Mortality in patients with epilepsy: 40 years of follow up in a Dutch cohort study

D P Shackleton, R G J Westendorp, D G A Kasteleijn-Nolst Trenité, J P Vandenbroucke

Abstract
To investigate the extent of and the causes of excess mortality in patients with epilepsy, mortality was studied in a cohort of patients with newly diagnosed epilepsy over an extended follow up period. All patients (both inpatients and outpatients) of the Instituut voor Epilepsiebestrijding in Heemstede, the Netherlands between 1953 and 1967 were included in the study. Complete follow up was obtained for 1355 patients, 746 men and 609 women. The mean follow up was 28 years (range 6 months–41 years). In total, 38 665 person years were surveyed, in which 404 patients died. All cause mortality was threefold increased (risk ratio (RR) 3.2; 95%CI 2.9–3.5), and was only slightly higher for men than for women. Mortality was highest under 20 years of age (RR 7.6; 95%CI 6.5–8.7), and during the first 2 years of follow up (RR 16; 95%CI 12–20).

Mortality directly related to epilepsy accounted for 18 of the 53 deaths in the first 2 years after diagnosis, which is equivalent to an incidence rate of 6.8 per 1000 person-years (95% CI 4.1–10). After 2 years 110 of the 351 deaths could be attributed to epilepsy itself, or were epilepsy related, with an incidence rate of 3.1 per 1000 person-years (95% CI 2.5–3.6). The data presented suggest that the increased mortality risk in patients with epilepsy is attributable in part to epilepsy itself, and is predominantly present at younger age and early after diagnosis. However, the absolute risk is moderate.

Keywords: epilepsy; epidemiology; mortality; standard mortality ratio

Contrary to Gower’s dictum,1 it is now generally accepted that mortality of patients with epilepsy is higher than that of the general population.2 In 1910 Munson reported that “...the disease carries with it very grave dangers, the span of life is shortened, and there is a special liability to certain diseases and to trauma.”3 This excess mortality ranges from twofold to 10-fold, as shown by various studies carried out this century.5–15 None the less, the extent of and causes of this increase remain unclear. Type of epilepsy, patient selection, duration of follow up, and chronology of study implementation are all determinants that possibly contribute to the differences between the estimates.

Data from contemporary studies, comprising newly diagnosed patients with epilepsy, show excess mortality in the first decade of life and the first few years after diagnosis. Excess mortality is predominantly present in patients with symptomatic epilepsy, whereas excess mortality is increased only slightly in patients with idiopathic or cryptogenic epilepsy.10 13 14 However, cohorts from institutions and specialist centres have consistently shown a significant excess mortality from the epilepsy itself.2 12 None the less, these findings have led authors to conclude that excess mortality can largely be explained by the predisposing causes of the seizures, rather than the seizures themselves.13 This conclusion, however, demands a sound classification method for epilepsy seizures and syndromes, and the present classification criteria proposed by the International League Against Epilepsy16 are not without problems.17

In this paper we investigated the hypothesis that excess mortality is in part due to epilepsy itself. Rather than determining mortality dependent on the types of epilepsy and epilepsy aetiology, we investigated causes of death directly, comparing mortality which could be ascribed to underlying causes, and mortality due to epilepsy itself or related to epilepsy. We were given the special opportunity of forming a large cohort of newly diagnosed epileptic patients with an extensive follow up of up to 40 years.

Methods

PATIENT SERIES
To obtain the data for those patients who had visited the Instituut voor Epilepsiebestrijding for the first time between 1953 and 1967, all 22 000 patient records (all inpatient and outpatient records were preserved in the archives of the Institute) were reviewed. These records were screened to identify patients with newly diagnosed epilepsy. Identification was based on the diagnosis made by a neurologist at the institute, within 1 year of the first consultation. The diagnosis was primarily based on a detailed patient history, and routine EEG

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10 13 Both status epilepticus and sudden acute and remote forms occur in the first 2 years of follow up. To assess the mortality in patients with genuine epilepsy by excluding the mortality that possibly could be attributed to underlying diseases, an analysis was performed excluding data of the first 2 years of follow up. This resulted in an SMR for all patients of 2.8 (95% CI 2.5–3.1). The SMRs by age at entry are summarised in table 2; the SMR is markedly high in the younger age groups. A second, lower peak is evident in the 60–69 age group.

