LETTERS

Predicting memory decline as a risk factor for Alzheimer's disease in older post-menopausal women: *quod erat demonstrandum*?

Alzheimer's disease (AD) is the major form of age-related dementia worldwide, accounting for more than two-thirds of all dementia cases. The disease is characterized by a progressive loss of cognitive and intellectual functioning (Gilman, 1997). A number of risk factors for AD have been identified. The prevalence of AD increases with age, diabetes, depression, family history of Parkinson's disease and following head injury or exposure to solvents (Jorm *et al.*, 1991; van Duijn *et al.*, 1991; Ott *et al.*, 1995; Yoshitake *et al.*, 1995; Devanand *et al.*, 1996). Published research further suggests that low education levels are associated with increased prevalence of clinical AD (Gatz *et al.*, 2001; Qiu *et al.*, 2001; Ravaglia *et al.*, 2002). Women also have a higher risk for developing the disease than men, with the risk being markedly increased following menopause (Sherwin, 2002; Sherwin 2003). Additionally, slightly more severe cognitive deficits have been reported in AD in women compared to men (Buckwalter *et al.*, 1993, Henderson and Buckwalter, 1994). These epidemiological trends may be a consequence of reproductive hormonal changes. Specifically, menopause results in a marked diminution in gonadal estrogen production in women (see Sherwin, 2003, for a review). Estrogen plays a pivotal role in the maintenance and function of neuronal circuits in the brain and in resistance to neuronal damage (McEwen, 2001). The neuroprotective properties of estrogen are thought to be mediated at least in part by anti-amyloidogenic, anti-oxidative and ant-inflammatory mechanisms (reviewed in Barron *et al.*, 2006a). However, limited and somewhat mixed data exist regarding the association between endogenous levels of estrogen and cognitive decline (Manly *et al.*, 2000; Schupf *et al.*, 2003). Based on some of our own findings, we here consider the factors that may be useful in predicting memory decline as a risk factor for Alzheimer's disease in older post-menopausal women.

We have previously noted the relationship between reproductive hormones (estrogen, leutinizing hormone (LH) and follicle stimulating hormone (FSH)) and global cognitive status in a large cohort of over 500 postmenopausal women (Rodrigues *et al.*, 2008). However, with respect to the symptomatology of early stage AD, specific deficits in episodic learning and memory are the most commonly occurring cognitive signs of the disease (Collie and Maruff, 2000; Remy *et al.*, 2005). We have noted a lack of independent or combined association between endogenous estrogen status and episodic memory capacity in the same cohort of over 500 older postmenopausal women studied by Rodrigues *et al.* (2008). This finding was observed despite the fact that the relatively large dataset allowed for the application of powerful statistical techniques, specifically with respect to multiple linear regression. This outcome is consistent with our previous report (Rodrigues *et al.*, 2008) that estrogen did not have a statistically significant impact on global cognitive status in the same cohort; instead, gonadotropins, LH and FSH showed significant associations with global cognition. Further, gonadotropins have been reported to exert a significant role in AD risk and pathogenesis (reviewed in Barron *et al.*, 2006b). However, in contrast to our findings, other studies have reported that endogenous estrogen does exert a significant effect on cognition (Drake *et al.*, 2000; Senanarong *et al.*, 2002; Wolf and Kirschbaum, 2002; Yaffe *et al.*, 2000), and that estrogen shows no associations with gonadotropin levels (Hoskin *et al.*, 2004; Tsolaki *et al.*, 2005). The discrepancies that exist in these studies merit further consideration, specifically with respect to issues concerning sample size, age of cohort, presence of other AD-associated risk factors (including the APOE ε4 allele) and the type of cognitive capacity being evaluated.

A specific threshold for estrogen may exist in relation to its influence on cognition: it is possible that clinically measurable effects of estrogen on cognition may only occur at higher concentrations (for example, after exogenous estrogen administration), compared with levels that are naturally present in post-menopausal women. In this context, it is relevant that several studies using measures of episodic memory have found an improvement in cognitive performance after exogenous estrogen replacement therapy (Phillips and Sherwin, 1992; Kampen and Sherwin, 1994; Jacobs *et al.*, 1998; Burkhardt *et al.*, 2004). Indeed, considering the substantial number of investigations into the effects of estrogen administration on memory in post-menopausal women, it is perhaps surprising that relatively little evidence exists concerning the relationship between endogenous estrogen concentration and episodic

memory. Exogenous treatments of estrogen in post-menopausal women may better match the naturally occurring biological levels found in pre-menopausal women, and may be more likely to have a significant impact on memory and learning. Further, given that the findings the we note here were obtained in a relatively older cohort (aged 75–86 years; Rodrigues *et al.*, 2008), it is possible that women's endogenous estrogen levels in the earlier post-menopause years are more strongly associated with episodic memory functioning.

