Traumatic Brain Injury and Time to Onset of Alzheimer's Disease: A Population-based Study

Peter N. Nemetz,1,2 Cynthia Leibson,1 James M. Naessens,1 Mary Beard,1 Emre Kokmen,3 John F. Annegers,1,4 and Leonard T. Kurland1

Controversy continues as to whether traumatic brain injury is a risk factor for Alzheimer's disease. The authors examined a related hypothesis that among persons with traumatic brain injury who develop Alzheimer's disease, time to onset of the disease is reduced. They used data on all documented episodes of traumatic brain injury that occurred from 1935 to 1984 among Olmsted County, Minnesota, residents. Community-based medical records were used to follow traumatic brain injury cases who were aged 40 years or older at last contact prior to June 1, 1988, for Alzheimer's disease until last contact, death, or June 1, 1988. The test of the hypothesis was restricted to those cases who developed Alzheimer's disease. The expected time to onset of Alzheimer's disease was derived from a life table constructed by using age-of-onset distributions within sex groups for a previously identified cohort of Rochester, Minnesota, Alzheimer's disease incidence cases without a history of head trauma. The authors found that of the 1,283 traumatic brain injury cases followed, 31 developed Alzheimer's disease, a number similar to that expected (standardized incidence ratio = 1.2, 95% confidence interval 0.8–1.7). However, the observed time from traumatic brain injury to Alzheimer's disease was less than the expected time to onset of Alzheimer's disease (median = 10 vs. 18 years, p = 0.015). The results suggest that traumatic brain injury reduces the time to onset of Alzheimer's disease among persons at risk of developing the disease. Am J Epidemiol 1999; 149:32–40.

Alzheimer's disease; brain injuries; cohort studies; head injuries; incidence; medical records; risk factors; traumatology

The number of Alzheimer's disease cases in the United States has been estimated at 1.1–3.4 million during the early 1980s, 2–4 million during the early 1990s, and more than 15.4 million by the year 2050 (1–3). Although research has focused on a broad range of potential risk factors or pathogenetic mechanisms including, among others, family history, specific genetic factors, autoimmune disorders, slow viruses, aluminum toxicity, and prior thyroid disease, the causes of this devastating and frequently occurring disease remain largely unknown (4–9).

One of the most controversial suggested risk factors for Alzheimer's disease is prior traumatic brain injury. Evidence in the medical literature of the potential role of this etiologic factor has been mixed (4, 5, 8–27), as illustrated in figure 1. Although most of these studies reported odds ratios of more than 1, very few of these odds ratios were statistically significant. A meta-analysis of seven case-control studies supported an association between head injury and Alzheimer's disease for males only (26). However, in a population-based cohort study of 821 persons with traumatic brain injury whose medical records were followed for subsequent evidence of Alzheimer's disease, the overall incidence of Alzheimer's disease was not greater than that expected based on rates for the general population (25).

While the controversial issue of prior traumatic brain injury and risk for Alzheimer's disease may not be resolved satisfactorily for some time, a related hypothesis has been advanced concerning traumatic brain injury and the timing of onset to Alzheimer's disease (28–30). This hypothesis suggests that for those who for some as yet unspecified reason are at risk of developing Alzheimer's disease, a head injury could hasten the onset of dementia. In this paper, we use the population-based resources of the Rochester Epidemiology Project to examine the hypothesis that among persons with traumatic brain injury who develop Alzheimer's disease, the
FIGURE 1. Odds ratios and 95% confidence intervals reported in previous investigations of the association between Alzheimer's disease and head injury. *, "mild intellectual impairment"; †, hospital controls; ‡, meta-analysis—only relative risk reported; §, population controls; †, medium to severe trauma; ‡, mild trauma. Four studies (11, 13, 16, 23) did not provide confidence intervals for their estimates but did provide p values for test of significance.

observed time to onset is less than the expected time to onset of Alzheimer's disease.

