ORIGINAL RESEARCH

Younger age of menopause in women with cerebral aneurysms

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ABSTRACT

Background The incidence of subarachnoid hemorrhage in women surges following menopause. Estrogen fluctuations have been implicated in cerebral aneurysm formation, growth and rupture and are thought to explain the well-known gender disparity. The aim of this study was to examine the association between age at menopause, which can determine lifetime estrogen exposure, and the presence of cerebral aneurysms.

Methods A retrospective case-control study was conducted by interviewing postmenopausal women with intradural cerebral aneurysms about their basic medical and gynecologic histories. This information was compared with the same data points collected from 4682 women contacted through random digit phone dialing in the National Institute of Child Health and Human Development-sponsored Contraceptive and Reproductive Experiences Study published in 2002.

Results Among 76 consecutive postmenopausal women with cerebral aneurysms who were treated by a single physician and interviewed, multivariate logistic regression showed that later menopause age (OR 0.79, CI 0.63 to 0.996, p=0.046) was significantly associated with a lower aneurysm incidence. Premature menopause (<40 years) was seen in 26% of cases and 19% of controls (p=0.15). Each categorical increase in menopause age (<40, 40–44, 45–49, 50–54, ≥55 years) decreased the likelihood by 21%. Despite a trend towards earlier mean age at menopause in the case group, the difference was not statistically significant.

Conclusion There is a trend showing that an earlier age at menopause is associated with the presence of a cerebral aneurysm. This suggests that loss of estrogen earlier in a woman's life may contribute to the pathogenesis of cerebral aneurysm. These data may identify a risk factor for cerebral aneurysm pathogenesis and also a potential target for future therapies.

BACKGROUND

Over the last 20 years the public health impact of subarachnoid hemorrhage (SAH) has remained largely unchanged despite increasing detection and treatment of unruptured and often incidentally discovered cerebral aneurysms.[1] Mortality rates for ruptured cerebral aneurysms continue to average near 50%, with 10% of patients dying before ever reaching the hospital and approximately 20% sustaining severe disability.[2]

For any meaningful decrease in the incidence and prognosis of SAH, we must re-evaluate our understanding of the pathogenesis of cerebral aneurysms. Unlike all other causes of stroke, SAH occurs more often in women (2:1), peaking in the 4–6th decades with an estimated frequency of 6–8 per 100 000 people.[3] The putative role of estrogen in these epidemiologic findings is further supported by the finding that hormone replacement therapy (HRT) seems to reduce the risk of SAH in postmenopausal women, possibly via the effects of estrogen on blood vessel walls, inflammation and homeostasis of the vascular wall matrix.[4]

Additionally, the age at which a woman reaches menopause may play a role in determining subsequent morbidity and mortality.[5] Women who experience earlier menopause have been shown to be at an increased risk for osteoporosis, neurological disease and cardiovascular disease, as well as higher rates of all-cause mortality.[6] In the North American population, the average age of menopause is between 50 and 52, whereas premature ovarian failure (POF) occurs before the age of 40 and early menopause before the age of 45.[7] For many women, except in iatrogenic cases (ie, surgically induced via oophorectomy and/or hysterectomy or due to chemical or radiation therapy), the etiology of POF and early menopause is unknown. However, factors that have been identified to trigger early menopause include genetics, gonadotropin-resistant ovary syndrome, autoimmune disorders and smoking tobacco.[7]

The aim of this study was to examine whether any association exists between age of menopause and the presence of cerebral aneurysms. Such an association would further support a central role for estrogen in cerebral aneurysm rupture and also in the pathogenesis. Because of the inherent difficulties in testing the effects of estrogen in women with cerebral aneurysms, particularly those with unruptured aneurysms, we sought to define its role in a way that circumvented the need to administer an unproven agent. To accomplish this, we compared the ages of menopause in a group of women diagnosed with cerebral aneurysms against the ages of menopause of a large sample of women in the general public.