**Table 1** All cause mortality in patients with epilepsy according to years of follow up

<table>
<thead>
<tr>
<th>Follow up (y)</th>
<th>Person-years</th>
<th>Obs</th>
<th>SMR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1</td>
<td>2646</td>
<td>53</td>
<td>16</td>
<td>11–20</td>
</tr>
<tr>
<td>2–4</td>
<td>3850</td>
<td>37</td>
<td>7.0</td>
<td>4.7–9.2</td>
</tr>
<tr>
<td>5–9</td>
<td>6116</td>
<td>78</td>
<td>6.9</td>
<td>5.4–8.4</td>
</tr>
<tr>
<td>10–14</td>
<td>5795</td>
<td>53</td>
<td>3.9</td>
<td>2.8–5.0</td>
</tr>
<tr>
<td>15–19</td>
<td>5588</td>
<td>40</td>
<td>2.4</td>
<td>1.6–3.1</td>
</tr>
<tr>
<td>20–24</td>
<td>5358</td>
<td>43</td>
<td>2.2</td>
<td>1.6–2.9</td>
</tr>
<tr>
<td>24–29</td>
<td>4834</td>
<td>46</td>
<td>2.0</td>
<td>1.4–2.6</td>
</tr>
<tr>
<td>30–34</td>
<td>3106</td>
<td>40</td>
<td>2.0</td>
<td>1.4–2.6</td>
</tr>
<tr>
<td>35–41</td>
<td>1372</td>
<td>14</td>
<td>0.9</td>
<td>0.4–1.4</td>
</tr>
<tr>
<td>40–41</td>
<td>38655</td>
<td>404</td>
<td>3.2</td>
<td>2.9–3.5</td>
</tr>
</tbody>
</table>

Obs=Observed number of deaths; SMR=observed number of deaths divided by expected number of deaths.
Table 2  All cause mortality in patients with epilepsy by age group at entry

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Obs</th>
<th>Males SMR (95% CI)</th>
<th>Obs</th>
<th>Females SMR (95% CI)</th>
<th>Obs</th>
<th>Both SMR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–9</td>
<td>66</td>
<td>12 (9–15)</td>
<td>33</td>
<td>13 (9–18)</td>
<td>99</td>
<td>13 (10–15)</td>
</tr>
<tr>
<td>10–14</td>
<td>51</td>
<td>4.9 (3.6–6.3)</td>
<td>27</td>
<td>5.4 (3.5–7.6)</td>
<td>78</td>
<td>5.0 (4.0–6.2)</td>
</tr>
<tr>
<td>20–24</td>
<td>51</td>
<td>4.5 (3.3–5.8)</td>
<td>20</td>
<td>2.9 (1.8–4.4)</td>
<td>71</td>
<td>3.8 (2.9–4.9)</td>
</tr>
<tr>
<td>30–39</td>
<td>43</td>
<td>2.5 (1.8–3.3)</td>
<td>22</td>
<td>2.2 (1.4–3.3)</td>
<td>65</td>
<td>2.4 (1.8–3.0)</td>
</tr>
<tr>
<td>40–49</td>
<td>29</td>
<td>1.5 (1.0–2.1)</td>
<td>16</td>
<td>1.3 (0.7–2.1)</td>
<td>45</td>
<td>1.4 (1.0–1.9)</td>
</tr>
<tr>
<td>50–59</td>
<td>19</td>
<td>2.8 (1.7–4.0)</td>
<td>9</td>
<td>0.8 (0.4–1.4)</td>
<td>18</td>
<td>1.6 (1.0–2.2)</td>
</tr>
<tr>
<td>60–69</td>
<td>6</td>
<td>1.8 (0.6–3.6)</td>
<td>10</td>
<td>2.4 (1.1–4.1)</td>
<td>16</td>
<td>2.1 (1.2–3.3)</td>
</tr>
<tr>
<td>70+</td>
<td>1</td>
<td>1.1 —</td>
<td>1</td>
<td>0.8 —</td>
<td>2</td>
<td>0.9 (0.1–2.6)</td>
</tr>
<tr>
<td>All</td>
<td>266</td>
<td>3.6 (3.1–4.0)</td>
<td>138</td>
<td>2.6 (2.2–3.0)</td>
<td>404</td>
<td>3.2 (2.9–3.5)</td>
</tr>
</tbody>
</table>

Obs=Observed number of deaths; SMR=observed number of deaths divided by expected number of deaths.

