Low serum cholesteryl ester-docosahexaenoic acid levels in Alzheimer’s disease: a case–control study

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Low n-3 polyunsaturated fatty acid (PUFA) status may be associated with neuro-degenerative disorders, in particular Alzheimer’s disease, which has been associated with poor dietary fish or n-3 PUFA intake, and low docosahexaenoic acid (DHA) status. The present case–control study used an established biomarker of n-3 PUFA intake (serum cholesteryl ester-fatty acid composition) to determine n-3 PUFA status in patients with Alzheimer’s disease, who were free-living in the community. All cases fulfilled the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer’s Disease and Related Disorders Association criteria for Alzheimer’s disease. Detailed neuropsychological testing and neuroimaging established the diagnosis in all cases. The subjects (119 females and twenty-nine males) aged 76·5 (SD 6·6) years had a clinical dementia rating (CDR) of 1 (SD 0·62) and a mini mental state examination (MMSE) score of 19·5 (SD 4·8). The control subjects (thirty-six females and nine males) aged 70 (SD 6·0) years were not cognitively impaired (defined as MMSE score ≥ 24): they had a mean MMSE score of 28·9 (SD 1·1). Serum cholesteryl ester-eicosapentaenoic acid and DHA levels were significantly lower (P < 0·05 and P < 0·001 respectively) in all MMSE score quartiles of patients with Alzheimer’s disease compared with control values. Serum cholesteryl ester-DHA levels were progressively reduced with severity of clinical dementia. DHA levels did not differ in patients with Alzheimer’s disease across age quartiles: all were consistently lower than in control subjects. Step-wise multiple regression analysis showed that cholesteryl ester-DHA and total saturated fatty acid levels were the important determinants of MMSE score and CDR. It remains to be determined whether low DHA status in Alzheimer’s disease is a casual factor in the pathogenesis and progression of Alzheimer’s disease.

Alzheimer’s disease: Docosahexaenoic acid: n-3 Polyunsaturated fatty acids

In developed countries, the incidence of Alzheimer’s disease (AD) is 2·8 % in the age range 70–74 years and rises to 11·1 % in the age range 80–84 years (Jorm et al. 1987). It has been estimated, based on demographic projections, that between 1990 and 2010, the number of cases of AD in developed countries will rise by nearly 40 %. In recent years, there has been an increased interest in the possible involvement of nutrition in AD. Nutrients and metabolites such as folic acid, vitamin B12, vitamin B6 and homocysteine have been the focus of attention (Nourhashémi et al. 2000). Docosahexaenoic acid (DHA) is present in large amounts in neuron membrane phospholipids, where it is required for optimal development and function of the nervous system. Recent studies suggest that n-3 polyunsaturated fatty acid (PUFA) consumption is beneficial in the treatment of depression (Hibbeln, 1998) and bipolar affective disorder (Stoll et al. 1999). Preliminary reports suggest that low n-3 PUFA status may also be associated with neuro-degenerative disorders, whereby poor dietary fish or n-3 PUFA intake, and low DHA status have been associated with the incidence of AD. The Rotterdam study, a prospective study of dietary fat composition and AD in elderly subjects, observed that high saturated fat intake and low levels of fish consumption in elderly subjects with a normal mini mental state examination (MMSE) score were risk factors for the subsequent development of Alzheimer’s disease (Kal-mijn et al. 1997b). In a study published in abstract form only, 1188 elderly subjects were studied prospectively for 10 years. It was observed that subjects who had a

Abbreviations: AD, Alzheimer’s disease; CDR, clinical dementia rating; DHA, docosahexaenoic acid; MMSE, mini mental state examination; PUFA, polyunsaturated fatty acid.

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lower initial serum phosphatidylcholine-DHA (22:6n-3) levels had a higher (67%) risk of subsequently developing AD, although the difference was not significant (Kyle et al. 1999). However, these results should be interpreted with caution, as a more than fivefold lower overall incidence of AD was observed in this study group compared with average US incidence rates (6–10%) (Hendrie, 1998).

