European Geriatric Medicine 7 (2016) 77–85

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Hot topic in geriatric medicine

Healthy brain ageing and cognition: Nutritional factors

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ARTICLE INFO

Article history:
Received 16 November 2015
Accepted 14 December 2015
Available online 22 January 2016

Keywords:
Ageing
Dementia
Diet
Micronutrient
Macronutrient
Medical food

ABSTRACT

Nutritional factors can influence the risk of Alzheimer's disease and its rate of clinical progression, suggesting that the association between diet, nutrient status and cognitive function deserves more attention. The European Union Geriatric Medicine Society (EUGMS) working group "Healthy Brain Ageing and Cognition" supports the development of practical recommendations for nutritional strategy, focused predominantly on the preventive aspects of diet and nutrition on cognitive decline. Adopting a healthy lifestyle and avoiding nutritional deficiencies in young or midlife adults is essential and there is compelling evidence to justify recommending a Mediterranean diet as a way of achieving these goals. There is currently insufficient evidence to endorse the use of specific nutrients to promote healthy brain ageing. In addition, currently there is no generally applicable evidence to recommend the use of single-agent micronutrient supplementation at any stage of dementia or for prevention. Omega-3 fatty acids or specific medical foods may be considered for selected patients with early dementia. When signs of malnutrition are detected, correction of specific deficiencies is necessary to improve nutritional status. Individuals at risk of malnutrition should be advised to improve nutritional intake from dietary food sources and should avoid taking high doses of specific nutrients as supplements. Nutritional awareness, advice and intervention are important in the general management and follow-up of people with cognitive problems.

1. Introduction

The global population is ageing, not only in Europe and North America but also in nearly all countries of the world [1]. Improvements in public health and healthcare provision contribute to people living longer and healthier lives, but also increase the number of people living with chronic diseases, including dementia, worldwide. The World Health Organisation recognises as a public health priority the expected global epidemic of Alzheimer's disease (AD) and other types of dementia and, in 2013, estimated 44 million people worldwide were living with dementia with numbers predicted to double every 20 years, reaching 135 million by 2050 [2]. In accord with other chronic conditions and geriatric syndromes, the processes underlying the development of dementia syndrome span a far longer period than previously thought [3]. The first changes in the brain occur long before the appearance of the first memory complaint and progressive cognitive impairment. Research into autosomal-dominant AD has identified pathophysiological changes in biochemical markers of AD in the

Abbreviations: AD, Alzheimer's disease; BMI, body mass index; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; MNA, Mini Nutritional Assessment; MUST, Malnutrition Universal Screening Tool; NRS, Nutritional Risk Score; RCT, randomised controlled trial; SGA, subjective global assessment; THF, 5-methyltetrahydrofolate.

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http://dx.doi.org/10.1016/j.eurger.2015.12.005
1878-7649/

cerebrospinal fluid (CSF), brain amyloid deposition and brain metabolism occurring over decades [4]. These findings indicate that minor cognitive disorders, such as mild cognitive impairment (MCI), and major cognitive disorders, such as dementia, reflect different clinical stages of long-standing, progressive changes in the brain. Such changes in cognitive abilities ultimately impact an individual's physical functioning, as they suffer the inexorable progression from independence to frailty and finally to dependence and disability [5]. The development of this devastating condition is driven by genetic and environmental risk factors. Many acquired risk factors for dementia, such as hypertension, diabetes, and obesity, may be modified by diet [6]. Increasing evidence showing that nutritional factors can influence both the risk of developing AD and its rate of clinical progression, suggests that the association between diet, nutritional status and cognitive function deserves more attention [7]. Specific nutrients or healthy dietary patterns may be potentially beneficial in the treatment or, more importantly, the prevention of cognitive disorders and associated nutritional deficiencies. The aim of this review is to provide practical recommendations for nutritional strategy, focused predominantly on the preventive aspects of diet and nutrition on cognitive decline, as supported by the European Union Geriatric Medicine Society (EUGMS) working group "Healthy Brain Ageing and Cognition".

2. AD and nutritional status

The perspective on nutritional status and potential scope for interventional strategies will vary throughout life as an individual progresses along the path towards AD [3]. In the very early stages of the disease course, prevention and intervention are important to influence the prevalence and incidence of cognitive disorders. While easy to say, this is challenging to do because of a lack of biomarkers for pre-clinical disease. General nutritional advice given to the public to encourage healthy brain ageing includes recommendations for specific actions they should take (primary prevention) or things that they should avoid (quaternary prevention). The relationship between nutritional status and cognitive function grows increasingly complex later in the disease course because levels of specific nutrients may play a role in pathophysiology, while cognitive decline can have repercussions on dietary intake of nutrients. At this point, the goals are to correct nutritional deficiencies and secondary prevention of (selective) malnutrition. In later stages, the goal is to use individual and collective approaches to reduce the impact of the disease on functioning and quality of life (tertiary prevention). Finally, in the terminal stage, ethical aspects become the main issue.