MATERIALS AND METHODS

The Rochester Epidemiology Project is particularly suitable for use in addressing the issue of traumatic brain injury and the timing of subsequent Alzheimer's disease because of its virtually complete longitudinal coverage of the relatively stable, geographically defined population of Rochester, Minnesota, and surrounding Olmsted County (total 1990 population, 106,470) (31). Established in 1966 with funding from the National Institutes of Health (grant AR30582), the Rochester Epidemiology Project affords access to complete medical records from essentially all sources of medical care available to and used by the local population. These data are drawn from the Mayo Clinic unit record system, in existence since 1907, and are supplemented by the records of subsequent non-Mayo providers. These records, together with indexes of virtually all clinical and histologic diagnoses and all surgical procedures for the local population, make population-based epidemiologic studies possible. Population-based studies alleviate problems of selective survival and referral and of recall bias that hamper most other studies of Alzheimer's disease etiology.

A previous population-based study (32) used the resources of the Rochester Epidemiology Project to identify all documented episodes of head trauma with presumed brain involvement among residents of Olmsted County, Minnesota. Brain involvement was defined as injury with loss of consciousness, post-traumatic amnesia, or neurologic signs of brain injury. Cases of head trauma with skull fracture were included, even if alterations in consciousness could not be documented. A subsequent study by Williams et al. (25) was limited to 821 traumatic brain injury cases who were aged 40 years or older at last medical contact. The medical records of these persons were reviewed for neurologic sequelae, including Alzheimer's disease. Standardized incidence ratios
were used to investigate whether the number of Alzheimer's disease cases was higher than expected; the expected number was based on published incidence rates of Alzheimer's disease for the community of Rochester, Minnesota (33). The investigation by Williams et al. was based on episodes of traumatic brain injury during 1935–1974 (25).

The Olmsted County traumatic brain injury cohort has subsequently been updated through 1984. The present study used the updated cohort to address the hypothesis that among persons with traumatic brain injury who developed Alzheimer's disease, the observed time to onset was less than the expected time to onset of the disease. Our study also replicated the Williams et al. (25) analysis of the standardized incidence ratios on the updated cohort. All Olmsted County residents with traumatic brain injury in 1935–1984 who were aged 40 years or older at last medical contact prior to June 1, 1988, were followed in their medical records for evidence of Alzheimer's disease until last contact, death, or June 1, 1988. Alzheimer's disease was defined by using the same criteria used to determine the incidence of this disorder in Rochester, Minnesota, between 1960 and 1984 (table 1) (34). For both the Rochester Alzheimer's disease incidence cohort and the Alzheimer's disease cases in the traumatic brain injury cohort, the diagnosis of Alzheimer's disease was confirmed by the study neurologist (E. K.), who used the best available information to review the records in a standardized manner across calendar time to establish a year of Alzheimer's disease onset (35). This date was usually the first mention in the medical record of cognitive or behavioral difficulties that subsequently were determined to be due to Alzheimer's disease.

To replicate the standardized incidence ratio analysis by Williams et al. (25) in their investigation of Alzheimer's disease incidence in the 1935–1974 traumatic brain injury cohort, we adopted the following procedure: we divided the observed number of Alzheimer's disease cases with traumatic brain injury in the updated cohort by the expected number of cases, based on age- and sex-specific incidence rates of Alzheimer's disease observed for the Rochester, Minnesota, population in 1960–1984 (34). We expanded on the earlier investigation by calculating standardized incidence ratios separately for men and women, for early (age <75 years) and late (age ≥75 years) Alzheimer's disease onset, and for short (<10 years) and long (≥10 years) periods of follow-up after traumatic brain injury. Ninety-five percent confidence intervals were calculated, assuming a Poisson distribution (36).

Our principal hypothesis was that among persons with traumatic brain injury who developed Alzheimer's disease, time to onset of the disease was shorter than expected. Observed time to onset was calculated as the date of Alzheimer's disease onset minus the date of the first documented traumatic brain injury. Persons who developed Alzheimer's disease prior to traumatic brain injury were excluded from the analysis. Expected time to onset was estimated by using a life table approach. This approach, frequently used in demography, is initiated by identifying all persons in a population who experience a particular event (e.g., death). Using distributions of the ages at which that event occurred, a life table is constructed that enables calculation of the length of survival free of that event for every age (e.g., remaining life expectancy at age 40 years, at age 45 years, at age 50 years). In our study, the event of interest was Alzheimer's disease rather than death. We took advantage of data from the previously identified cohort consisting of all Rochester Alzheimer's disease incidence cases in 1965–1984, after excluding 151 cases previously identified as having a history of head trauma. By using age at Alzheimer's disease onset for each of the 689 Rochester Alzheimer's disease incidence cases without

