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Abstract

The potential role of dietary poly-unsaturated fatty acids (PUFA) in the prevention of dementia and Alzheimer's disease arouses increasing interest. Fatty fish is very rich in long-chain n-3 PUFA, in particular in DHA which is also a major component of neuron membranes. The Rotterdam Study, the French PAQUID and Three-City studies, and the Chicago Health and Aging Project found a protective effect of fish or long-chain n-3 PUFA consumption against dementia or cognitive decline. In the Three-City Study we showed that regular use of omega3 rich oils was also associated with a decreased risk of borderline significance for all cause dementia. Biological data are congruent with the results obtained with dietary data. No intervention study evaluating the effect of n-3 PUFA in the primary prevention of dementia in human has been published. Despite the negative results of the OmegAD intervention trial in patients with moderate AD, these results considered all together suggest a protective effect of long-chain n-3 PUFA against cognitive decline and dementia. However, the complex mechanisms of action of PUFA at the different stages of brain aging and their interaction with the apolipoprotein E genotype still have to be elucidated.

Key-words

Nutrition – fatty acids – dementia – Alzheimer – cognition – epidemiology

Résumé

Le rôle potentiel des acides gras poly-insaturés (AGPI) dans la prévention de la démence et de la maladie d'Alzheimer suscite un intérêt croissant. Le poisson gras est très riche en AGPI n-3 à longue chaîne, en particulier en DHA qui est aussi un composant majeur de la membrane des neurones. La Rotterdam Study, les études françaises PAQUID et des Trois-Cités (3C), et le Chicago Health and Aging Project ont trouvé un effet protecteur de la consommation de poisson ou d'AGPI n-3 à longue chaîne contre la démence ou le déclin cognitif. Dans l'étude 3C nous avons aussi montré que l'utilisation régulière d'huiles riches en oméga3 était associée à un risque diminué de démence toutes causes, à la limite de la signification. Les données biologiques concordent avec les données alimentaires. Aucune étude d'intervention concernant la prévention primaire de la démence chez les humains avec les AGPI n-3 n'a été publiée. Malgré les résultats négatifs de l'essai OmegAD chez des patients atteints de maladie d'Alzheimer modérée, ces résultats considérés dans leur ensemble suggèrent un effet protecteur des AGPI n-3 contre le déclin cognitif et la démence. Cependant les mécanismes d'action complexes des AGPI aux différents stades du développement cérébral et leurs interactions avec le génotype de l'apolipoprotéine E doivent encore être élucidés.

Mots-clés

Nutrition – acides gras – démence – Alzheimer – cognition - épidémiologie

As a consequence of population ageing, the prevalence of dementia is increasing all around the world [1]. The most frequent cause of dementia is Alzheimer's disease (AD), an irreversible condition in our present state of knowledge [2]. The main risk factors of AD, age and the epsilon4 allele of the gene of the apoliprotein E (ApoE4), offer no possibility of prevention. In the absence of curative treatment, the identification of environmental risk factors of AD is therefore a research priority [3]. The role of nutrition, a potentially modifiable factor, and particularly that of dietary poly-unsaturated fatty acids (PUFA) arouses increasing interest for the prevention of dementia and AD [4].

Indeed, PUFA are major components of neuron membranes and they are essential for brain development. Long-chain PUFA (in particular arachidonic acid C20:4(n-6), EPA C20:5(n-3) and DHA C22:6(n-3)) are synthesized respectively from linoleic (LA) C18:2(n-6) and alpha-linolenic (ALA) C18:3(n-3) essential fatty acids by elongase and desaturase enzymes. However, the rate of conversion from ALA to DHA is very low. Moreover, this enzymatic activity seems to decrease with aging [5]. DHA status is then even more dependent on dietary supply [6]. In addition to their role in the composition and fluidity of neuron membranes [7], the regulation of neurotransmitter release, and their vascular properties [6, 8], several cellular mechanisms could explain the effect of PUFA on cognition [9]. Firstly, the role of PUFA in inflammation could explain their effect on brain aging. Indeed, several studies have shown an association between neuro-inflammation and neurodegenerative pathology [10]. Pro-inflammatory cytokines released by immune cells trigger the expression of brain cytokine by microglia [11, 12]. During aging, the increase of peripheral cytokines leads to an increase of brain cytokines that could be responsible for the development of cognitive disorders. Because n-3 PUFA are highly incorporated in the brain and have potent anti-inflammatory effects, they could counteract the development of neuro-inflammation and its neuropsychological effects. Another innovative hypothesis suggests an effect of PUFA through their impact on retinoid

receptors and the retinoid signalling pathway [9]. Indeed, PUFA are important modulators of gene expression in the brain.[13] In particular, the retinoid signalling pathway may be activated by some PUFA [14] including DHA [15]. There is increasing evidence that hypo-functioning of retinoid signalling is a key factor in development of toxicity caused by the Abeta peptides which form Alzheimer plaques [16].