A limited number of intervention studies have explored the impact of increased fish or n-3 PUFA on the severity of existing AD. One such study supplemented sixty volunteers for 4 weeks with an n-6 PUFA + n-3 PUFA oil (ratio 4:1) with α-linolenic acid (18:3n-3) as the n-3 PUFA source. Improvement in severity of disease (mood, cooperation, appetite, sleep, ability to navigate and short-term memory) was observed (Yehuda et al. 1996). In a study of moderately severe dementia from thombotic cerebrovascular disease, Terano et al. (1999) reported, in abstract form, an improvement in the severity of the disease when subjects were supplemented for 1 year with 0.72 g DHA/d.

Thus, while there are some studies linking fish consumption and/or n-3 PUFA status with AD, the literature is limited by either the crude estimates of fish intake (Kalmijn et al. 1997b) or the limited clinical details presented in abstract form (Peers, 1990; Yehuda et al. 1996; Terano et al. 1999). Therefore, the objective of the present case–control study was to use an established biomarker of n-3 PUFA intake (plasma cholesteryl ester-fatty acid composition) to determine n-3 PUFA status in patients with AD with precise clinical definition and who were free-living in the community.

Methods

Study population

Ethical approval for the study was granted by the Ethics Committee of the Federated Dublin Voluntary Hospitals in Ireland. Patients were recruited from the Mercer Institute for Research on Ageing, St James Hospital, as part of an ongoing multi-factorial study on patients with AD. All patients attending the clinic were community-based; none was institutionalised. All cases fulfilled the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer’s Disease and Related Disorders Association for probable and possible AD (McKhann et al. 1984) and the International Classification of Diseases, 10th revision (ICD-10) criteria for mixed and vascular dementia (World Health Organization, 1992). Detailed neuropsychological testing and neuroimaging was used to establish the diagnosis in all cases (Swanwick et al. 1996). The subjects were 119 females and twenty-nine males with a mean age of 76.5 (SD 6.6) (range 49–92) years and mean clinical dementia rating (CDR) (Hughes et al. 1982) of 1 (SD 0.62). The attendance at the clinic showed a marked preponderance towards women. The mean MMSE score (Folstein et al. 1975) of the subject group was 19.5 (SD 4.8) (Range 2–27). The diagnoses included probable AD (n 108), possible AD (n 16), mixed AD (n 13 subjects) and vascular dementia (n 11). Non-fasting serum samples were taken from AD subjects, centrifuged, divided into portions and stored at −20°C until analysis for cholesteryl ester-fatty acid composition.

The elderly control subjects were recruited from local active retirement groups; they were not cognitively impaired (MMSE score <24). Each control subject underwent an assessment that included taking a medical history, brief neurological assessment, and height, weight and blood-pressure measurements. Global cognition of the healthy control was also assessed by the MMSE (Folstein et al. 1975; Reisberg et al. 1985), a screening test of dementia in older people. The control subjects were thirty-six females and nine males with a mean age of 70 (SD 6) (Range 53–81 years) and a mean MMSE score of 28.9 (SD 1.1) (range 25–30). Habitual dietary supplement use was also examined in the control group. Five control subjects were habitual consumers of cod-liver oil supplements and two subjects reported occasional supplement use. Non-fasting serum samples were taken from control subjects, centrifuged, divided into portions and stored at −20°C until analysis. Exclusion criteria were: (1) history of stroke; (2) hypertension; (3) MMSE score <24; (4) current warfarin therapy.

