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Original article

Serum α-linolenic and other ω-3 fatty acids, and risk of disabling dementia: Community-based nested case–control study

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SUMMARY

Background & aims: It has been hypothesized that ω-3 polyunsaturated fatty acids have anti-atherosclerotic and neuronal protective functions and may benefit prevention of dementia, but the epidemiological evidence, especially for α-linolenic acid, is quite limited. The aim of this study was to examine whether serum ω-3 polyunsaturated fatty acids are associated with risk of dementia.
Methods: We performed an intracohort case–control study nested in a community-based cohort, the Circulatory Risk in the Community Study, involving 7586 Japanese individuals aged 40–74 years at the baseline period of 1984–1994. Omega-3 polyunsaturated fatty acid constituents (α-linolenic, eicosapentaenoic, and docosahexaenoic acids) in serum total lipid were measured in 315 cases of incident disabling dementia in the above-mentioned cohort between 1999 and 2004, and in 630 controls whose age, sex, area, and baseline year were matched with the cases.
Results: As we had postulated, serum α-linolenic acid was inversely associated with risk of disabling dementia: the multivariate odds ratios (95% confidence intervals) were 0.57 (0.39–0.85), 0.51 (0.34–0.76), and 0.61 (0.41–0.90) for persons with the second, third, and highest quartiles of serum α-linolenic acid, respectively, as compared with the lowest quartile (P for trend = 0.01). Associations of other ω-3 fatty acids with disabling dementia were not statistically significant.
Conclusions: Serum α-linolenic acid was inversely associated with risk of disabling dementia. Although the causality needs to be confirmed by randomized control trials, we identified serum α-linolenic acid as a biomarker that predicts future dementia.

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1. Introduction

Alpha-linolenic acid (ALA), a plant-derived ω-3 polyunsaturated fatty acid, is an essential fatty acid, with anti-atherosclerotic and neuronal protective functions. Several studies have reported that long-chain ω-3 polyunsaturated fatty acids of marine origin, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), may be useful in preventing dementia [1–3]. ALA, a ω-3 polyunsaturated fatty acid of plant origin, is also expected to have a similar effect, but such evidence is limited.

The association between fish and coronary heart disease was non-linear and had a threshold effect [4], whereas that between dietary ALA intake and coronary heart disease may be linear [5]. In

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this context, we hypothesized that serum proportions of ALA, rather than of other ω-3 fatty acids, are inversely associated with risk of incident disabling dementia among Japanese individuals, because most Japanese may consume higher amounts of fish than those recommended for prevention of coronary heart disease [6], but may not do so for ALA.

2. Materials and methods

The Circulatory Risk in Communities Study (CIRCS) is an ongoing dynamic community-based prospective study involving 5 communities in Japan. Details of the CIRCS protocol have been described elsewhere [7]. In the present study, we included 2 communities, Ikawa and Kyowa, where disabling dementia surveillance is being conducted and sera were stored.

We set the baseline risk set as 7586 people aged 40–74 years living in these 2 communities who participated in annual health checkups in Ikawa from 1989 to 1991 and 1995 and in Kyowa from 1984 to 1994 (except for 1988), and whose stored sera were available. Of these, a total of 315 patients were identified who were diagnosed in Kyowa between 1999 and 2004 and in Ikawa between 1999 and 2013 as having disabling dementia between 60 and 89 years of age and who participated in annual health checkups (baseline) at least 5 years before receiving the dementia diagnosis and provided sera for storage at baseline.

The diagnosis of disabling dementia was performed by attending physicians under the National Long-Term Care Insurance System (which is a compulsory insurance for all individuals aged 40 years or over in Japan); the criteria of disabling dementia were the same as those of our previous study [8], wherein the validation of the criteria and the details of the study protocol are also described. As supplemental analysis, we further classified the dementia cases into cases with and without history of stroke on the basis of a systematic stroke registration described elsewhere [7].

In total, 630 randomly selected controls, whose age (±3 years), sex, area, and baseline year were matched at a ratio of 2:1 with the cases, were also identified from the risk set by incident density methods. Venous blood was collected at baseline at the checkup sites, and sera were prepared from the blood samples as soon as possible thereafter. The serum samples were collected in 0.3-mL tubes and stored at −80 °C until measurement. The extraction of total lipids and measurements of serum fatty acid compositions using gas chromatography were described in detail elsewhere [9]. Of the studied sera, 92% were drawn in the nonfasting state (<8 h from the last meal).