Epidemiological studies are necessary to establish the relationship between dietary intake of various sources and types of fat and risk of cognitive decline, dementia and AD in humans. The purpose of this paper is to summarize and up-date a previous review of epidemiological studies supporting a link between dietary fat and brain aging published in the same journal [17].

Data from observational epidemiological studies

Only prospective longitudinal studies (i.e. cohort studies) are relevant in a disease whose main symptom is memory decline. The epidemiological cohorts analysing the relationships between nutrition and brain aging must record dietary and biological data in large samples representative of the elderly population, with a follow-up long enough to ensure the anteriority of dietary behaviour relatively to cognitive decline assessed by repeated neuropsychological testing and an active search for incident cases of dementia. Very few studies presently meet these requirements in the world.

Few longitudinal epidemiological studies have examined the relationships between dietary fat and risk of dementia or cognitive decline but most of their results converge to show a protective effect of n-3 PUFA despite the great variability in dietary habits (table 1). Fatty fish is very rich in long-chain n-3 PUFA, in particular in DHA which is also a major component of neuron membranes. The protective effect of fish consumption on risk of dementia was first found in the Rotterdam Study [18], but with a mean follow-up of only 2.1 years, thus the participants might

have modified their dietary behaviour because of incipient cognitive impairment. Participants eating more than 18.5 g of fish per day (highest tertile of consumption) had a 60% decreased risk of total dementia (p for trend 0.03) and a 70% decreased risk of AD (p for trend 0.005). The same study evidenced a considerably increased risk of all cause dementia (Odds Ratio (OR) = 2.4, p for trend 0.02), and in particular vascular dementia (OR = 3.0, p for trend 0.02), for subjects in the highest quartile of total fat consumption. High saturated fat intake was also associated with an increased risk of vascular dementia (OR = 2.9, p for trend 0.01), but not AD, in that study. However, a second analysis from the same study after a mean follow-up of 6 years failed to find any association between dietary fat intake and risk of dementia or its subtypes [19]. In the French Personnes Agées QUID (PAQUID) study, we showed an inverse association between the frequency of fish consumption and the risk of developing dementia in the 7 subsequent years [20]. Subjects who ate fish or seafood at least once a week had a significant reduced risk (age- and sex-adjusted hazard ratio (HR) = 0.66 ; 95% confidence interval (CI) 0.47-0.93) of being diagnosed as demented in the seven subsequent years. The risk of developing specifically Alzheimer's disease was also reduced, with borderline significance (HR = 0.69, 95% CI 0.47- 1.01).

A similar result was observed in the Chicago Health and Aging Project (CHAP) study which also found a protective effect of overall n-3 PUFA consumption against dementia [21], and a protective effect of fish consumption against cognitive decline [22]. Conversely, consumption of saturated fat and trans PUFA was associated with increased risk of AD [23] and cognitive decline [24] in that study. Recently, the Zutphen Elderly Study also evidenced that fish consumption was associated with less subsequent cognitive decline over 5 years in older men [25]. Moreover, a dose-response relationship was observed between the combined intake of EPA and DHA and cognitive decline in that study.

Three studies found interactions between dietary fat intake and genetic characteristics for genes involved in the metabolism or transportation of lipids such as the apolipoprotein E whose epsilon 4 allele is also a risk factor for AD. The Washington Heights Inwood Columbia Aging Project (WHICAP) study found no association between PUFA intake and risk of AD, but this study showed a deleterious effect of total energy intake and total fat intake in participants with the apoE4 allele [26]. In the Cardiovascular Health Cognition Study (CHCS), consumption of at least four servings of fatty fish par week was associated with a significantly reduced risk of dementia only in ApoE4 non-carriers in fully adjusted models [27]. There was no association with consumption of lean fried fish. In the French Three-City (3C) study, weekly consumption of fish was also associated with a reduced risk of incident AD and all cause dementia over 4 years of follow-up but only among ApoE4 non-carriers for the latter [28]. Regular use of n-3 PUFA rich oils (rapeseed or nut oil) was also associated with a significantly decreased risk for all cause dementia (HR = 0.41, 95% CI 0.17- 0.995) which was of borderline significance after adjustment for the ApoE genotype. Regular consumption of n-6 rich oils (sunflower or grape seed oil) not compensated by consumption of n-3 rich oils nor fish was associated with a considerably increased risk of dementia but only among ApoE4 non-carriers (RR = 2.12, 95% CI: 1.30-3.46) [28]. Our results therefore support a protective effect of both sources of precursor (vegetable oils) and long-chain (fish) PUFA against dementia.