METHODS

We conducted a case-control study of patients under the care of a single physician (MC) with at least one intradural saccular aneurysm >3 mm in maximal diameter not due to an arteriovenous malformation, trauma, dissection or infection. From this sample of patients, only postmenopausal women were selected to be part of this study. The women were then interviewed by trained personnel using scripted questions. In cases where patients

were not interviewed, the reason was noted (eg, inability to locate patient, refusal to participate, mental impairment due to stroke or other health complication, or patient death). A reliable proxy was interviewed when available for patients who had died and for those who were mentally impaired.

Data for our control group were obtained from the National Institute of Child Health and Human Development-sponsored Contraceptive and Reproductive Experiences Study (CARES), which sought to examine whether any link existed between oral contraceptive pill (OCP) and HRT usage and the risk of developing breast cancer. Between 1994 and 1998, 4682 women from Atlanta, Detroit, Los Angeles, Philadelphia and Seattle were randomly selected for telephone interviews conducted by trained and supervised interviewers. A standardized questionnaire was used to elicit detailed information about the participants' OCP and HRT use; family, reproductive, exercise and health histories; as well as demographic information.[8]

We designed our case data collection around this CARES questionnaire so that more accurate comparisons could be made between the two groups. Data from patients in the case group included age, race, education level, menopausal status/age at menopause, past medical history, family history and alcohol and tobacco history. Age at menopause was then subdivided into premature menopause (defined as occurring at <40 years), early menopause (41–44 years), normal menopause (45–55 years) and late menopause (>56 years).

As part of their past medical history, patients were asked to indicate whether they had ever been diagnosed with hypertension, diabetes mellitus, high cholesterol or hypothyroidism; whether the aforementioned conditions were controlled; and the duration of each condition. Patients' smoking history was categorized as 'stopped' or 'current' cigarette smoking and the number of pack years was calculated for both current and past smokers. Alcohol usage was likewise categorized as 'stopped' or 'current'; the total number of alcohol years was also noted. Body mass index (BMI) was calculated from patients' height and weight.

Patients were asked to provide the following information about their obstetric history: age at menarche, gravidity, parity or nulliparity, age at first birth, age at menopause, use of HRT and OCP including types and duration and whether they had ever undergone tubal ligation, oophorectomy or hysterectomy plus indications for these procedures.

The case group data were matched with that of the control group for age (in categories of <45, 45–54 and >54 years) and education level (≤12th grade, >12th grade). The χ^2 test was used to determine differences between the case and control groups for categorical values, while continuous values were examined with the Student t test. Univariate regression analysis was performed to determine the association of cerebral aneurysm with BMI, current smoking, current alcohol consumption, nulliparity, number of pregnancies ≥3, HRT use, hysterectomy and early menopause age. Menopause age (in categories of <40, 40–44, 45–54, ≥55 years) and variables with a p value <0.15 were included (except for the variable of age at first live birth) in the subsequent multivariate logistic regression.

RESULTS

Between 2007 and 2011, 151 patients with cerebral aneurysms were under the care of a single physician of which 76 were postmenopausal women. Table 1 presents the health and reproductive profiles as well as selected cardiovascular risk factors of the two groups matched for age and education level.

Table 1 Demographic and clinical profiles of cases and controls matched for age and educational level

Variable	Cases (n=76)	Controls (n=532)	p Value
Age			
Mean (SD)	60.6 (10.8)	58.9 (7.7)	0.19
Median	59.5	59.5	
BMI			
Mean (SD)	27.8 (7)	27.4 (7)	0.64
Median	27.1	26.7	
Current smoker			
n (%)	27 (35.5%)	139 (26.1%)	0.09
Menarche age			
Mean (SD)	12.6 (1.5)	12.9 (1.8)	0.17
Median	13	12.9	
Nulliparous (Yes)			
n (%)	7 (9.2%)	79 (14.9%)	0.19
Number of pregnancies (≥3)			
n (%)	49 (64.5%)	314 (59%)	0.36
Age at first live birth			
Mean (SD)	19.3 (7.8)	21.5 (5.7)	0.03
Median	20	22	
Age at first live birth ≥30			
n (%)	4 (5.7%)	31 (6.8%)	0.73
Menopause age			
Mean (SD)	44.3 (8.3)	44.7 (8.2)	0.69
Median	45.5	47	
n (%)			
<40	20 (26.3%)	102 (19.2%)	0.3
40–44	13 (17.1%)	94 (17.7%)	
45–49	21 (27.6%)	172 (32.3%)	
50–54	15 (19.7%)	136 (25.6%)	
≥55	7 (9.2%)	28 (5.3%)	
n (%)			
<40	20 (26.3%)	102 (19.2%)	0.15
Pack years			
Mean (SD)	21.5 (21.1)	16.1 (21.5)	0.04
Median	15	3.4	
Hysterectomy			
n (%)	29 (38.2%)	214 (40.2%)	0.73
HRT			
n (%)	21 (27.6%)	313 (58.8%)	<0.0001
Current drinker			
n (%)	16 (21.1%)	175 (32.9%)	0.04

