Surgical menopause and cognitive decline

Early age at menopause is associated with several adverse, long-term health outcomes, including cardiovascular morbidity, incidence of cancer and total mortality [1-3]. It is therefore interesting to look at data on the consequences of surgical menopause, a major cause of early menopause. A recent publication by Bove and colleagues reported on 1884 female subjects from two longitudinal studies of cognitive decline (Religious Orders Study and Rush Memory and Aging Project) [4]. Mean age at closure of the database was 78 years, when a mean 18-year follow-up was available. Participants had to be cognitively normal at baseline, later on undergoing an annual clinical evaluation. Autopsies were performed in 80% of those who died during the study period. The primary analysis examined the association between age at surgical menopause and decline in a global cognition score. Secondary analyses examined additional outcomes: (1) decline in five cognitive subdomains, and (2) a global measure of the burden of Alzheimer's disease pathology. In exploratory analyses, the effect of hormone replacement therapy (HT) was addressed. All models were adjusted for age, education, smoking and cohort and stratified by surgical versus natural menopause. For the 32% of subjects with surgical menopause, earlier age at menopause was associated with faster decline in global cognition (p = 0.0007), specifically episodic memory (p = 0.0003) and semantic memory (p = 0.002). Earlier age at menopause was also associated with increased neuropathology of Alzheimer's disease (p = 0.038), in particular neuritic plaques (p = 0.013). HT use for at least 10 years, when administered within a 5-year perimenopausal window, was associated with decreased decline in global cognition. No associations were seen in women who had natural menopause.

Overview

The association between menopause and cognitive decline has been long discussed. The unfavorable results of the Women's Health Initiative Memory Study (WHIMS), a substudy of the Women's Health Initiative (WHI), investigating postmenopausal HT versus placebo in women older than 65 years, fueled the negative sentiments on the potential effects of HT in this context. WHIMS data were reported in several papers, which were nicely
summarized by Craig and colleagues in 2005 [5]. While the combined estrogen–progestin arm was associated with an increased risk for dementia, the estrogen-alone arm (hysterectomized women) had neutral effect. In both study arms, there was no difference from placebo when results of the Mini Mental State Examination (MMSE) scores were analyzed, yet women on the continuous combined estrogen–progestin regimen seemed to slightly underperform. The WHI raised a debate whether the cardiovascular and neurological ill-outcomes actually reflected the older age of its participants. Examination of the available data for the younger age group of the WHI (age 50–59 years) led to the concept of the 'window of opportunity' which basically pointed at potential cardiovascular benefits of HT when started early, but such information on cognition and dementia was not available for the WHIMS study, which focused on the subset of older women. It therefore seems imperative to look for such data in other relevant studies which investigated the role of estrogen, whether endogenous or prescribed, on neurological parameters in a younger population.

Henderson and colleagues recently reported on a cohort of 643 healthy postmenopausal women not using hormone therapy who were recruited into early (< 6 years after menopause) and late (10+ years after menopause) groups [6]. Women were administered a comprehensive neuropsychological battery. Cognitive outcomes were standardized composite measures of verbal episodic memory, executive functions, and global cognition. Results for the early and late groups did not differ significantly and failed to support the hypothesis that temporal proximity to menopause modifies the relationship between endogenous serum levels of estradiol and verbal memory, executive functions, or global cognition. As for exogenous estrogen, a review by Rocca and colleagues [7] pointed at beneficial outcomes of HT: 'Comparison of women who underwent bilateral oophorectomy with referent women provided evidence for a sizeable neuroprotective effect of estrogen before age 50 years. Several case–control studies and cohort studies showed neuroprotective effects in women who received HT in the early postmenopausal stage (most commonly at ages 50–60 years). The majority of women in those observational studies had undergone natural menopause and were treated for the relief of menopausal symptoms.'