In the 3C study, we also showed that regular fish consumers had better general cognitive performances, a better perceived health status and less depressive symptoms [29]. Similarly, the Doetinchem Cohort Study evidenced a protective effect of fish and long-chain n-3 PUFA (EPA and DHA) consumption on cognitive performance at middle age [30]. Although these are cross-sectional analyses, they are congruent with longitudinal analyses and they also support the hypothesis of an impact of PUFA on well-being through their effect on neuro-inflammation [31].

Biological data give strong support to the results obtained with dietary data. The French *Epidémiologie du Vieillissement Artériel* (EVA) study found a significant increase of the risk of cognitive decline with increasing level of n-6 PUFA in erythrocyte membranes [32]. Conversely, the level of total n-3 PUFA, and more specifically that of EPA and DHA, was inversely associated with cognitive decline in that study. In the Framingham Heart Study, subjects in the top quartile of plasma DHA level had a significantly reduced risk of developing dementia [33]. The mean dietary intake of these subjects was estimated to be equivalent to 180 mg DHA per day or three servings of fish per week in a sub-sample. Plasma fatty acids were also associated with cognitive decline after age 60 in the Atherosclerosis Risk in Communities Study but in an unexpected way [34]. In that study, total PUFA, total n-6 PUFA and linoleic acid were all inversely related to cognitive decline, whereas palmitic acid (a saturated fatty acid) was positively associated with the risk of cognitive decline. Total n-3 PUFA in general and EPA+DHA in particular had no significant effect on global cognitive decline. However, total EPA+DHA was associated with less decline in verbal fluency in particular among hypertensive patients and among ApoE4 non-carriers.

Despite adjustment for many covariates in multivariate analyses, we cannot rule out residual confounding in observational studies. In the PAQUID study, the protective effect of fish consumption was partly explained by the higher educational level of regular fish consumers [20]. In the 3C study, regular fish consumers were more educated and had a higher income [29]. They also had a healthier diet including a higher consumption of fruits and vegetables. Paradoxically, they suffered more often from hypertension and past stroke. All these factors have previously been found to be associated with risk of dementia, either in a protective or a deleterious way [35]. They could therefore act as confounders in the relationship between fish consumption and dementia. Moreover, measurement errors may hamper the validity of the results obtained with dietary data. Randomized controlled trials (RCT) conducted with supplements are the only

means to definitely rule out such confounding effects and identify the specific effect of a given nutrient.

Data from intervention studies

In spite of increasing evidence from observational studies of a link between dietary fat intake and risk of dementia or cognitive decline, no RCT evaluating the effect of n-3 PUFA in the primary prevention of dementia in humans has been published [36]. An experiment which showed a significant decrease in the number and burden of amyloid plaques in the brain of an aged Alzheimer mouse model fed a high DHA diet raises considerable hope for its use as an adjuvant treatment of dementia or AD [37]. For ten years, there have been only two RCT assessing the efficacy of n-3 PUFA in demented patients [38, 39]. A single blind RCT showed a positive effect of joint PUFA (with a n-6/n-3 ratio = 4.5) and vitamin E supplementation on memory, mood and appetite of 100 Alzheimer patients as reported by their caregivers [38]. However, this small trial suffers from several methodological flaws. Another RCT was conducted in elderly Japanese suffering from dementia with thrombotic cerebrovascular disease [39]. The 10 patients in the intervention group received 720 mg DHA daily whereas the 10 participants in the control group received usual care for one year. The intervention group showed significant improvements on the Dementia Rating Scale and Mini Mental status Examination (MMSE). Although promising, this trial relies on a very small sample affected by a very specific cause of dementia.