### TABLE 1. Diagnostic criteria for dementia and Alzheimer's disease*

<table>
<thead>
<tr>
<th>Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Documented evidence:</td>
</tr>
<tr>
<td>Previously normal intellectual and social function</td>
</tr>
<tr>
<td>Progressive decline of intellectual/cognitive/social function that cannot be reversed with medical or psychiatric treatment</td>
</tr>
<tr>
<td>Memory impairment</td>
</tr>
<tr>
<td>Dementia sufficient to impair age/education/occupation-appropriate lifestyle adjustment</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alzheimer's disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical diagnosis (probable Alzheimer's disease):</td>
</tr>
<tr>
<td>Presence of dementia (as defined above)</td>
</tr>
<tr>
<td>Insidious onset of symptoms of dementia</td>
</tr>
<tr>
<td>Gradual progression and irreversible course</td>
</tr>
<tr>
<td>Other potential causes of dementia either not present or occurring definitely after the onset of symptoms of dementia</td>
</tr>
</tbody>
</table>

| Neuropathologic diagnosis (definite Alzheimer's disease): |
| Presence of clinical Alzheimer's disease (as defined above) |
| Presence of abundant neuritic (senile) plaques and/or neurofibrillary tangles in neocortical regions excluding the hippocampus and subiculum |

* Adapted from Kokmen et al. (34).
a history of head trauma, we constructed a life table to calculate the length of survival free of Alzheimer’s disease for each age. For all traumatic brain injury cases who developed Alzheimer’s disease, we compared their observed length of survival from traumatic brain injury to Alzheimer’s disease with their expected length of survival free of Alzheimer’s disease (as obtained from the life table estimate, specific for the age at which that traumatic brain injury case experienced traumatic brain injury).

The analysis excluded persons for whom both traumatic brain injury and Alzheimer’s disease onset occurred in the same year, because it was not possible to determine whether Alzheimer’s disease onset preceded traumatic brain injury. By excluding these persons, we drastically reduced the likelihood of including any Alzheimer’s disease events that occurred in the first 6 months following traumatic brain injury. Therefore, the first 6 months of follow-up were ignored in the analysis of time to onset. Observed time to Alzheimer’s disease onset was compared graphically with expected time to Alzheimer’s disease onset. The significance of observed versus expected time to onset of Alzheimer’s disease was tested by using a one-sample log-rank test (37). Separate analyses were also performed for men and women, for traumatic brain injury before age 65 years and at age 65 years or older, and for duration of follow-up after traumatic brain injury of less than 10 years and of 10 years or longer.

RESULTS

The 1935–1984 Olmsted County, Minnesota, traumatic brain injury cohort consisted of 5,023 persons. The 1,283 who were aged 40 years or older as of last medical contact prior to June 1, 1988, contributed a total of 17,279 person-years of follow-up, during which 31 persons were identified as subsequently developing Alzheimer’s disease. Because traumatic brain injury was more frequent among men than women (65 percent of the 1,283 traumatic brain injury cases were men), the proportion of men among the 31 traumatic brain injury cases who developed Alzheimer’s disease (55 percent) was higher than the proportion of men in the 1960–1984 Rochester Alzheimer’s disease incidence cohort (28 percent). For the 31 traumatic brain injury cases, the calendar year of Alzheimer’s disease onset ranged from 1954 to 1986; the median age at onset was 76 years for men and 80 years for women. Although the median age of the Rochester Alzheimer’s disease incidence cohort in the first quinquennium (1960–1964) was also 76 years for men and 80 years for women, these ages had increased to 80 and 83 years, respectively, by 1980–1984, due in part to a shift in the age distribution of the underlying population (34).

