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VALVULAR AND STRUCTURAL HEART DISEASES

Original Studies

Association of Ischemic Stroke, Hormone Therapy, and Right to Left Shunt in Postmenopausal Women

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Background: Postmenopausal hormone therapy (HT) increases the risk of venous thrombosis and ischemic stroke. Objectives: We postulated that HT might increase the risk of ischemic stroke by promoting venous clots that travel to the brain through a right to left shunt (RLS). Methods: A total of 2,389 records were studied. After eliminating the premenopausal patients, and those with TIAs and non-ischemic strokes, the medical records of 1846 postmenopausal women hospitalized at four institutions for ischemic stroke were reviewed to identify those who had undergone an adequate study to assess for RLS. The proportion of women with a shunt in users and non-users of HT was compared in stroke patients and in a reference population consisting of postmenopausal women undergoing elective cardiac catheterization. Results: There were 363 (20%) records that had complete data and were included in the analysis. A shunt was more prevalent in patients with a cryptogenic stroke than in patients with a stroke of known cause (55/88 (63%) vs. 53/275 (19%), $P < 0.001$). In patients with a stroke of known cause, the frequency of a shunt was similar to that in reference women 31/136 (23%), and the proportion of women with a shunt was similar in non-users and current users of HT (14% vs. 20%, $P = 0.40$). However, among patients with a cryptogenic stroke, the prevalence of a shunt was 1.5 times higher in current users than non-users of HT (82% vs. 56%, $P = 0.04$). Conclusions: Approximately 23% of older women have a RLS. HT in these women may increase the risk of ischemic stroke by promoting paradoxical embolism. © 2014 Wiley Periodicals, Inc.

Key words: cryptogenic stroke; hormone therapy; patent foramen ovale

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INTRODUCTION

Hormone therapy (HT) has been associated with an increased risk of ischemic stroke [1,2] and venous thromboembolism [3]. Approximately 40% of ischemic strokes are classified as cryptogenic because the etiology of the stroke cannot be identified after an evaluation which historically has not included a study for a right to left shunt (RLS) [4]. It also has been shown that up to 50% of cryptogenic stroke patients have a RLS [5–7] most commonly due to patent foramen ovale (PFO) [8]. We hypothesized that paradoxical embolism of a venous clot could help explain how HT increases the risk of ischemic stroke. To address this question, we reviewed stroke databases from four geographically separated institutions and determined whether a RLS was more common in women with an ischemic stroke who were on HT compared to those who were not on HT. For comparison, the frequency of a RLS was determined in a group of postmenopausal outpatient women undergoing elective cardiac catheterization.

METHODS

Study Population

Cases were drawn from the databases of patients hospitalized with stroke at four medical centers: University of California Los Angeles (1993–2008), Scripps Mercy Hospital in San Diego, California (2002–2008), Mayo Clinic in Scottsdale, Arizona (2002–2008), and Tufts University in Boston, Massachusetts (1998–2008). Each database was prospectively maintained and a neurologist did data entry. The institutional review board of all institutions approved the study. For a case to be eligible for study inclusion, women had to be postmenopausal, have medications documented upon admission, and have undergone an adequate study for a RLS. A positive shunt study was defined as a positive agitated saline contrast study done by transcranial Doppler (TCD), transesophageal echocardiogram, or transthoracic echocardiogram. Because of the high false negative rate of the latter [9], patients whose study was negative were not included because they could not be classified accurately as RLS negative. Strokes were categorized according to the TOAST criteria [10] and then divided into those of known and cryptogenic cause. Charts were abstracted for information on demographic variables, vital status, and stroke risk factors [11] and then de-identified. Current use of HT was defined as use of systemic therapy of estrogen with or without a progestin at the time of the index stroke or within the preceding three months (users of topical vaginal estrogen were excluded).

To determine the frequency of a RLS in postmenopausal women not hospitalized with an acute stroke, a reference population of women was drawn from a convenience sample of outpatients undergoing elective diagnostic cardiac catheterization at the University of California, Los Angeles (2009–2011). After informed consent, a TCD was performed according to a published protocol [12].

Statistical Analysis

Descriptive statistics: Mean, standard deviation, and frequency distributions were generated to characterize the study population. We used a two-sample *t*-test to compare continuous variables and Pearson's chi-squared test or Fisher's exact test to compare categorical variables.

Analytic statistics: A case-only analysis was carried out to evaluate the interaction effect of a RLS and HT on the risk of stroke. The case-only study design cannot evaluate the main effect of either HT or RLS on the risk of stroke, but can evaluate an interaction between them if independence between a RLS and HT is assumed [13], a reasonable assumption since the existence of a RLS would have been unknown to the prescribing physician. Because an interaction between a RLS and HT may be different in patients with known versus cryptogenic causes of stroke, analyses were carried out separately for these two subsets.

Statistics were calculated on Statistical Package for the Social Sciences version 20 (SPSS, IBM Inc, Chicago IL). All *P* values are two-sided.