HRT, hormone replacement therapy.

Compared with the control group, the case group showed no statistically significant difference in age, BMI, menarche age, mean age at menopause and percentage of women who had undergone a hysterectomy. The case group showed an increased trend towards premature menopause, although again this difference was not statistically significant (p=0.15). In contrast, factors that did demonstrate a statistically significant difference between the two study groups included younger mean age at first live birth (p=0.03), lower percentage of current drinkers (p=0.04), greater mean number of pack years (p=0.04) and lower percentage of patients who had ever used HRT (p<0.0001) in the case group.

From this information, adjusted ORs were calculated with multivariate logistic regression analysis for the presence of cerebral aneurysms and menopause age, ever usage of HRT, number of pack years, current drinking and current smoking (table 2).

Both later menopause age (OR 0.79, CI 0.63 to 0.996, p=0.046) and ever use of HRT (OR 0.23, CI 0.13 to 0.42, p<0.0001) were significantly associated with a lower risk of

Table 2 Multivariate logistic regression analysis

Variable	OR (95% CI)	p Value
Menopause age	0.79 (0.63 to 0.996)	0.046
HRT (yes vs no)	0.23 (0.13 to 0.42)	<0.0001
Pack years	1.2 (1.08 to 1.33)	0.001
Current drinker (yes vs no)	0.55 (0.3 to 1.01)	0.056
Current smoker (yes vs no)	0.75 (0.39 to 1.43)	0.38

HRT, hormone replacement therapy.

aneurysm in women in the case group. For each categorical increase in menopause age, the risk of cerebral aneurysm decreased by 21%. Interestingly, although fewer pack years (OR 1.2, CI 1.08 to 1.33, p=0.001) demonstrated a slight protective effect against the risk of developing cerebral aneurysms, we did not find any association between current smoking status and the risk of cerebral aneurysm in our patients (OR 0.75, CI 0.39 to 1.43, p=0.38). However, current drinking was of borderline significance (OR 0.55, CI 0.3 to 1.01, p=0.056).

DISCUSSION

In this case-control study we found a significant association between early menopause and the presence of a cerebral aneurysm. Despite showing a similar overall mean age at menopause, a greater proportion of women in the case group showed a trend toward early menopause compared with the control group. This suggests that loss of estrogen earlier in a woman's life may contribute to the pathogenesis of cerebral aneurysm. In contrast, the use of HRT, which maintains near physiologic levels of estrogen, may protect against this.

Numerous studies have demonstrated a similarly salient impact of menopause on gender disparities in vascular disease. Regardless of age at menopause, postmenopausal women appear to be at increased risk of developing cardiovascular disease compared with age-matched men and premenopausal women.[9 10] In fact, by the time women reach age 60–64 they will have a comparable rate of cardiovascular disease per year to that of men aged 50–54 (18.1/1000 vs 16.5/1000).[11] This surge in prevalence is alarming because, before the age of 60, men are more than twice as likely as women to develop cardiovascular disease (27.5% vs 10.1%) despite having similar cardiovascular risk factor profiles.[12]

In comparing the total incidence of cardiovascular disease between premenopausal and postmenopausal women under the age of 55 years, the Framingham Heart Study found that postmenopausal women were twice as likely to develop new cardiovascular disease.[9] Furthermore, the same study demonstrated that women who had gone through menopause before the age of 42 showed a higher risk of stroke than those with menopause after the age of 42. Women in this early menopause group also showed double the stroke risk compared with all other women. These data remained consistent even among women who had never smoked and women who had never used HRT.[9] Consequently, the loss of estrogen that occurs at menopause has been cited as a central contributing factor to this increase in risk for postmenopausal women, a risk which is further exacerbated by early timing of the menopause.