For the 31 persons with traumatic brain injury who developed Alzheimer’s disease, observed time from injury to Alzheimer’s disease onset was compared with expected time to onset of Alzheimer’s disease. As shown in figure 2, the observed time to onset was shorter than expected (median 10 vs. 18 years; one-sample log-rank test, \( p = 0.015 \)). The observed time to onset was significantly shorter than the expected time to onset of Alzheimer’s disease regardless of whether onset occurred less than 10 years after traumatic brain injury \( (n = 15, p = 0.004) \) or 10 years or more after traumatic brain injury \( (n = 16, p < 0.001) \). When stratified by age at time of brain injury, the observed time from injury to Alzheimer’s disease onset was significantly shorter than the expected time to onset for the 16 cases whose injuries occurred before age 65 years \( (p < 0.001) \) but was not different from the expected time to onset of Alzheimer’s disease for the 15 cases whose injuries occurred after age 65 years \( (p = 0.867) \).

Of those with traumatic brain injury who developed Alzheimer’s disease, the median age at traumatic brain injury was 66 years for the 14 women compared with 58 years for the 17 men (rank sum test, \( p = 0.1 \)). Among these men, a significant reduction in time to Alzheimer’s disease onset was apparent only for the 11 cases whose traumatic brain injuries occurred before age 65 years \( (p = 0.01) \). The observed time to onset of Alzheimer’s disease was not different from the expected time to onset \( (p = 0.20) \) for the six men whose injuries occurred after age 65 years, although the relatively small numbers contributed to low statistical power. For the 14 women, the observed time to onset was significantly shorter than the expected time to onset, irrespective of age at time of injury \( (p < 0.001) \) for age <65 years, \( p = 0.03 \) for age ≥65 years.

We were concerned that the significant reduction in time to onset was due to an outlier, that is, a single female whose age at Alzheimer’s disease onset was less than 45 years. This person was excluded, and the analyses were rerun; the differences between the observed and the expected time to onset remained significant \( (p < 0.001) \) for women, \( p < 0.001 \) for age at head trauma of <65 years.

Age- and sex-specific Alzheimer’s disease incidence rates for the 1,283 persons with traumatic brain injury were compared with 1960–1984 Alzheimer’s disease incidence rates for the community of Rochester, Minnesota (table 2). The number of cases of Alzheimer’s disease among persons with traumatic brain injury \( (n = 31) \) was not higher than expected (standardized incidence ratio (SIR) for both sexes combined \( = 1.2, 95 \) percent confidence interval (CI)
0.8–1.7), a result consistent with the findings of Williams et al. (25) in their analysis of Alzheimer's disease incidence in the 1935–1974 traumatic brain injury cohort (SIR = 1.0, 95 percent CI 0.6–1.5). The findings were similar when stratified by sex (SIR for men = 1.4, 95 percent CI 0.8–2.3; SIR for women = 1.0, 95 percent CI 0.5–1.6). However, the analysis stratified by age at onset of Alzheimer's disease revealed that the 11 traumatic brain injury cases who experienced the onset of Alzheimer's disease before age 75 years were more than twice the number expected (SIR = 2.2, 95 percent CI 1.1–4.0). The standardized incidence ratio for Alzheimer's disease onset at age 75 years or older was 0.9 (95 percent CI 0.6–1.5). The number of observed cases did not differ from that expected when stratified by years of observation (SIR for <10 years of follow-up = 1.2, 95 percent CI 0.7–1.9; SIR for ≥10 years of follow-up = 0.9, 95 percent CI 0.5–1.5).

**DISCUSSION**

This study took advantage of the fact that all documented cases of traumatic brain injury that occurred in

**TABLE 2. Incidence rates* of Alzheimer's disease among Olmsted County, Minnesota, residents with traumatic brain injury in 1935–1984 who were aged ≥40 years at last medical contact and among Rochester, Minnesota, residents in 1960–1984**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Incidence in the traumatic brain injury cohort</th>
<th>Incidence in Rochester</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men No. Rate</td>
<td>Women No. Rate</td>
</tr>
<tr>
<td>40–44</td>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>45–54</td>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>55–64</td>
<td>1</td>
<td>38.62</td>
</tr>
<tr>
<td>65–74</td>
<td>6</td>
<td>352.96</td>
</tr>
<tr>
<td>75–84</td>
<td>13</td>
<td>999.41</td>
</tr>
<tr>
<td>≥85</td>
<td>132</td>
<td>1,119.48</td>
</tr>
</tbody>
</table>