We further observed in this cohort (Rodrigues *et al.*, 2008) that the possession of an APOE $\varepsilon4$ allele did not have a statistically significant impact on verbal episodic memory performance. This finding is again consistent with our previous investigation of global cognitive status in this cohort of older post-menopausal women (Rodrigues *et al.*, 2008). This point notwithstanding, considerable empirical evidence exists regarding the APOE genotype and its role in modifying the risk of age-related cognitive decline and AD. However, the presence of the $\varepsilon4$ allele is associated with less than 50% of the population of patients with AD (Evans *et al.*, 1997). Furthermore, this allele may not be a significant risk factor in all ethnic groups (Evans *et al.*, 2003). In this cohort of post-menopausal women, other modulating factors such as education, age and other relevant biomarkers may have attenuated the impact of APOE genotype. We believe that this issue also warrants further discussion and investigation.

Elderly people have an enhanced risk of depressive disorders and symptoms (Wells *et al.*, 1989; Judd and Akiskal, 2000; Judd *et al.*, 2000). Moreover, a number of studies have reported a potentially important link between age-related depression and memory decline (Kral, 1983; Alexopoulos *et al.*, 1993; Devanand *et al.*, 1996). In our cohort (Rodrigues *et al.*, 2008), depression was found not to be a significant factor associated with episodic learning or memory performance. The existing literature suggests that symptoms of depression can have quite specific effects on elements of cognitive functioning. This consideration might be highly relevant in this context.

Our data were consistent with established findings linking increased age, reduced educational level and increased blood-borne beta amyloid to lower episodic memory capacity. Further, one element of memory capacity that was evaluated (delayed recognition performance) was significantly associated with statin use and with hypertension status in this cohort (Rodrigues *et al.*, 2008). Statins are used as pharmaceutical agents to reduce plasma levels of cholesterol, by inhibiting the activity of the enzyme 3-hydroxy-3-methyl-glutaryl-coenzyme. Accumulating evidence suggests that the use of statins lowers the risk of dementia, most likely via amyloid-related mechanisms (Jick *et al.*, 2000; Fassbender *et al.*, 2001; Pedrini *et al.*, 2005). Statins may also improve endothelial homeostasis by increasing the accessibility of nitric oxide (Vaughan, 2003), which may facilitate chemical messaging between cells.

Our findings indicated that hypertension was a risk factor for lower episodic memory capacity. A number of previous studies have linked high arterial blood pressure to increased risk of late-life dementia and cognitive decline (Knopman *et al.*, 2001; van Dijk *et al.*, 2004; Whitmer *et al.*, 2005). Indeed, studies have reported that hypertension may increase the rate of cognitive decline both in patients with AD (Hanon *et al.*, 2003) and in controls (Bellew *et al.*, 2004). However, other studies have indicated no significant association between hypertension and age-related decline in cognitive performance (Farmer *et al.*, 1987, 1990; Scherr *et al.*, 1991; van Boxtel *et al.*, 1998). With respect to our own findings pertaining to hypertension, high blood pressure may cause cerebrovascular disease (particularly ischemia), including relatively minor but chronic disturbances in cerebral perfusion, producing unfavorable effects on brain cell metabolism (Elias *et al.*, 1993). These changes may increase the likelihood that individuals with incipient AD pathology will express symptoms of dementia, including cognitive decline. Hypertension may also accelerate the AD process directly (Skoog and Gustafson, 2003), insofar as similar biological mechanisms may be involved in the pathogenesis of both hypertension and AD.

In summary, we have noted here that, in our cohort (Rodrigues *et al.*, 2008) age, beta amyloid concentration and hypertension were negatively associated with episodic memory function, whereas education and statin use had positive associations with episodic memory. A relationship between endogenous estrogen and memory functioning was not evident. In future, additional insight will be gained from extended longitudinal investigations of similar cohorts, employing a wider range of cognitive and functional assessments in enriched groups of individuals who are at increased risk of prodromal AD. Further, although a wealth of literature exists on the relationship between reproductive hormones and cognitive decline, AD risk and AD pathogenesis, the precise role of estrogen still remains unclear. This is reiterated in the controversy that exists concerning the putative benefits of hormone replacement therapy for improving cognitive capacity and as a therapeutic for AD (for recent review and meta analysis, see

Hogervorst *et al.*, 2009). It is clear that in future large clinical studies which control for a number of relevant factors (as adumbrated herein) are required to address some of the discrepancies in the extant literature (Manly *et al.*, 2000; Schupf *et al.*, 2003).

Conflict of interest

None.

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