Table 3  All cause mortality in patients with epilepsy by 5 year age bands

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Obs</th>
<th>Males SMR (95% CI)</th>
<th>Obs</th>
<th>Females SMR (95% CI)</th>
<th>Obs</th>
<th>Both SMR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–4</td>
<td>11</td>
<td>39 (19–67)</td>
<td>9</td>
<td>64 (29–114)</td>
<td>20</td>
<td>48 (29–71)</td>
</tr>
<tr>
<td>5–9</td>
<td>18</td>
<td>41 (25–65)</td>
<td>5</td>
<td>26 (8.0–55)</td>
<td>23</td>
<td>38 (24–55)</td>
</tr>
<tr>
<td>10–14</td>
<td>11</td>
<td>20 (10–34)</td>
<td>9</td>
<td>35 (16–64)</td>
<td>20</td>
<td>25 (15–37)</td>
</tr>
<tr>
<td>15–19</td>
<td>16</td>
<td>10 (5–20)</td>
<td>7</td>
<td>12 (4.8–23)</td>
<td>33</td>
<td>15 (10–21)</td>
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<tr>
<td>20–24</td>
<td>15</td>
<td>6.5 (3.6–10)</td>
<td>7</td>
<td>8.8 (3.4–17)</td>
<td>22</td>
<td>7.1 (4.4–11)</td>
</tr>
<tr>
<td>25–29</td>
<td>19</td>
<td>8.6 (5.1–13)</td>
<td>10</td>
<td>11 (5.0–18)</td>
<td>29</td>
<td>9.2 (6.1–13)</td>
</tr>
<tr>
<td>30–34</td>
<td>17</td>
<td>6.9 (3.9–11)</td>
<td>12</td>
<td>9.6 (4.9–16)</td>
<td>29</td>
<td>7.8 (5.2–11)</td>
</tr>
<tr>
<td>35–39</td>
<td>19</td>
<td>5.8 (3.5–8.8)</td>
<td>12</td>
<td>6.2 (3.1–10)</td>
<td>31</td>
<td>6.0 (4.0–8.3)</td>
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<tr>
<td>40–44</td>
<td>17</td>
<td>3.8 (2.5–2.8)</td>
<td>2</td>
<td>2.6 (1.0–5.0)</td>
<td>24</td>
<td>3.4 (2.1–4.9)</td>
</tr>
<tr>
<td>45–49</td>
<td>15</td>
<td>2.5 (1.4–3.9)</td>
<td>5</td>
<td>1.4 (0.4–2.9)</td>
<td>20</td>
<td>2.1 (1.3–3.1)</td>
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<tr>
<td>50–54</td>
<td>21</td>
<td>2.9 (1.7–4.2)</td>
<td>5</td>
<td>1.3 (0.4–2.7)</td>
<td>26</td>
<td>2.3 (1.5–3.3)</td>
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<tr>
<td>55–59</td>
<td>21</td>
<td>2.1 (1.2–3.2)</td>
<td>15</td>
<td>3.5 (1.9–5.5)</td>
<td>33</td>
<td>2.5 (1.7–3.5)</td>
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<tr>
<td>60–64</td>
<td>22</td>
<td>2.4 (1.5–3.5)</td>
<td>7</td>
<td>1.4 (0.8–2.6)</td>
<td>20</td>
<td>2.0 (1.3–2.8)</td>
</tr>
<tr>
<td>65–69</td>
<td>15</td>
<td>1.7 (0.9–2.7)</td>
<td>8</td>
<td>1.3 (0.6–2.4)</td>
<td>23</td>
<td>1.6 (1.0–2.3)</td>
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<tr>
<td>70–74</td>
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<td>0.8 (0.3–1.6)</td>
<td>6</td>
<td>0.9 (0.3–1.9)</td>
<td>13</td>
<td>0.9 (0.5–1.4)</td>
</tr>
<tr>
<td>75+</td>
<td>15</td>
<td>1.9 (1.0–2.9)</td>
<td>15</td>
<td>1.0 (0.5–1.5)</td>
<td>29</td>
<td>1.2 (0.8–1.7)</td>
</tr>
<tr>
<td>All</td>
<td>266</td>
<td>3.6 (3.1–4.0)</td>
<td>138</td>
<td>2.6 (2.2–3.0)</td>
<td>404</td>
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</table>

Obs=Observed number of deaths; SMR=observed number of deaths divided by expected number of deaths.
Mortality in Dutch patients with epilepsy followed up for 40 years

Although most studies have a follow up period of less than 30 years, they show a similar trend.