* Per 100,000 person-years.
A few studies have compared age at onset for Alzheimer’s disease cases with and without mention of head trauma; these studies have yielded conflicting results (26, 28–29). A study by Rasmussen et al. (38) of 68 Alzheimer’s disease cases found no effect of head injury on age at onset. However, a study by Sullivan et al. (29) of 17 Alzheimer’s disease cases reported a younger mean age at onset for cases with a history of head trauma than for cases without head trauma. Gedye et al. (28) studied 148 referral patients with confirmed probable Alzheimer’s disease and also found that the mean age of Alzheimer’s disease onset was significantly younger for Alzheimer’s disease cases with a history of head injury than for cases with no history of head injury. However, persons with a history of head injury after age 65 years were excluded from the exposed group in this comparison. Since no comparable adjustment was made or could have been made in the unexposed group, the average age of onset among those with a history of head injury may have been biased downward, thus contributing to the observed statistical difference. In all of these studies, a history of head trauma was obtained by proxy report.

In addition to the potential for recall bias with proxy or self-report, most previous investigations of the association between traumatic brain injury and time to Alzheimer’s disease onset or age at Alzheimer’s disease onset were also subject to problems of referral bias and selective survival. By using the Rochester Epidemiology Project resources, we were able to address a number of these issues. Advantages included the following: 1) identification of all documented episodes of traumatic brain injury in a geographically defined population, 2) comparison with population-based age- and sex-specific Alzheimer’s disease incidence rates for unaffected persons, and 3) a historic cohort study design with sufficient follow-up from first documented traumatic brain injury to last medical contact, death, or end of study period to accumulate a relatively large number of Alzheimer’s disease cases. Thus, the problems of insufficient power and the potential for selection bias, recall bias, and/or referral bias were minimized in the present study.

Our study is not without limitations. Confirmation of a diagnosis of dementia, classification as Alzheimer’s disease, and assignment of year of Alzheimer’s disease onset were based on retrospective record review. Not all persons underwent neuropsychological or imaging tests, and some were never evaluated by either a neurologist or a psychiatrist. The progress of all medical conditions and symptoms of dementia over time was assessed with the longitudinal information available from the complete community-based medical records. Cases were often followed
until death. Information was accumulated over many years from multiple sources, including autopsy, to reconstruct a clear clinical picture of the dementing illness. Postmortem findings took precedence over clinical evaluation results. In a previous Rochester study (33) of 177 patients with a clinical diagnosis of Alzheimer's disease, only 42 underwent microscopic examination of brain tissue; however, the clinical diagnosis was confirmed by histopathologic examination in 40 of the 42.

This study would miss those Alzheimer's disease cases who never came to the attention of medical personnel or for whom Alzheimer’s disease or dementia-like diagnoses were not noted in the patient record. However, the likelihood of this occurring is low in light of the comprehensive medical coverage of the target population. For example, it has been demonstrated that between 1989 and 1991, more than 96 percent of elderly female Olmsted County residents were seen at least once by medical care providers, whose diagnoses are systematically included in the centralized records linkage file (39). Even if several cases were missed by using this system, the analysis of time to onset would be biased only if ascertainment was selective against persons who had traumatic brain injury and experienced late onset of Alzheimer's disease.

Our results are potentially vulnerable to observation and/or detection bias, as it could be hypothesized that clinicians might observe traumatic brain injury patients more closely in subsequent years, thereby leading to an earlier estimated date of onset of Alzheimer’s disease. If this is the case, a shorter time period between Alzheimer’s disease onset and the clinical diagnosis of Alzheimer’s disease for the traumatic brain injury cases would be expected. To test for this problem, we compared the time from Alzheimer’s disease onset to Alzheimer’s disease diagnosis for the 631 persons with no prior head injury for whom dates of both Alzheimer’s disease onset and diagnosis were available in the 1965-1984 Rochester Alzheimer’s disease incidence cohort and the 31 Alzheimer’s disease cases in the traumatic brain injury cohort. The median time lag between estimated onset and diagnosis for the Rochester Alzheimer’s disease incidence cases without prior head injury was 1.47 years compared with 2.06 years for the 31 Alzheimer’s disease cases with traumatic brain injury (rank sum test, \( p = 0.08 \)), essentially minimizing if not eliminating the possibility of observation bias. An alternative possible explanation is that preclinical features of Alzheimer’s disease could have predisposed some patients to falls or other causes of head injury. To determine whether this type of explanation is possible, a neurologist must estimate precisely the date of onset of the disease.