Cholesteryl ester-fatty acid analysis

Lipid extractions were performed using the procedure of Folch et al. (1957). Cholesteryl esters were isolated using TLC on silica 60 LKD 19 Lane TLC plates (Whatman, Clifton, NJ, USA) using a solvent system of light petroleum (40–60°C)–diethyl ether–formic acid (80:20:2, by vol.) (Gibney & Bolton-Smith, 1988). Cholesteryl esters were hydrolysed using 0.5 M NaOH in methanol and incubated at 80°C for 30 min (Glatz et al. 1989). Component fatty acids were methylated using BF3 in methanol. GLC was used to identify fatty acid methyl esters of cholesteryl esters using a Shimadzu CG-14A Series GC (Mason Technologies, Dublin, Ireland). Specific fatty acid levels were expressed as g/100 g total fatty acids and fatty acid compositions of patients and controls were analysed randomly. The average storage period of the patient serum samples was 2.54 years. The long-term stability of frozen serum samples for cholesteryl ester-fatty acid compositional analysis was demonstrated by Simon et al. (1995), who showed that serum cholesteryl ester-fatty acid composition of samples frozen for 3 years was not significantly different from that of freshly analysed samples.

Data handling and statistical analysis

All statistical analyses were completed with the Apple Macintosh compatible statistical package Data Desk 4.1 (Data Description Inc., New York, USA). Repeated-measures ANOVA was used to describe differences between groups. Step-wise multiple regression analysis was performed to determine the relative importance of age, sex and fatty-acid composition on AD status. Fatty acids were log transformed to give a normal Gaussian distribution to permit parametric statistical analysis to be performed.

Results

The age, sex and cholesteryl ester-fatty acid composition of the AD patients, compared with control values, are presented in Table 1. The patients were divided according
Table 1. Cholesteryl ester fatty-acid composition (g/100 g total fatty acids) in subjects with Alzheimer’s disease classified as quartiles of mini mental examination score compared with control subjects†

<table>
<thead>
<tr>
<th>Quartiles of MMSE score for Alzheimer’s disease patients</th>
<th>Control subjects (n 45)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td>MMSE score§</td>
<td>12·9**</td>
</tr>
<tr>
<td>Clinical dementia rating</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>76**</td>
</tr>
<tr>
<td>18:2n-6</td>
<td>35·4*</td>
</tr>
<tr>
<td>18:3n-3</td>
<td>2·1</td>
</tr>
<tr>
<td>20:4n-6</td>
<td>2·3</td>
</tr>
<tr>
<td>20:5n-3</td>
<td>1·04*</td>
</tr>
<tr>
<td>22:6n-3</td>
<td>0·58**</td>
</tr>
<tr>
<td>Total SFA</td>
<td>22·5</td>
</tr>
<tr>
<td>Total n-3 PUFA</td>
<td>5·4</td>
</tr>
<tr>
<td>Total n-6 PUFA</td>
<td>44·6*</td>
</tr>
<tr>
<td>n-3 PUFA:n-6 PUFA</td>
<td>0·14</td>
</tr>
</tbody>
</table>

MMSE, mini mental state examination; SFA, saturated fatty acid; PUFA, polyunsaturated fatty acid.

Mean values were significantly different from those of control subjects: *P<0·05, **P<0·001.
† For details of subjects and procedures, see p. 484.
‡ Female (n)/male (n): first quartile 33/9; second quartile 33/9; third quartile 34/8; fourth quartile 31/11; control subjects 36/9.
§ For details, see Folstein et al. (1983).
‖ For details, see Hughes et al. (1982).

Discussion

The present case–control study provides evidence that patients with AD have low n-3 PUFA status. The level of DHA in the serum cholesteryl ester fraction of AD patients was consistently half that in the control group. The cohort of patients with AD, who attended the memory clinic for assessment, are particularly interesting because they were diagnosed with precise clinical markers and were free-living in the community. The patients with AD were well nourished and generally physically healthy, apart from common medical complaints and medications associated with ageing. A recent paper has shown similar prevalence of medical conditions (e.g. hypertension, atrial fibrillation, cerebro- or cardiovascular disease) and general use of medications in both community–dwelling AD subjects and control subjects in this population (Cunningham et al. 2001). While other diseases could be associated with lower levels of n-3 PUFA, clinical notes recorded that both groups were essentially healthy, apart from the

