Factors associated with psychotic symptoms in Alzheimer’s disease

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Abstract

Objectives—Many clinical and biological factors have been reported to be associated with the presence of psychosis in patients with Alzheimer’s disease, although the associations were variable. The aim of this study was to clarify factors associated with the presence of psychosis in patients with Alzheimer’s disease.

Methods—Psychiatric functioning was studied in 228 patients with Alzheimer’s disease based on the results of the behavioural pathology in Alzheimer’s disease rating scale or the neuropsychiatric inventory. The effects of sex, education level, age, duration of illness, cognitive function, and apolipoprotein E genotype were investigated for dichotomous psychotic status with a multiple logistic regression analysis.

Results—Of the 228 patients with Alzheimer’s disease, 118 (51.8%) showed evidence of delusions or hallucinations. Of these, 94 had delusions only, three had hallucinations only, and 21 had both. Older age, female sex, longer duration of illness, and more severe cognitive impairment were the factors independently associated with the presence of psychosis. The presence of psychosis was not significantly related to either educational level or apolipoprotein E genotype.

Conclusions—Age, sex, and severity of illness were independent factors associated with the presence of psychosis in patients with Alzheimer’s disease. The reason why some patients with Alzheimer’s disease develop psychosis remains unclear. There may be distinctive subtypes of Alzheimer’s disease or the presence of individual factors which affect the development of psychosis.

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Keywords: Alzheimer’s disease; psychotic symptoms; apolipoprotein E
The factors associated with psychotic symptoms in Alzheimer's disease were studied. The Alzheimer's disease assessment scale—cognitive (11.9) for full-IQ. The mean number of words IQ, 75.1 (13.7) for performance-IQ, and 74.3 scale—revised. The mean values of the remaining complete the Wechsler adult intelligence was 18.5 (5.1). Twenty-three patients could not the mini mental state examination (MMSE) was 72.7 (8.2) months respectively. The mean value of the mini mental examination was 72.7 (8.2) years and the mean educational attainment was 8.9 (2.2) years. The functional severity was very mild in 30 patients, mild in 119 patients, moderate in 63 patients, and severe in 16 patients as determined by the clinical dementia rating scale. The mean age at symptom onset and duration of symptoms determined with informant based interviews were 67.1 (7.5) years and 37.3 (28.8) months respectively. The mean value of the mini mental state examination (MMSE) was 18.5 (5.1). Twenty-three patients could not complete the Wechsler adult intelligence scale—revised. The mean values of the remaining 205 patients were 77.0 (10.4) for verbal IQ, 75.1 (13.7) for performance-IQ, and 74.3 (11.9) for full-IQ. The mean number of words recalled in the 10 word list recall substest of the Alzheimer's disease assessment scale—cognitive part was 3.3 (1.6).

According to DSM-IV, delusion was defined as a firmly sustained, false belief based on incorrect inference about external reality not attributable to the patient's cultural or subcultural experience, and hallucination was defined as sensory perception that has the compelling sense of reality of a true perception but that occurs without external stimulation of the relevant sensory organ. With the behavioural pathology in Alzheimer's disease rating scale or the neuropsychiatric inventory, a single rater assessed each patient's psychiatric condition during an interview with the care giver. In this study, delusions and hallucinations were rated on a present or absent basis. The patient was rated as psychotic when he or she had either delusions or hallucinations.

The age at onset and the duration of the disease were ascertained through an interview with the primary care giver. Age at onset was defined as the age of the first appearance of symptoms of sufficient severity to interfere with social or occupational functioning and the duration was defined as the time in months between the onset and the admission.

The detailed method for ApoE genotyping is described elsewhere. In brief, genomic DNA was extracted from whole blood samples by the phenol/chloroform method and was amplified by the polymerase chain reaction (PCR) as described by Wenham et al. The PCR products were digested with 10 units HhaI for five hours at 37°C. The DNA fragments were electrophoresed for five hours at 60 mA through a 15% non-denaturing polyacrylamide gel. The gel was stained with ethidium bromide and photographed under ultraviolet light. The genotypes were determined by the size of DNA fragments. The patients with one or more ApoE ε4 alleles were rated as ε4 positive and the others were rated as ε4 negative.

We used the χ² test for binary variables, and the two tailed t test for continuous variables for unadjusted comparisons of patients with and without psychosis. For correlational analyses, we used Pearson correlation coefficients. To examine the specific characteristics that predict psychosis, a multiple logistic analysis was used, with psychosis as a dependent variable and the patients' characteristics (sex, education level, duration of illness, MMSE, ApoE genotype, and either age at onset or age at examination) as independent variables. Because age at examination and age at onset were strongly correlated, which causes multicolinearity, each variable was examined in separate models. All statistical analyses were carried out with SAS Release 6.10 software (SAS Institute Inc).