The finding that time to onset of Alzheimer’s disease among persons with traumatic brain injury who developed Alzheimer’s disease was shorter than the expected time to onset could also have occurred if there were preferential loss to follow-up at older ages in the traumatic brain injury cohort relative to the Rochester population. We investigated that possibility by calculating the proportion of all person-years of follow-up for those aged 75 years or older. The proportions were 12 percent for men and 21 percent for women in the traumatic brain injury cohort and 12 percent for men and 23 percent for women in the Rochester population. Therefore, it does not appear as if preferential loss to follow-up at older ages in the traumatic brain injury cohort was a problem.

A number of recognized Alzheimer’s disease risk factors were not considered in the analysis, for example, apolipoprotein E genotype. The extent to which the prevalence of these other risk factors differed between the traumatic brain injury cohort and the Rochester population is not known.

The findings presented here may help clarify some apparent contradictions arising from earlier research. Our study found that the overall risk of Alzheimer’s disease for persons with traumatic brain injury was not greater than expected but that the risk of early-onset Alzheimer’s disease was more than twice that expected. Among traumatic brain injury cases who developed Alzheimer’s disease, the observed time to onset was shorter than the expected time to onset, and the effect of traumatic brain injury on time to onset was greatest when the injury occurred before age 65 years. These findings are consistent with the interpretation that traumatic brain injury interacts with other risk factors to hasten the onset of Alzheimer’s disease in persons susceptible to the disease but that the effect of traumatic brain injury on time to onset may be diluted by the exponential increase in the risk of Alzheimer’s disease that occurs with advancing age.

If there is indeed a reduced time to onset of Alzheimer’s disease among Alzheimer’s disease-susceptible persons following traumatic brain injury, then the question remains as to the causative factors involved. One central issue in the study of Alzheimer’s disease is the role of \( \beta \)-amyloid, which forms the main component of senile plaques (40-42). Deposition of \( \beta \)-amyloid occurs in most persons during the process of aging (3), and Selkoe states that “the distinction between Alzheimer’s disease and ageing of the brain is essentially quantitative rather than qualitative” (43, p. 433). Several papers (10, 17, 44-50) have reported an association between traumatic brain injury and subsequent deposition of \( \beta \)-amyloid. It has also been reported that synthesis of apolipoprotein E, a plasma protein
involved in the transport of cholesterol, a vital component in cell structure and repair (51–55), increases markedly after injury and that the apolipoprotein E *e4 allele, a recognized independent risk factor for Alzheimer’s disease, binds closely to the β-amyloid type 4 peptide (54, 56–62). It has been posited that β-amyloid is transported into brain cells by the apolipoprotein E *e4 allele (55). Several recent studies lend credence to a possible interaction between the presence of an apolipoprotein E *e4 allele and traumatic brain injury (63–66), although a more recent study did not find evidence of an interaction (67). Although we remain agnostic with respect to the question of β-amyloid causality and Alzheimer’s disease, the linkages between traumatic brain injury, subsequent β-amyloid deposition, and posited direct or indirect neurotoxicity are sufficiently compelling to require further study.

Our research suggests that Alzheimer’s cases with prior traumatic brain injury exhibit a reduced time to onset of Alzheimer’s disease relative to those cases without prior head injury. These conclusions are strengthened because we used the population-based resources of the Rochester Epidemiology Project, thereby significantly reducing or eliminating problems of selective survival and of referral and recall bias.

This study, as well as the discrepant findings in the medical literature, supports the argument that the etiology of Alzheimer’s disease is multifactorial. Biologic mechanisms consistent with the results of this study have been proposed in the literature, therefore suggesting that further research in this area is warranted.

REFERENCES

34. Kokmen E, Beard CM, O’Brien PC, et al. Is the incidence of