to quartiles of MMSE score. Therefore, both the MMSE score and the CDR differed significantly across all MMSE score quartiles compared with control values (P<0·001). Subjects in all MMSE score quartiles were significantly older (P<0·001) than control subjects. There were no significant differences in the female (n)/male (n) ratio. Plasma cholesteryl ester levels of linoleic acid (18:2n-6) and total n-6 PUFA levels were significantly lower (P<0·05) in the lowest quartile of MMSE score among patients compared with control values. The remaining quartiles of MMSE score did not exhibit significantly lower levels of linoleic acid or n-6 PUFA compared with control subjects. Plasma cholesteryl ester-eicosapentaenoic acid (20:5n-3) and DHA (22:6n-3) levels were significantly lower (P<0·005 and P<0·001 respectively) in all MMSE score quartiles of patients with AD compared with control values. When total n-3 PUFA were considered (including α-linolenic acid (18:3n-3), the three highest MMSE score quartiles were significantly different from control values (P<0·001). It was also observed that patients in the two lowest MMSE score quartiles had significantly (P<0·05) higher (12·03 (SD 3·4) and 12·20 (SD 3·2) g/100 g total fatty acids respectively) levels of the saturated fatty acid palmitic acid (16:0) compared with control values (10·64 (SD 2·01) g/100 g total fatty acids). Table 2 shows the level of the two long-chain n-3 PUFA, eicosapentaenoic acid and DHA, in plasma cholesteryl esters in the patient group, classified according to CDR, clinical diagnosis of AD and quartile of age. It demonstrates that in almost all cases, the patients with AD had significantly lower levels (P<0·001) of both long-chain n-3 PUFA compared to control values. This was especially true for DHA. It is important to note that the levels of DHA did not differ significantly in patients with a clinical diagnosis of AD across age quartiles, but they were all consistently lower than control values. Step-wise multiple regression analysis was performed to determine the relative importance of age, sex and fatty acid composition (linoleic acid, arachidonic acid, eicosapentaenoic acid, DHA, saturated fatty acids, monounsaturated fatty acids, n-6 PUFA, n-3 PUFA, n-3:n-6 PUFA ratio) on AD status. For CDR, cholesteryl ester-DHA (β = 0·517, P = 0·0006), followed by cholesteryl ester-total saturated fatty acid levels (β = 1·224, P = 0·0044) and age (β = 0·021, P = 0·0052) were important determinants of MMSE score, according to the regression equation (r = 0·429, P = 0·0008). Similarly, MMSE score was also predicted cholesteryl ester-DHA (β = 0·484, P = 0·001) and cholesteryl ester-total saturated fatty acid levels (β = 0·48, P = 0·0034), but age was not a significant predictor (β = 0·101, P = 0·100), according to the regression equation (r = 0·352, P = 0·0001).
The presence of different stages of AD, as defined using strict diagnostic criteria. Nevertheless it is possible, albeit unlikely, that another undiagnosed underlying condition that could alter n-3 PUFA status may have accounted for the differences between groups.

DHA is the most abundant n-3 PUFA in vivo. It is present in the retina and a principal component of neuronal membrane phospholipids, where it is required for optimum development and function of the nervous system. The present study used plasma cholesteryl ester fatty acid composition as a biomarker of DHA status, which may be related to AD. Cholesteryl ester fatty acid composition is a well-established biomarker of fatty acid status in vivo and a marker of dietary fat intake (Nikkari, 1986; Simon et al. 1995). It is not subject to inherent methodological errors associated with available dietary assessment techniques to cognitive impairment and incomplete food composition databases. Our present results agree with the results of the Rotterdam study, a large prospective population-based study, which showed that high saturated fat and low n-3 PUFA intake were associated with an increased incidence of AD (Kalmijn et al. 1997a). They also agree with results reported in an abstract that reported a 10-year follow-up study of more than 1000 elderly US subjects that demonstrated that low levels of serum phosphatidylcholine-DHA was a significant risk factor for low MMSE score and the development of AD (Kyle et al. 1999). Furthermore, Prasad et al. (1998) demonstrated that DHA concentrations were significantly lower in the phosphatidylethanolamine and phosphatidylcholines of brain membrane phospholipids in AD patients compared with control subjects: In vitro studies show that DHA plays an important role in the survival of neuron cells, and it has been postulated that it may be modulator phosphatidylserine biosynthesis, which in turn can effect neuronal signalling (Kim & Edsall, 1999). Hence, the present study adds to the growing evidence that poor DHA status is either a risk factor or marker of AD. A possible limitation of our present study is that cholesterol ester fatty acid composition was demonstrated in frozen serum samples because long-chain fatty acids are susceptible to oxidative damage. However, the long-term stability of frozen serum samples of cholesteryl ester fatty acid compositional analysis was demonstrated by Simon et al. (1995), who showed little oxidative damage and no significant alteration in the serum cholesteryl ester fatty acid composition of samples frozen for 3 years.