Rivera *et al* found that, of the total group of women who had undergone bilateral oophorectomy, only those who had the procedure before age 45 years showed an increase in risk of mortality from cerebrovascular disease compared with referent women of the same age. However, the association did not reach statistical significance.[12] The Nurse's Health Study supported these results and also found a statistically significant increase of 149% in the risk of all types of stroke, including SAH, in women who had undergone hysterectomy with bilateral oophorectomy before the age of 50 without subsequent HRT.[13] Moreover, in a study of postmenopausal women, those who had undergone menopause before the age of 40 had a 56% increased risk of all types of stroke compared with women with a normal age at menopause. These results did not vary after adjustment for age and conventional cardiovascular risk factors.[14] However, the association between early menopause and risk of cerebrovascular disease still remains unproven and other studies have suggested that reproductive and hormonal factors other than age at menopause may be involved.[15–18]

In animal studies, Jamous *et al* sought to elucidate the role of estrogen in cerebrovascular homeostasis and aneurysm formation by comparing rats that had undergone bilateral oophorectomy with those that had not. Despite inducing cerebral aneurysms in all experimental rats, the incidence of cerebral aneurysm formation in oophorectomized rats was found to be three times higher than in rats with intact ovaries. The researchers subsequently concluded that estrogen plays a protective role in the pathogenesis of cerebral aneurysms.[19]

The relationship between estrogen and ruptured cerebral aneurysms has also been the focus of a number of human studies. Longstreth *et al* found a significantly reduced risk of SAH in premenopausal women (OR=0.24) compared with age-matched postmenopausal women. Postmenopausal women with ever use of HRT also showed a reduced risk (OR=0.47) compared with postmenopausal women who had never used HRT.[17] Both female sex and the postmenopausal state were found to be significantly associated with the development of multiple intracranial aneurysms in patients as opposed to single aneurysms.[20] Furthermore, the predominance of women in the 50–59 year age group in the total aneurysm population (60.2%), and in particular among patients with internal carotid aneurysms, led Stober *et al* to implicate loss of estrogen in the pathogenesis of cerebral aneurysms.[14]

Biochemical and molecular studies have further supported this hypothesized association. Estrogen has been shown to scavenge reactive oxygen species such as oxidized LDL following endothelial injury and also to inhibit their formation.[21–24] Ling *et al* found that, in mice deficient in endogenous estrogen (via aromatase knockout), there was both decreased vascular smooth muscle proliferation and increased apoptosis.[25] These findings are consistent with the vascular pathology observed in cerebral aneurysms.[26] Additionally, the observed abnormalities were corrected once exogenous estrogen was administered.[27]

Tightly regulated proteolytic degradation of the extracellular matrix is an important component of normal vascular homeostasis but, if poorly controlled, it may contribute to the pathogenesis of cerebral aneurysms.[28] Of particular interest is matrix metalloproteinase-2 (MMP-2) which degrades type IV collagen and has been found to be elevated both in the serum of patients with cerebral aneurysms[29] and within aneurysmal vessel wall tissue. While this may appear to directly contradict the aforementioned protective role of estrogen in maintaining vascular wall integrity, many regulatory mechanisms exist that explain and further support the advantage of premenopausal women that is seen both clinically and in the laboratory.

Study limitations

An important limitation of this study is that age at menopause was based on patient self-report or report by a reliable proxy. Data regarding the validity and reliability of self-reported ages

of menopause are scarce and variable. Colditz *et al* found that reproducibility to within 1 year was 82–95%.[30] However, a more recent Swedish study found that the accuracy of reported menopause ages decreased 1 year after menopause, with a trend toward reporting ages approaching the mean.[31] As menopause age was not available to be verified in the majority of patient records, this may have resulted in misclassification of exposures.