Recently, the OmegAD intervention trial was the first published large scale RCT with n-3 PUFA in 204 patients with mild to moderate AD (MMSE between 15 and 30) [40]. In addition to acetylcholine esterase inhibitors, the participants received four 1-g capsules daily, each containing either a combination of 430 mg of DHA and 150 mg of EPA (intervention group) or an isocaloric placebo oil (1 g of corn oil, including 0.6 g of linoleic acid) for 6 months, followed by 6 months of open treatment with n-3 PUFA fatty acid supplementation

in all patients. There was no statistically significant difference for cognitive decline over 12 months between the two groups. However, in the sub-group of 32 patients with very mild AD (scoring above 27 on the MMSE at baseline), there was a significant effect of treatment on cognitive decline. Although this post-hoc analysis should be taken with caution, it suggests a protective effect of long-chain n-3 PUFA at the early phase of dementia.

Conclusion

These results considered all together suggest a protective effect of long-chain n-3 PUFA against cognitive decline and dementia. However, the complex mechanisms of action of PUFA at the different stages of brain aging and their interaction with the apoE genotype still have to be elucidated. It is necessary to determine the specific role of the various long-chain PUFA, to define the optimal n-6/n-3 ratio for the prevention of cognitive decline, to study interactions with other nutrients, in particular anti-oxidants, and to characterise the persons who would be more susceptible to benefit from a prevention by nutrition. This requires a coordinated research program, including epidemiologic studies to complete observational data in an aged general population, and fundamental research to identify the mechanisms involved. In a recent review, a task force of the International Academy on Nutrition and Aging stressed the need to develop further prospective studies of adequate duration, including subjects whose diet is monitored at a sufficiently early stage or at least before the onset of disease or cognitive decline [41]. The COGINUT (COGnition, anti-oxidants, and fatty acids: Interdisciplinary approach of the role of NUTrition in brain aging) research program is a collaborative project organised around the 3C epidemiological cohort and funded by the French National Agency for Research (http://www.inra.fr/layout/set/print/les_partenariats/programmes_anr/alimentation_nutrition_humaine/appel_a_projets_2006/resultats_aap_2006). COGINUT involves a consortium of epidemiological and fundamental research teams, a technical centre (Department of Nutrition

of the ITERG, Technical Institute for Fat) and the Lesieur company (http://www.prodinnov.fr/projets_collaboration_industrielle.php). The general aim of the COGINUT project is to analyze the relationships between nutritional status and pathological brain aging (dementia, cognitive decline, mood disorders) in older persons, with a particular interest in the joint role of anti-oxidants and PUFA. We shall analyze more specifically the impact of PUFA on inflammation and on the retinoid signalling pathway. This project is a preliminary step before the implementation of nutritional interventions in elderly persons at high risk of pathological brain aging because of their nutritional, medical, psychosocial or genetic characteristics. These interventions could take the form of nutritional recommendations, supplements or functional food.

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Table 1. Main longitudinal epidemiological studies of the association between dietary fat intake and risk of dementia or cognitive decline.

Study (country)	N	Age (years)	Dietary factors	Outcomes	Results (multivariate analyses)
Rotterdam Study (The Netherlands) [18] [19]	5434	≥ 55	Fish Total fat Fatty acids	All cause dementia AD Vascular dementia	Protective effect of fish consumption against dementia and AD No association with total fat nor specific fatty acids.
PAQUID (France) [20]	1416	≥ 68	Fish	All cause dementia AD	Protective effect of fish consumption against dementia, borderline significance for AD
CHAP (USA) [21] [23]	815	≥ 65	Fish Fatty acids	AD	Protective effect of consumption of fish, total n-3 PUFA and DHA. Increased risk with saturated fat and trans-unsaturated fat intake
CHAP (USA)	2560	≥ 65	Total fat Fatty acids	Cognitive decline	Deleterious effect of saturated fat and trans-unsaturated fat, protective effect of

[24]					monounsaturated fat and a high ratio of polyunsaturated to saturated fat intake. Protective effect of fish consumption.
[22]					
WHICAP (USA) [26]	980	≥ 65	Caloric intake Total fat	AD	Increased risk with total energy and total fat intake among ApoE4 carriers
CHCS (USA) [27]	2233	≥ 65	Fatty and lean fried fish	Dementia AD	Protective effect of fatty fish against dementia among ApoE4 non-carriers
3C (France) [42]	8085	≥ 65	Fish Vegetable oils	All cause dementia AD	Protective effect of regular consumption of n-3 PUFA rich oils against dementia. Protective effect of regular fish consumption against AD, and all cause dementia among ApoE4 non-carriers
Zutphen Study (The Netherlands)	210	70-89	Fish Fatty acids	Cognitive decline	Protective effect of consumption of fish, EPA and DHA.

[25]

AD = Alzheimer’s disease