A potential criticism of the present study is that the control subjects were younger than the patient group, since cognitive performance decreases with increasing age (Kalmijn et al. 1997b). However, even when the patients with AD were divided according to age quartiles, plasma cholesteryl ester-DHA levels were still consistently less than half that of the control subjects, irrespective of age. In addition, a subgroup of forty-one age- and sex-matched patients and control subjects were compared, and this analysis showed that the patients had significantly lower eicosapentaenoic acid and DHA concentrations than control subjects (P < 0.001) (Table 3). Furthermore, age was included as a variable in the step-wise multiple regression analysis and it was only a significant predictor of CDR, after cholesteryl ester-DHA and SFA levels. Another study has demonstrated that the decrease in brain phosphatidylethanolamine-DHA levels in AD patients was not due to ageing, and ageing was shown to have no influence on the fatty acid composition of the brain (Soderberg et al. 1991).

Table 2. Serum cholesteryl ester-eicosapentaenoic acid (20:5n-3) and docosahexaenoic acid (22:6n-3) levels (g/100g total fatty acids) in Alzheimer’s disease patients classified according to clinical dementia rating, clinical diagnosis and age quartiles† (Mean values and standard deviations)

<table>
<thead>
<tr>
<th>Age quartile of probable Alzheimer’s disease patients:</th>
<th>Age EPA (20:5n-3)</th>
<th>DHA (22:6n-3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27</td>
<td>68</td>
</tr>
<tr>
<td>2</td>
<td>27</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>27</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>27</td>
<td>84</td>
</tr>
</tbody>
</table>

EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

Mean values were significantly different from those of control subjects: *P < 0.05, ***P < 0.001.
† For details of subjects and procedures, see p. 484.
‡ For details, see Folstein et al. (1984) and the World Health Organization (1992).
It was beyond the scope of the present study to evaluate how low DHA and/or n-3 PUFA status is associated with an increased incidence of AD. Nevertheless, there are several plausible hypotheses to support the apparent inverse association. First, n-3 PUFA and/or fish intake may protect against dementia by reducing cardiovascular disease risk. Epidemiological, case–control, secondary prevention and intervention studies show a strong inverse association between n-3 PUFA and cardiovascular disease (Bang et al. 1971; Kromhout et al. 1988; Caughey et al. 1997), and therefore it may be that Δ5- and Δ6-desaturase activities and/or peroxisomal β-oxidation are adversely affected in AD and reduce DHA synthesis in vivo. Nakada et al. (1990) found elevated levels of α-linolenic acid and reduced levels of DHA in brain-membrane phospholipids taken from autopsied AD patients compared with age-matched controls. This alteration in ALA and DHA in AD disease indicated a possible abnormality in Δ6-desaturase activity or a peroxisomal defect and it was proposed that the resultant membrane abnormalities play a key role in the pathogenesis of AD. In our present study, AD patients had a higher α-linolenic acid:DHA ratio compared with control subjects, which would again imply an accumulation of α-linolenic relative to DHA due to a defect in retroconversion by peroxisomal β-oxidation and/or Δ5- or Δ6-desaturase activities. Indeed, the patients with the lowest MMSE scores who were most severely affected by the disease showed an accumulation of α-linolenic compared with control subjects, but the more mildly affected patients did not.

