Gender differences in the occurrence of Alzheimer’s disease

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Summary
Prevalence studies on dementia generally show a higher risk in women than in men. American studies reported equal rates whereas European ones showed higher rates in women. Observational studies on hormone replacement therapy showed that treated women had a lower risk than untreated ones. Two large clinical trials in menopausal women did not find any protective effect of therapy with oestrogens or oestrogens plus progestin. However, as regards a potential protective role of female gonadal hormones on brain neurodegenerative diseases, this result cannot be considered conclusive since a large cohort study showed an increased risk of Alzheimer’s disease (AD) in women who underwent early oophorectomy. A possible gender difference in the risk of AD is further supported by recent evidence suggesting that the brain’s so-called cognitive reserve is reduced in women. The area of gender differences in AD and in neurodegenerative processes generally, although still largely unexplored, appears to offer great promise for the future development of better strategies of intervention for patients.

KEY WORDS: Alzheimer’s disease, gender differences, occurrence.

The prevalence of dementia
Among patients with Alzheimer’s disease (AD), clinicians commonly see more women than men. For example, in the Italian Cohort study on dementia, a multicentre study promoted by the Italian Society for the Study of Dementias (SINDEM), of a total of 213 consecutive patients, more than 70% were women. This clinical observation cannot simply be interpreted as due to a higher disease risk in women. In the general population, the longer life expectancy of women results in a greater prevalence of old and very old women with respect to old and very old men. Since the prevalence of AD doubles with every five years of age it is hardly surprising that in clinical patient series the number of women is greater than that of men.

Prevalence population studies have, in general, confirmed that more women than men have dementia. As an example, figure 1 presents the results of a recent survey in China that reproduced the findings of almost all the population prevalence studies. The prevalence of dementia was increased twofold in women aged 75 years, and this increase rose to threefold at 80 years of age.

The incidence of dementia
Interpretation of this difference is rendered complicated by the fact that dementia is a syndrome caused by various diseases. Therefore, while one form, or some forms, of dementia might be more frequent in women, this gender difference might not apply to AD. Another problem is the fact that prevalence, unlike incidence, which is a more appropriate measure of the risk of disease, increases as a function of disease duration. AD is a disease of long duration and many patients die of other causes during the course of it. Since women have a longer life expectancy, more females than males survive with AD, particularly at the older ages, when the risk of disease is higher. For these reasons, gender-specific risks have to be discussed in the light of studies that evaluated incidence and not prevalence and that considered specifically the incidence of AD. Many incidence studies carried out in Europe and America are available in the scientific literature. Most of these studies analysed small populations and their estimates of the differences between genders show considerable variability. However, at least one large meta-analysis confirmed that the risk of having AD is
increased 1.6 fold in women (2). This finding is not confirmed in recent American studies that, unlike European studies, reported equal incidences in the two genders. In figure 2, which shows the age- and gender-specific AD incidence rates in three American and three European studies, it is clear that the finding of a higher incidence among women is specific to the European studies (3).

This finding, poorly explained by methodological differences, suggests that premorbid exposures of some kind, causally linked with AD and showing different patterns in the “Old World” and the “New World”, might play a different role in the two genders.

Gonadal steroids and dementia

As regards the possible existence of a different AD and, more generally, dementia risk between the two genders, the findings of descriptive epidemiological population studies are inconclusive. However, there exists biological evidence which suggests that the risk of AD might be different in men and women. Indeed, oestrogens and other gonadal steroids act on target sites in the brain and groups of neurons in the brain possess intranuclear oestrogen receptors (4). Table I lists the potential actions of oestrogens on the brain. Most of these actions have the potential to contrast the neurodegenerative process that characterises AD.

The beneficial effects of oestrogens on the brain might explain why AD in women is rarely seen before the menopause and why, in observational studies, hormone replacement therapy (HRT) is associated with a reduced incidence of AD (6). Unfortunately the presence of a protective effect of HRT on AD was not confirmed in the experimental setting of two large randomised controlled trials on oestroprogestinic and oestrogen replacement therapy.
therapy (7,8). Conversely, in these studies, the women taking oestrogen and progestin were found to have an increased risk of dementia (Fig. 3).

Despite these disappointing results, there is still considerable interest in the effects of oestrogens on the brain and the potential role of gonadal hormones in neurodegenerative disorders. In particular, one study that investigated the relationship between premenopausal oophorectomy and AD showed that only early oophorectomy was associated with an increased risk of dementia. These results suggest that the timing of the action of female gonadal hormones during life might have a crucial bearing on neurodegenerative processes (9).

Gender differences in the brain’s cognitive reserve

Other authors have offered a different viewpoint on the issue of the differences in dementia occurrence between men and women. Cognition is not merely related to the anatomical integrity of the brain but depends largely on functional connectivity (10). In particular, it has been suggested that men are more resistant to the pathological process of AD and that a possibly greater brain reserve in men could explain why the disease is more likely to manifest itself clinically in women.

A study comparing the results of 18FDG-PET imaging in men and women with equally severe AD showed that the women had significantly higher glucose metabolism in the areas primarily involved in the pathological process of AD (the right inferior frontal, superior temporal and insular cortices, and the hippocampus) (Fig. 4). In other words, the fact that the women showed less marked cerebral metabolic deficits compared with the men, who nevertheless showed the same level of cognitive impairment, suggests that the so-called brain reserve was higher in the men (11). These results seem particularly interesting since they...
confirm, almost entirely, the findings of a previous post-mortem study which concluded that the neuropathology of AD is more likely to be expressed as dementia in women than in men. These conclusions were based on the observation of more tangles and amyloid plaques in men compared with women with AD, who had, before death, shown comparable levels of neuropsychological impairment (12).

**Concluding remarks**

In conclusion, while the issue of gender differences in AD leaves many questions unanswered, it offers an even greater number of intriguing suggestions. Well-designed studies combining epidemiological, laboratory and clinical experience could make a real contribution to furthering knowledge in this area and to the development of better strategies of intervention for patients.

**References**