Alois Alzheimer described weight loss in his first patient in 1907 [8]. Weight loss, a characteristic of undernutrition [9], is currently recognised as a clinical feature of AD [10], affecting approximately 15% to 45% of community-dwelling patients with AD [11–13]. Other studies in community-dwelling patients with AD reported even higher prevalence rates for the risk of undernutrition (evaluated with the Mini Nutritional Assessment [MNA]), ranging from 26% to 80% [14–16]. Additional studies showed that weight loss and (risk of) undernutrition are associated with accelerated progression of AD [17], a higher rate of institutionalisation [18], and increased mortality [19]. These data demonstrate a high prevalence of weight loss and risk of undernutrition in community-dwelling patients with AD, which is associated with negative health outcomes.

Although there are several guidelines and studies on the management of undernutrition and risk for undernutrition in older people without AD [20], these data cannot be extrapolated to patients with AD for two important reasons. Firstly, the mechanisms of weight loss and undernutrition in AD patients are probably not the same as in individuals without AD. This belief is supported by studies showing that the prevalence of weight loss is higher in patients with AD compared with control subjects without AD [13,21]. Secondly, there will be differences in adherence to nutritional interventions between individuals with and without cognitive impairment. Recent studies showed that community-dwelling patients with moderate AD did not lose weight during 4 years of follow-up [22] and that the prevalence of undernutrition in community-dwelling patients with newly diagnosed AD was 0%, although one in seven individuals was identified as being at risk of undernutrition [12]. This low proportion of undernourished patients is in line with other studies, which showed the prevalence of undernutrition in community-dwelling patients with AD patients ranged from 0% to 9% [16].

Although malnutrition is established as a later feature of disease, there is evidence that nutritional status itself may in fact be compromised much earlier. Many studies have investigated differences in levels of circulating nutrients between people with AD and healthy age-matched controls, particularly B vitamins, vitamin C, vitamin E, choline and long-chain omega-3 fatty acids, the majority reporting lower levels in AD [23]. A recently published meta-analysis of these studies confirmed this notion by reporting strongly significantly lower levels of a range of nutrients, including folate ($P < 0.001$), vitamin B12 ($P < 0.001$), vitamin E ($P < 0.001$) and vitamin C ($P < 0.001$) [23]. This meta-analysis also indicated that the low levels of nutrients are independent from, and may precede, the classic protein/energy malnutrition prevalent in advanced stages of the disease [23]. Other meta-analyses showed that levels of DHA, eicosapentaenoic acid (EPA) and selenium are lower in dementia and AD [24,25]. Another recently completed study in Europe showed significantly lower plasma levels of selenium, uridine and DHA in red blood cells in patients with early AD, compared with age-matched control subjects [26]. A US study recently confirmed lower levels of plasma uridine levels in AD [27]. Lower levels of several nutrients in the brain, the target organ for their contribution to neurologic function, have also been demonstrated with CSF and post-mortem brain sampling. These techniques revealed reduced brain levels of omega-3 fatty acids [28–30], uridine [31], folate [32–35], vitamin B12 [33], vitamin C [36] and vitamin E [37], and a shift to catabolism for choline [38,39].

Various factors contribute to lower nutrient status in AD. Firstly, inadequacies in food choices among people with AD result in lower intake of several nutrients, including folate, vitamins B6, B12, C, E and DHA in early AD compared with age-matched controls [40]. Secondly, it has been suggested that patients with AD have an altered metabolism, particularly lower endogenous biosynthesis of DHA in the liver [41]. Finally, the brain's consumption of nutrients may be increased by the pathological processes of AD [42].

3. Screening and assessment of nutritional status

The lack of universally agreed criteria to assess nutritional status has hindered efforts to implement routine screening to detect undernutrition or malnutrition. Consequently, a variety of nutritional tools incorporating different anthropometric, biochemical and clinical criteria have been developed for particular settings or specific patient groups. Currently, however, there is no evidence to suggest that any tools other than those used for the general older population should be used specifically to screen and assess the nutritional status of patients with dementia. Most available instruments screen for nutritional risk rather than existing malnutrition. Actually, this indicates that the first screening level is based on simple measurements that identify people who may be at risk for malnutrition. Subsequently, a complete nutritional