To conclude, our present study shows that free-living AD patients have lower DHA status compared with healthy control subjects. It remains to be determined whether and/or how low DHA status plays an aetiological role in the pathogenesis and/or progression of AD low DHA status.

Table 3. Characteristics and plasma cholesteryl ester composition (g/100 g total fatty acid) of age- and sex-matched patients with Alzheimer’s disease and healthy elderly controls† (Mean values and standard deviations)

<table>
<thead>
<tr>
<th>Patients (n 41)‡</th>
<th>Control Subjects (n 41)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CDR</strong>§</td>
<td><strong>MMSE score</strong></td>
</tr>
<tr>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>1.06***</td>
<td>0.66</td>
</tr>
</tbody>
</table>

CDR, clinical dementia rating; MMSE, mini mental state examination.

Mean values were significantly different from those of control subjects: ***P<0.001.

† For details of subjects and procedures, see p. 484.
‡ Female (n)/male (n): patients 32/9; control subjects 32/9.
§ For details, see Polstein et al. (1995).
|| For details, see Hughes et al. (1982).

The observed low DHA status in our present study may be either a risk factor or simply a marker of AD. Low DHA status associated with AD could be due to: reduced dietary intake of n-3 PUFA; reduced long-chain n-3 PUFA elongation and/or desaturation enzyme activity; reduced synthesis and/or increased utilisation of EPA and DHA as a result of the disease process. Dietary sources of DHA are oily fish and n-3 PUFA supplements, such as cod-liver oil. However, it cannot be concluded that the absence of fish in the diet predisposes to AD. Broe et al. (1990) found no association between the absence of fish in the diet and AD in a large group of elderly volunteers in a case–control study. Nevertheless, it has been shown that AD patients, whose diet was originally high in n-6 PUFA and almost devoid of n-3 PUFA, show improvement in severity and rate of decline of the condition when supplemented with oily fish two times per week (Peers, 1990; Yehuda et al. 1996; Terano et al. 1999).

Membrane structure and cellular functions are influenced by fatty-acid composition, which in turn is regulated by a synthesis–degradation system that involves Δ5- and Δ6-desaturase activities and peroxisomal β-oxidation (Voss et al. 1991). DHA may be synthesized from its precursor α-linolenic acid, through elongation and desaturation of α-linolenic acid into eicosapentaenoic acid, then elongation and peroxisomal β-oxidation into DHA (Périchon et al. 1998). This process is quite inefficient. It has been shown that 15.4 g α-linolenic acid/d is required to cause an equivalent increase in platelet eicosapentaenoic acid levels as 70 mg eicosapentaenoic acid/d (Li et al. 1999). There is little information in relation to the conversion of α-linolenic acid into DHA, but it can be assumed that this is even less efficient. It has been proposed that the metabolic capacity of fatty acid synthesis and/or degradation declines with age and age-related diseases, which could contribute to the reduction in DHA in AD disease (Périchon et al. 1998; Babin et al. 1999). Hence it may be that Δ5- and Δ6-desaturase activities and/or peroxisomal β-oxidation are adversely affected in AD and reduce DHA synthesis in vivo. Nakada et al. (1990) found elevated levels of α-linolenic acid and reduced levels of DHA in brain-membrane phospholipids taken from autopsied AD patients compared with age-matched controls. This alteration in ALA and DHA in AD disease indicated a possible abnormality in Δ6-desaturase activity or a peroxisomal defect and it was proposed that the resultant membrane abnormalities play a key role in the pathogenesis of AD. In our present study, AD patients had a higher α-linolenic acid:DHA ratio compared with control subjects, which would again imply an accumulation of α-linolenic relative to DHA due to a defect in retroconversion by peroxisomal β-oxidation and/or Δ5- or Δ6-desaturase activities. Indeed, the patients with the lowest MMSE scores who were most severely affected by the disease showed an accumulation of α-linolenic compared with control subjects, but the more mildly affected patients did not.

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may simply a marker of the disease process. Nevertheless, in light of the cardio-protective and anti-inflammatory capabilities of n-3 PUFA, it is important that the true nature of the effect of DHA on AD is investigated.

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