In an attempt to account for any potential baseline differences between our study groups, we controlled for age and educational level. We were unable to match the case group with the control group for race and for a number of significant cardiovascular risk factors including diagnosis of diabetes mellitus, hypertension and hyperlipidemia because they did not exist as part of the control data. The incidences of diabetes mellitus, hypertension and hyperlipidemia appear to be increased in postmenopausal women compared with premenopausal women of the same age, implicating the loss of the protective effect of estrogen as a possible explanation in the pathogenesis of these conditions. Nevertheless, without matching for these factors, it is difficult to determine with a high degree of certainty that the increased risk of cerebral aneurysm in women who had undergone early menopause was predominantly due to the early loss of estrogen rather than to a higher prevalence of other pre-existing cardiovascular risk factors in our case group. However, a number of recent studies have shown that women's risk of ischemic stroke increases significantly after both natural and induced menopause prior to the age of 45 years, even after adjusting for confounding cardiovascular risk factors including history of diabetes, high blood pressure, hypercholesterolemia, smoking, alcohol consumption, physical exercise, BMI and use of aspirin.[15 18]

Additionally, although a history of chemotherapy and/or radiation therapy contributes to the development of POF in some women,[6] this variable was not included in our tables or calculations as only one patient in our case group had undergone such treatment.

It is important to mention that the marked disparity in the prevalence of HRT usage between the two study groups can be attributed to the significant decline in prescriptions of HRT following the publication of the results of the 2002 Women's Health Initiative (WHI) study.[32] The study followed 16 608 postmenopausal women who were randomly assigned to receive either estrogen plus progestin or a placebo to assess the major health benefits and risks associated with HRT usage. After 5.2 years of follow-up, the project was halted because researchers found a statistically significant increase in the risk of developing coronary heart disease, breast cancer, stroke and pulmonary embolism in the intervention group. Because a portion of our case group experienced menopause after the publication of the WHI study and the data for the control group were collected between 1994 and 1998, the case group was therefore subject to this confounding variable whereas the control group was not. However, the impact of this confounding factor may be limited to only 18 (23%) of the 76 cases who underwent menopause after the year 2002. Therefore, the majority (77%) of our cases did in fact undergo menopause prior to 2002, as did all of the controls.

Lastly, using a control group comprising postmenopausal women with normal brain vascular imaging was also considered. However, a potential confounder included the reasons why such women would undergo brain vascular imaging in the first place. Furthermore, it would have been challenging to obtain a sufficient number of controls to then be able to match each case subject for age. Given the large, robust and validated data available from the CARES study which allowed us to match seven controls representative of the general population for every case, the shortcomings of the roughly 5% of controls who may harbor cerebral aneurysms along with the confounding effects from the WHI study, affecting a minority of our cases, seemed acceptable.

CONCLUSION

The results of our study provide further support for the role of estrogen in the development of cerebral aneurysms. The lower cumulative lifetime dose of endogenous estrogen that is associated with early menopause has been shown in numerous previous reports to be associated with compromised vascular homeostasis. Because our results include mostly unruptured aneurysms, estrogen may be contributing not just to rupture, as has been previously published, but also aneurysm formation and growth as well.

This has a number of important clinical implications. First, this study provides additional insight into the pathogenesis of cerebral aneurysms. Second, it may contribute to the development of alternative treatments, particularly non-surgical treatments for cerebral aneurysms. Current non-surgical medical therapy for unruptured cerebral aneurysms consists largely of smoking cessation and management of hypertension. Surgical interventions including aneurysm clipping, coiling, flow diversion—while able to reduce the risk of rupture in many cases—ultimately fail to address the underlying pathophysiology that leads to cerebral aneurysm formation. The findings of this study suggest preventive medical management strategies for high-risk patients.

Growing evidence from randomized trials and observational studies has suggested the importance of the 'timing hypothesis' when determining whether HRT will be beneficial in postmenopausal women[33]—that is, the hypothesis that HRT may prove to be beneficial if initiated in the perimenopausal period or shortly after menopause but may pose an extra cardiovascular risk the longer the period of time that has passed since menopause. The implications of this hypothesis, along with the results of our study, may prove to be important additional factors to take into consideration for women who undergo early menopause and who may be considering HRT.

Contributors CD and MC designed the study, collected data and wrote the manuscript. VT collected data. BO provided statistical analysis.

Competing interests None.

Patient consent Obtained.

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