**Results**

The ApoE genotyping was ε2/3 in eight patients, ε2/4 in three patients, ε3/3 in 78 patients, ε3/4 in 115 patients, and ε4/4 in 24 patients. Thus, the ApoE ε4 gene was positive in 142 patients and negative in 86 patients. As expected, the age at examination was highly correlated with the age at onset (r = 0.96, p < 0.0001). The educational attainment was inversely correlated with both age at examination (r = −0.31, p < 0.0001) and age at onset (r = −0.32, p < 0.0001). Both mean age at examination and age at onset were significantly greater in women than in men (73.3 (SD 7.8) vs 70.7 (9.2), p = 0.046; 70.4 (8.30) vs 67.5 (9.37), p = 0.034). The mean educational attainment was significantly less in women than in men (8.6 (SD 2.1) vs 9.6 (2.3), p = 0.0048). Although age, education level, and the MMSE score did not differ significantly between the ApoE ε4 positive patients and the ε4 negative patients, the mean duration of illness was significantly greater in the ε4 positive patients than in the ε4 negative patients (39.0 (SD 30.9) vs 23.6 (23.6) months, p = 0.038).

Of the 228 patients, 118 (51.8%) were rated as psychotic. Of these 118 patients, 21 had both delusions and hallucinations, 94 had delusions only, and three had hallucinations only. Thus 115 (50.4%) of the patients had delusions. Of these, 91 patients had persecutory delusions (88 patients had delusions that "people are stealing things", 10 patients had delusions of "being conspired against or harassed", and three patients had a delusion of abandonment), 58 patients had misidentification delusions (42 patients had delusions that "someone was in the house", 11 patients had...
Table 1  Comparison of characteristics between patients with and without psychosis

<table>
<thead>
<tr>
<th></th>
<th>Psychotic (n=118)</th>
<th>Non-psychotic (n=110)</th>
<th>Statistical value</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at examination (y)</td>
<td>74.5 (6.9)</td>
<td>70.7 (9.0)</td>
<td>t(226) = 3.50</td>
<td>0.0006</td>
</tr>
<tr>
<td>Sex  (female : male)</td>
<td>97 : 21</td>
<td>76 : 34</td>
<td>χ² (1) = 5.35</td>
<td>0.021</td>
</tr>
<tr>
<td>Education (y)</td>
<td>8.5 (2.0)</td>
<td>9.2 (2.4)</td>
<td>t(226) = 2.20</td>
<td>0.029</td>
</tr>
<tr>
<td>Duration of illness (months)</td>
<td>39.7 (30.7)</td>
<td>31.8 (25.7)</td>
<td>t(226) = 2.09</td>
<td>0.037</td>
</tr>
<tr>
<td>Age at onset (y)</td>
<td>71.1 (7.7)</td>
<td>68.2 (9.3)</td>
<td>t(226) = 2.62</td>
<td>0.009</td>
</tr>
<tr>
<td>ApoE e4 (positive : negative)</td>
<td>76 : 42</td>
<td>66 : 44</td>
<td>χ² (1) = 0.47</td>
<td>0.49</td>
</tr>
<tr>
<td>MMSE</td>
<td>18.5 (4.2)</td>
<td>19.5 ± 4.0</td>
<td>t(226) = 2.71</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Mean (SD): ApoE = apolipoprotein E; MMSE = mini mental state examination.

Table 2  Results of multiple logistic regression analysis with age at onset included

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>Wald χ²</th>
<th>p Value</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset</td>
<td>1.73</td>
<td>1.19 - 2.52</td>
<td>8.33</td>
<td>0.0039</td>
<td>10 year increase</td>
</tr>
<tr>
<td>Sex</td>
<td>2.01</td>
<td>1.03 - 3.96</td>
<td>4.12</td>
<td>0.042</td>
<td>female increase relative to male</td>
</tr>
<tr>
<td>Education</td>
<td>0.95</td>
<td>0.83 - 1.09</td>
<td>0.58</td>
<td>0.45</td>
<td>1 year increase</td>
</tr>
<tr>
<td>Duration of illness</td>
<td>1.18</td>
<td>1.03 - 1.36</td>
<td>5.71</td>
<td>0.017</td>
<td>12 month increase</td>
</tr>
<tr>
<td>ApoE e4 positive</td>
<td>1.06</td>
<td>0.59 - 1.88</td>
<td>0.03</td>
<td>0.86</td>
<td>ε4+ increase relative to ε4-</td>
</tr>
<tr>
<td>MMSE</td>
<td>0.94</td>
<td>0.88 - 0.99</td>
<td>4.77</td>
<td>0.029</td>
<td>1 point increase</td>
</tr>
</tbody>
</table>

CI = confidence interval; ApoE = apolipoprotein E; MMSE = Mini Mental State Examination.

Discussion

The present study provides further evidence that psychotic symptoms are a common manifestation of Alzheimer's disease. The prevalences of delusions (51.8%) and hallucinations (10.5%) were well within the ranges reported in the literature. The finding that persecutory delusions (especially the belief that people are stealing or hiding objects) were the most common psychotic manifestations was also compatible with the findings of previous studies. Because patients who had Parkinson's were excluded from this study, the chance of erroneous inclusion of those with dementia with Lewy bodies, which are parkinsonian symptoms, were common, was small. The major findings of our study were that sex, age, and severity of cognitive impairment were each significantly and independently associated with psychosis, and that the level of education and the frequency of the ApoE ε4 allele were not significant predictors of the presence of psychosis.