The underlying causes of epilepsy have always been reported as the predominant cause of death in the disease. Many studies have reported that around 20% of all deaths were attributable to the epilepsy. 

Using causes of death as an end point of a study has its limitations as some death certificates could be misclassified, and sudden death in epilepsy cannot be established. Another approach would be the use of hospital records and those of general practitioners, in combination with witness accounts, to obtain more specific causes of death. By design, such an approach is impossible to use in this study.

Deaths in our patients with epilepsy occurred from their 50s to their 90s. Using both death certificates and clinical information, which are available for a large proportion of our patients, is not likely to improve the validity of the study. This clinical information is undoubtedly unevenly distributed over patients and time, and would seriously distort the outcomes of the study.

The mortality risk from epilepsy in the first 2 years was as high as the mortality from underlying causes, and was consistent in the remainder of the follow up period. Despite the care that was taken to exclude patients with remote symptomatic unprovoked seizures, this high mortality may reflect a subgroup similar to the congenital neurodeficit group found in other epidemiological studies. If we also included causes of death indirectly related to epilepsy, such as accidental deaths and suicides, the proportion of epilepsy related death increases, and is larger than the proportion of deaths related to the underlying causes, malignant CNS neoplasms, cerebrovascular diseases, and CNS diseases other than epilepsy. This has been reported in many of the older studies.

Mortality from malignant neoplasms excluding tumours of the CNS increased the excess occurring in the older age groups and in the follow up period of 2–41 years. This indicates that undiagnosed cancer was unlikely to have been a cause of epilepsy in the patients included in the cohort, as mortality from this cause occurs long after diagnosis.

The mortality risk for all accidents was greatly increased, predominantly later in the follow up and in the older age groups. This might reflect the supervision of children and youngsters with epilepsy, as opposed to the more independent adult. The mortality risk for suicide showed a similar trend; however, the numbers involved are rather small. The mortality ratio for traffic (motorised and bicycle) accidents was also increased, again, predominantly in the older age groups, and in the later stages of follow up. In this older age group, the mortality in men was higher than in women. This is possibly distorted by the fact that more men hold a driver's license than women do.

The predisposing or underlying causes of epilepsy have always been reported as the predominant cause of death in the disease. Many studies have reported that around 20% of all deaths were attributable to the epilepsy.

CAUSES OF DEATH

The underlying causes of epilepsy have been implicated as the cause for this increased mortality, rather than the epilepsy itself. Data from recent mortality studies on epilepsy suggest that underlying causes of disease are responsible for the increased mortality ratios in the first decade of life and the first few years after diagnosis. Nevertheless, data from our study indicate that epilepsy itself contributes to the increased mortality. Up to 20% of the mortality in patients with newly diagnosed epilepsy during the first 2 years after diagnosis is directly related to epilepsy. However, the absolute risk of dying from epilepsy in the first 2 years after the diagnosis has been made is relatively low. From the mortality rates it can be recalculated that roughly one out of 100 newly diagnosed patients with epilepsy will die from epilepsy itself.

Using causes of death as an end point of a study has its limitations as some death certificates could be misclassified, and sudden death in epilepsy cannot be established. Another approach would be the use of hospital records and those of general practitioners, in combination with witness accounts, to obtain more specific causes of death. By design, such an approach is impossible to use in this study.

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The predisposing or underlying causes of epilepsy have always been reported as the predominant cause of death in the disease. Many studies have reported that around 20% of all deaths were attributable to the epilepsy.
However, many of these studies included prevalent epileptic patients, mainly of older ages, and could therefore not give an adequate answer as to the mortality risk attributable to epilepsy. Our study of incident epileptic patients, however, gives results that are similar to these older studies, suggesting that epilepsy indeed carries a mortality risk in itself, albeit low. This excess mortality is more evident in the younger age groups and shortly after diagnosis.

This study was made possible by a grant from the Dutch Commission Landelijke Epilepsie Onderzoek (CLEO); Subsidy: NEF/CLC A-101. We thank the medical and administrative staff of the Instituut voor Epilepsiebestrijding for giving us access to the archives and outpatient clinics of the Institute and professor Dr H Meinardi for critical reading. We also thank the Department of Health Statistics of the Netherlands Central Bureau of Statistics in Voorburg, The Netherlands for use of their mortality statistics and database coupling. Special thanks are due to Mrs L Velmans for compiling the database and to Dr A de Boer for his initial ideas.

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