denmark in the period 1977–1982 according to age. The 95% CL are indicated.

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</thead>
<tbody>
<tr>
<td>Men</td>
<td>2.0</td>
<td>2.4</td>
<td>6.5</td>
<td>10.5</td>
<td>24.6</td>
<td>49.9</td>
<td>14.4</td>
</tr>
<tr>
<td>Women</td>
<td>2.8</td>
<td>8.4</td>
<td>12.0</td>
<td>14.6</td>
<td>21.1</td>
<td>39.7</td>
<td>15.5</td>
</tr>
</tbody>
</table>
CEREBRAL THROMBOEMBOUSM AMONG YOUNG PEOPLE/Ungeaard et al

INCIDENCE /100.000

28
24
20
16
12
8
4
0
15-24 25-34 35-44 AGE

BRAIN INFARCTION

FEMALE

MEN

TIA

FIGURE 4. The mean annual incidence rates of cerebral infarction* and transitory ischemic attacks (TIA) among women and men aged 15-44 in the period 1977-1982 in Denmark. The 95% CL are indicated. *Cerebral infarction = cerebral thrombosis + cerebral embolism + the unspecified group (apoplexia cerebri).

The relative risk of CTA among pregnant women has been analysed by Cross, Castro & Jennett to be 4.8. In a Danish study from 1982 comprising 91 Danish female CTA-patients, aged 15-40 years, the relative risk was found to be 6.3 (2.7-13.5) compared to non-pregnant women not using OC.

The relative risk of CTA among OC-users has in retro- and prospective studies been calculated to be about 4-9.

If we assume: 1) that the relative risk of developing CTA using OC or being pregnant is equal, and 2) that the "over-incidence" of CTA among young women is caused alone by OC-use and pregnancies, and 3) that the "background incidence rate" (BIR) of CTA among women aged 15-44 is equal to that of men, it is possible from the present data to calculate the theoretical magnitude of the relative risk of developing CTA using OC or being pregnant.

The average percentage of OC-use in the age group 15-44 is 24 (fig. 6). The mean percentage of pregnant women among women aged 15-44 is 4 (fig. 6). Thus, 28% have an increased risk of CTA. The average ratio between the observed incidence rates among women, and the incidence rates among men is 1.63. The relative risk of developing CTA (RR) being pregnant or using OC can now be calculated:

\[
\frac{0.28 \times \text{BIR} \times \text{RR} + 0.72 \times \text{BIR}}{1 \times \text{BIR}} = 1.63, \quad \text{=> RR} = 3.25.
\]

If, alternatively, it was assumed that the BIR of CTA among women aged 15-44 lies 30% below that of men, as is the case in older age groups, the average
incidence rate ratio was 2.52, and the RR using OC or being pregnant was consequently 6.4. For almost 20 years, there has been a controversy as to whether the statistic correlation between cerebral thromboembolism and the use of OC was based on a causative relationship or on other factors, e.g. life style or smoking habits. The present results, demonstrating an absolute difference in the incidence rates of CTA between women and men, the magnitude of which follows the percentage of OC-use according to age, support the suspicion of an aetiological connexion between the use of OC and the development of CTA, so much more as a relative risk of about 3-7, found in other studies corresponds to the present data.

The longer duration of stay among the female patients with CTA aged 15–24 indicates that young women with CTA, whether cerebral infarction or TIA, experience more serious attacks compared to those of men of same age. The reverse seems to be the case among patients aged 25–44 years, corresponding to the higher mortality among male patients compared to female patients. The mean duration of stay in hospital corresponds to Swedish studies of the same age groups.

The high percentage of neurological admissions amongst young CTA-patients is contrary to older patients, the majority of whom are admitted to medical departments.

The occurrence of hypertension in about 15% of the CTA patients corresponds to findings elsewhere, but is less frequent than among older CTA-patients.

References

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Incidence of Stroke in a Finnish Prospective Population Study

ANTTI REUNANEN, M.D., KARI AHO, M.D., ARPO AROMAA, M.D., PAUL KNEKT, M.Sc.

SUMMARY The incidence of stroke was investigated in a large Finnish prospective population study. The study population consisted of 11,984 men and 11,682 women aged 15 years and over drawn from four geographical regions of the country. In a mean follow-up time of six years, 174 men and 169 women suffered a fatal or non-fatal stroke. The incidence of cerebral infarction was statistically significantly higher than the annual incidence in women, 3.3/1000. In twelve percent of the cases, cerebral infarction was ascertained as the cause of the stroke; in 49 percent of the cases, the type of stroke could not be specified with certainty. The incidence of stroke was significantly higher in non-attendants than in attendants at the initial survey. The incidence of cerebral infarction appeared to be higher in men from eastern Finland than in men from southwestern Finland.

THE INCIDENCE OF CEREBROVASCULAR DISEASES has recently been studied in many countries by means of stroke registers. The completeness of ascertainment of cases makes them invaluable in stroke epidemiology. However, incidence studies of stroke in connection with prospective population studies provide a more valid basis for the study of stroke precursors. Large population studies are also a good basis for the description of variation of the incidence of stroke by various demographic and social factors. Little is known about regional variation of stroke incidence in Finland although morbidity and mortality of coronary heart disease are known to differ substantially between various parts of the country.

The Social Insurance Institution's (SII) Mobile Clinic Health Examination Survey is a large prospective population study in which special emphasis is being paid to risk factors and incidence of various atherosclerotic cardiovascular diseases in different parts of Finland. This report describes the incidence rates of stroke in this study.

Population and Methods

The study population comprised 12,602 men and 12,145 women aged 15 years and over invited to the baseline examination of the SII Mobile Clinic Health Examination Survey carried out in 12 cohorts from the southwestern, western, central and eastern parts of Finland (fig. 1). Details of the study population has been presented earlier. In brief, nine of the cohorts consisted all or a random sample of the population from a defined geographical area. Four of these areas were urban or semiurban and five rural. Three of the study population, consisted of all employees of a factory (two paper mills, one steel factory). The first nine cohorts were studied in 1966-68 and the last three in 1972. The participation rate in the initial survey was 83 percent.

After a mean follow-up time of six years all persons invited to the initial survey were invited to the re-
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O Lidegaard, M Soe and M V Andersen

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