Previous studies have disagreed on the contribution of cognitive impairment in psychotic symptoms. Some studies failed to show a difference in cognitive impairment between the patients with and without psychosis, whereas others showed that psychotic symptoms were associated with poor cognitive function or preserved cognitive function. These controversies are likely due to the inclusion of patients with different severities of dementia. Psychotic symptoms were considered to be uncommon in both the very mild and very severe stages of Alzheimer's disease. A longitudinal study disclosed that delusions in patients with Alzheimer's disease were relatively more frequent during the moderate stage. The small proportion of advanced patients included in our study contributed to the positive correlation between psychosis and cognitive impairments. In any case, as the difference in MMSE between groups was small, the effect of cognitive impairment in psychosis would be modest. Nevertheless, it is conceivable that a dysfunction of specific cognitive domains is associated with psychosis.

In this study, duration of illness was shown to be an independent predictor of psychosis in the logistic regression model in which age at onset was the variable, although it was not significant in the model when age at examination was the variable. It is plausible that the effect of duration of illness was masked by the effect of the age at examination, because the age at examination is a function of age at onset and duration of illness. Our results supported the conclusion of the study of Migliorelli et al, who reported that patients with Alzheimer's disease with delusions had a significantly longer duration of illness than those without delusions, whereas most previous studies failed to show a significant association between duration of illness and psychosis.
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association between development of psychotic symptoms and a rapid mental deterioration has been found in several longitudinal studies. This does not disagree with our finding that psychotic patients with Alzheimer’s disease had a significantly longer duration of illness, because long duration does not necessarily imply slow progression of the disease. Our findings that a decreased MMSE and a longer duration of illness were separate factors associated with the presence of psychosis would suggest that deterioration of both cognitive and non-cognitive functions promotes psychosis independently.

Older age was shown to be a significant risk factor for psychosis in both logistic regression models in this study. The issue of the effect of age on psychosis in Alzheimer’s disease is highly controversial. Several investigators showed that older patients were more likely to have psychotic symptoms, whereas Gilly et al. reported that early onset was significantly associated with psychosis when cognitive functions were severely impaired. Devanand et al. maintained that age at examination was associated with paranoid delusions and inversely correlated with hallucinations. Moreover, many studies failed to show a significant relation between age and psychosis. However, evidence that supports the relation between older age and development of psychosis is available in studies focusing on localisation of pathological changes in relation to age and psychosis. Senile plaques both in the temporal neocortex and in the hippocampus were more frequent in younger patients with Alzheimer’s disease than in older patients, whereas psychosis in Alzheimer’s disease is reported inversely related to the preservation in those areas.

We also found a significant association between female sex and development of psychosis. Although female sex has been implicated as a risk factor for Alzheimer’s disease, few studies have considered whether sex specifically predisposes patients to the development of psychotic symptoms in Alzheimer’s disease. Devanand et al. reported that women’s scores of delusion on the Columbia University scale for psychopathology were significantly higher than those of men. Reisberg et al. found that women tended to exhibit behavioural symptoms more often. On the other hand, Burns et al. reported a higher prevalence in men of delusions of theft. Other studies failed to show an association of psychosis with sex. However, in other domains of neurological disease, there is evidence of female sex as a risk factor of psychosis. Comparing psychotic and non-psychotic epileptic patients, Taylor showed that female sex was a risk factor for development of psychosis. Our finding and those of others remain unexplained, and relevant factors involving genetic traits, as well as cultural and psychosocial involvements, should be investigated.

The multivariate analysis showed that the level of education was not an independent protection factor for psychosis. The association between psychosis and fewer years of education shown in the univariate analysis is likely to be an epiphenomenon which can be accounted for by the inverse correlation between the educational attainment and age and by the negative association between the level of education and female sex. Although one study reported that education was inversely related to psychosis, the results of our multivariate analysis agreed with most studies, which denied this effect.

It has been postulated that patients with Alzheimer’s disease with and without the ε4 allele have distinguishing phenotypic characteristics. Ramachandran et al., in a preliminary report, showed that patients with Alzheimer’s disease and the ApoE ε4/ε4 genotype had more than a threefold increase in psychosis when compared with those with the ApoE ε3/ε3 genotype. As female patients with late onset Alzheimer’s disease carried the ε4 allele more often than did male patients, their finding might be attributable to the effects of sex and age. Lehtovirta et al., Lopez-Alberola et al., and Lopez et al. showed no association between the ApoE ε4 gene and development of psychosis in our study, in which other variables were concurrently examined, this association was clearly denied.

These findings clearly suggest that a subgroup of patients with Alzheimer’s disease who are female, of late onset, of severe cognitive impairment, and of long duration of illness, have a high risk for development of psychosis. One possible explanation for our findings is that a particular subtype of Alzheimer’s disease which preferentially involves old women has distinctive clinical and neuropathological features. An alternative explanation is that characteristics including genetic, psychosocial, and environmental factors may affect development of psychosis in individuals. Further studies are needed to consider these hypotheses.

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