RESULTS

Cases From Institutional Stroke Databases

Between the four institutions there were 2,389 cases of women in the stroke databases available for review (Supporting Information Fig. e-1); 2,051 (86%) were postmenopausal and 1,846 had experienced an ischemic stroke. The most common reason for exclusion from the study was absence of adequate shunt data (79%) with the remainder due to lack of information on use of HT. Absence of shunt data was usually because no shunt study had been done (43% and 42% of patients with a stroke of known and cryptogenic cause, respectively). Of 845 transthoracic echocardiograms, 609 (72%) were excluded because a bubble study had not been performed. Of the remaining 236 transthoracic echocardiograms, 89% were negative and therefore excluded because they were considered uninformative. Of the final 363 cases with complete data on RLS and HT use, 275 (76%) had an ischemic stroke of known cause and 88 (24%) had a cryptogenic stroke.

TABLE I. Clinical Characteristics of Patients by Type of Stroke and Use of Hormone Therapy

Variable	All hospitalized stroke cases ($n=363$)	Reference women ($n=136$)[a]	P value[b]	Stroke of known cause ($n=275$)	Cryptogenic stroke ($n=88$)	P value[c]	Stroke cases hormone non-users ($n=297$)	Stroke cases hormone users ($n=66$)	P value[d]
Age, mean ± SD	72.9 ± 10.3	64.3 ± 11.9	<0.001	73.9 ± 9.9	69.8 ± 10.8	0.001	73.7 ± 10.1	69.4 ± 10.5	0.002
Years postmenopausal, mean ± SD	18.9 ± 9.9	10.2 ± 7.7	<0.001	19.9 ± 9.7	15.9 ± 10.1	0.001	19.2 ± 9.8	17.7 ± 10.5	0.27
Race, no. (%)[e]									
African American	20 (5%)	4 (3%)		17 (6%)	3 (3%)		16 (5%)	4 (6%)	
Asian	28 (8%)	12 (9%)		24 (9%)	4 (5%)		26 (9%)	2 (3%)	
Caucasian	276 (76%)	106 (78%)	0.75	206 (75%)	70 (80%)	0.24	222 (75%)	54 (82%)	0.43
Hispanic	34 (9%)	13 (10%)		23 (8%)	11 (12%)		28 (9%)	6 (9%)	
Other, unknown	5(1%)	1 (1%)		5 (2%)	0 (0%)		5 (2%)	0 (0%)	
Body mass index, mean ± SD (kg/m^2)	26.6 ± 5.9	27.1± 6.7	0.42	26.6 ± 6.2	26.9 ± 4.7	0.77	26.9 ± 6.2	25.4 ± 4.5	0.15
Hyperlipidemia, no. (%)	210 (58%)	83 (61%)	0.54	159 (58%)	51 (58%)	>0.99	177 (60%)	33 (50%)	0.17
Diabetes, no. (%)	93 (26%)	20 (15%)	0.01	82 (30%)	11 (13%)	0.001	83 (28%)	10 (15%)	0.04
Hypertension, no. (%)	293 (81%)	75 (55%)	<0.001	231 (84%)	62 (70%)	0.008	247 (83%)	46 (70%)	0.02
Smoking, no. (%)	84 (23%)	6 (4%)	<0.001	58 (21%)	26 (30%)	0.11	67 (23%)	17 (26%)	0.63
Atrial fibrillation, no. (%)	95 (26%)	16 (12%)	<0.001	95 (35%)	0 (0%)	<0.001	85 (29%)	10 (15%)	0.03
RLS shunt, no. (%)	108 (30%)	31 (23%)	0.14	53 (19%)	55 (63%)	<0.001	84 (28%)	24 (36%)	0.23
Hormone therapy use, no. (%)	66 (18%)	16 (12%)	0.10	44 (16%)	22 (25%)	0.08	0 (0%)	66 (100%)	<0.001
Prior hysterectomy, N (%)	38 (10%)	18 (13%)	0.43	27 (10%)	11 (12%)	0.54	23 (8%)	15(23%)	0.001
Stroke etiology, no.[e] (%)									
Cardioembolic	108 (30%)	–	–	108 (39%)	0 (0%)		94 (32%)	14 (21%)	
Large artery	102 (28%)	–	–	102 (37%)	0 (0%)		81 (27%)	21 (32%)	
Small vessel	41 (11%)	–	–	41 (15%)	0 (0%)	<0.001	36 (12%)	5 (8%)	0.03
Other cause	6 (2%)	–	–	6 (2%)	0 (0%)		3 (1%)	3 (4%)	
Cryptogenic	88 (24%)	–	–	0 (0%)	88 (100%)		66 (22%)	22 (33%)	
>1 cause	18 (5%)	–	–	18 (7%)	0 (0%)		17 (6%)	1 (1%)	
Previous stroke, no. (%)	52 (14%)	15 (11%)	0.38	43 (16%)	9(10%)	0.23	42 (14%)	10 (15%)	0.85
Death within 1st year post stroke, no. (%)	73 (20%)	–	–	47 (17%)	26(30%)	0.01	63 (21%)	10 (15%)	0.31
Coronary artery disease, no. (%)	59 (16%)	75 (80%)[f]	<0.001	46 (17%)	13 (15%)	0.74	44 (15%)	15 (23%)	0.14
Venous thromboembolism, no. (%)	43 (12%)	10 (7%)	0.19	23 (8%)	20 (23%)	<0.001	36 (12%)	7 (11%)	0.84
Hypercoagulable state[g], no. (%)	70 (19%)	23 (17%)	0.61	37 (13%)	33 (38%)	<0.001	54 (18%)	16 (24%)	0.30
History of cancer, no. (%)	71 (20%)	15 (11%)	0.02	44 (16%)	27 (31%)	0.005	57 (19%)	14 (21%)	0.73
Autoimmune state, no. (%)	33 (9%)	8 (6%)	0.28	28 (10%)	5 (6%)	0.29	25 (8%)	8 (12%)	0.35
Migraine headache, no. (%)	45 (12%)	19 (14%)	0.65	30 (11 %)	15 (17%)	0.14	30 (10%)	15 (23%)	0.01