A new trial looking at the effects of HT on cognition in the perimenopause recently released its preliminary results: some of the KEEPS (Kronos Early Estrogen Prevention Study) data were presented by Dr Asthana at the 2012 North American Menopause Society congress. The design of KEEPS has already been published several months ago [8], and its results may be summarized as follows: after 4 years of follow-up in healthy women with a mean age of 52 years, no differences between hormone users and a placebo arm were recorded concerning memory and certain cognition domains. This is probably because the study numbers were too small to show a difference in a population not recruited because of cognitive deficit.

The current study by Bove and colleagues [4] highlights further aspects of this debated issue. The studied cohort was fairly large and the follow-up period was long enough; it included women having either natural or surgical menopause, and both users/non-users of HT. Patho-histological brain examinations were available. The main findings were:

1. Earlier age at surgical menopause was associated with a steeper slope of global cognitive decline; each year of earlier surgical menopause was equivalent to an effect associated with 6 months of aging.
2. The cognitive domains that were more significantly affected were episodic and semantic memory.
3. Earlier age at surgical menopause was associated with a higher burden of the global measure of Alzheimer's disease neuropathology, the strongest association being with neuritic amyloid plaques.
4. There was no significant association between age at natural menopause and any clinical or neuropathologic outcome.
5. In surgically menopausal women initiating HT within 5 years of menopause and using it for at least 10 years, a decreased slope of decline in global cognition was recorded.
6. Contrarily, when HT was initiated beyond 5 years from surgical menopause, there was no association between duration of HT use and any cognitive outcome.
7. There was no association of HT with Alzheimer's disease neuropathology, suggesting either that the study was underpowered to assess such effects, or that HT's protective effects may occur independently of neuropathologic changes.

Data on prevention of postmenopausal cognitive decline by HT are controversial, even when therapy is initiated in proximity to the beginning of menopause. Maki and colleagues reported on some beneficial effects of HT in a very small cohort [9]. Using the sophisticated method of functional magnetic resonance imaging, the investigators examined patterns of brain activation in the medial temporal lobe during verbal encoding and recognition of words. Study conclusions were that perimenopausal use of HT might confer long-term benefits to verbal memory and the brain systems underlying verbal memory. The much larger, observational French Three City study found that current HT users performed significantly better than never-users on the tasks of verbal fluency, visual memory, and psychomotor speed; however, there was no significant association with global function, verbal memory, or executive function [10]. The authors also commented that there was no evidence that HT needs to be initiated close to the menopause in order to have a beneficial effect on cognitive function in later life. These results were not in line with the Kaiser Permanente database, which pointed at a 26% reduction in risk for dementia when HT...
was taken only in the early phase of menopause (mean age 49 years), whereas women who took HT only in older age (mean 76 years) demonstrated a 48% increased risk for dementia [11]. Thus the 'window of opportunity' theory for HT with regard to neuroprotection has not been supported enough by hard, high-quality clinical data. Perhaps the most relevant remarks were made by the US Preventive Services Task Force after a thorough review of the available clinical materials: ‘In women with menopausal symptoms, HT may have specific cognitive effects, and future studies should target these effects.’ The meta-analysis found a decreased risk of dementia in HT users but most studies had important methodological limitations [12].

Should women with surgical menopause be regarded as a specific clinical subset when discussing menopause-associated cognitive impairment? The few longitudinal studies which have examined the corresponding data (being a model for an acute, permanent decrease in circulating estrogen level, occurring in a relative younger age) pointed at some detrimental neurological consequences of castration on the one hand, and highlighted the potential benefits of HT when started early and taken on a long-term basis, on the other hand.

**Take-home message**

- Among the most frequent problems of aging is cognitive decline, which may be associated with the estrogenic milieu.
- The WHIMS study raised the issue of potential cognitive adverse effects of postmenopausal hormone therapy, but this is likely to be relevant only to older women.
- Surgical menopause, which is characterized by an abrupt decrease in circulating estrogen levels in relatively young women, correlates with a faster decline in certain cognitive domains, whereas early start of postmenopausal hormone therapy seems to have protective effects in this respect.

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