Potential risk factors for disabling dementia were measured at the baseline examination at the same time as the blood collection. Well-trained study physicians measured the arterial systolic and fifth-phase diastolic blood pressures using standard mercury sphygmomanometers on the right arm of the participants, who were quietly seated after having rested for at least 5 min. If the first systolic blood pressure reading was ≥140 mmHg and/or the diastolic blood pressure was ≥90 mmHg, the physicians repeated the measurement. For these cases, the second reading was used in the analyses; otherwise, the first reading was used. Height without shoes and weight in light clothing were measured and body mass index was calculated as weight in kilograms divided by height in meters squared. Face-to-face interviews were conducted to determine drinking (non-current or current) and smoking (never, ex, or current) status, antihypertensive medication, cholesterol-lowering medication, and diabetes. Serum glucose and total cholesterol were measured at baseline without fasting requirement. Diabetes mellitus was defined as fasting serum glucose ≥ 126 mg/dL or nonfasting serum glucose ≥ 200 mg/dL, or being under medication for diabetes.

We conducted conditional logistic analyses using SAS 9.1.3. Service Pack 4 (SAS Institute, Cary, NC, USA) with adjustments for age, smoking status, systolic blood pressure, diabetes mellitus, and use of antihypertensive medication. For the missing values for these variables (<2% of each variable), we set dummy variables and included them in the models. All probability values for the statistical tests were 2-tailed, and probability values below 0.05 were considered significant. Informed consent was obtained from community leaders and verbally from individual participants according to the guidelines of the Council for International Organizations of Medical Science [10], which was common practice at that time in Japan. The study was approved by the institutional review boards of the Osaka Center for Cancer and Cardiovascular Disease Prevention and of the University of Tsukuba.

3. Results

Systolic blood pressures and prevalence of diabetes were significantly higher in the dementia cases than in the non-cases (Table 1). Diastolic blood pressure and prevalence of current smokers were slightly higher among the cases than among the non-cases. The mean value of ALA, but not of EPA or DHA, was significantly lower among the cases than among the non-cases. The other baseline characteristics did not differ materially between them. As expected, EPA (3.6% total fatty acid) and DHA (5.5% total fatty acid) were very high among this Japanese population.

After follow-up (median, 12.5 years and maximum, 23.8 years), we found an inverse association between serum ALA and the risk of incident dementia (Table 2). The multivariate odds ratios and 95% confidence intervals for persons with the second, third, and highest quartiles of ALA were 0.57 (0.39–0.85), 0.51 (0.34–0.76), and 0.61 (0.41–0.90), respectively, compared with the lowest quartile (P for trend = 0.01). As for EPA and DHA, no associations with incident dementia were observed.

As supplemental analyses, we classified the dementia cases further into cases with and without history of stroke, and examined the associations of ALA, EPA and DHA with them by means of unconditional logistic regression models. The association of ALA with disabling dementia was generally similar between them: For dementia with history of stroke (cases n = 110), the multivariate odds ratios and 95% confidence intervals were 0.62 (0.35–1.11), 0.55 (0.30–1.01), and 0.70 (0.40–1.22) for persons with the second, third, and highest quartiles of ALA, respectively, as compared with the lowest quartile (P for trend = 0.20). For dementia without history of stroke (cases n = 205), those were 0.52 (0.33–0.81), 0.48 (0.30–0.75), and 0.55 (0.35–0.85), respectively (P for trend = 0.009). As for EPA and DHA, no associations with dementia either with or without of history of stroke, were observed.

4. Discussion

A strong inverse association between serum ALA proportion and incident disabling dementia was found in the Japanese population. No such association was found for EPA or DHA. This is the first prospective study to find an inverse association of serum ALA with risk of disabling dementia.

A few animal and human studies supported our finding that ALA may have a beneficial impact on neural protection. Rats fed a low ALA diet had inferior learning capacity [11]. Mice fed a high ALA diet had greater learning ability and less hyperactive behavior than did those fed a low ALA diet [12]. Human erythrocyte ALA, but not EPA and DHA, was correlated with cognitive decline in a cross-sectional study of 57 Korean research participants [13]. Another cross-sectional study of 1299 Italian research participants showed that those with dementia had lower concentrations of ALA than did

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