[a]Women undergoing elective cardiac catheterization.
[b]Differences between all hospitalized women with strokes from databases and reference women.
[c]Differences between women with stroke of known cause and cryptogenic stroke.
[d]Differences between all stroke cases who were hormone users and hormone non-users.
[e]In some subsets, percentages do not add up to 100 because of rounding.
[f]Based on the 94 patients who underwent coronary angiography during catheterization.
[g]Antiphospholipid antibody (AB), Homocysteinemia, Malignancy, elevated lipoprotein (a), Anticardiolipin AB, Elevated Factor VIII, B - 2 glycoprotein 1 AB, Thrombocytosis, Iatrogenic, Factor V Leiden, Prothrombin G-20210 mutation, Protein C deficiency, Protein S deficiency, Antithrombin 3 deficiency, Unknown.

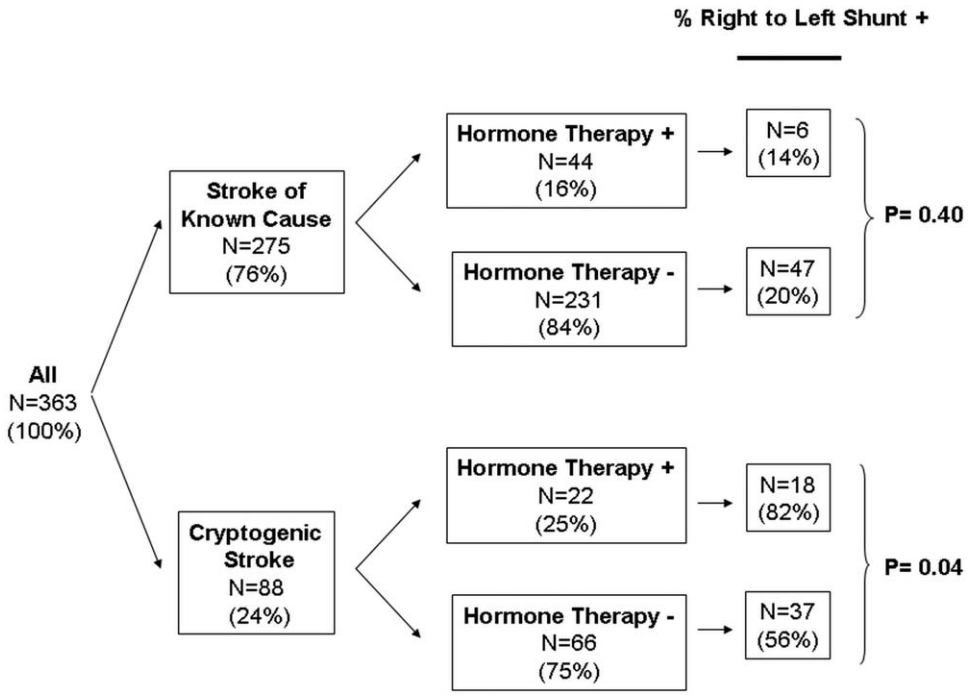

Fig. 1. Prevalence of a RLS by type of stroke and use of HT.

The clinical characteristics of all patients by stroke type and HT use are shown in Table I. The mean age was 72.9 years and 76% were Caucasian (range 62–95% depending on the institution). Systemic HT was used in 16% and 25% of patients with a stroke of known cause and cryptogenic stroke, respectively. The most common form of estrogen used was oral conjugated estrogens ≥ 0.625 mg.

A RLS was 3.3 times more common in postmenopausal women with a cryptogenic stroke than in women with a stroke of known cause (63% vs. 19%, $P < 0.001$). The frequency of a RLS in patients with a stroke of known cause was similar to that reported in the general population [14] and in this study's postmenopausal women undergoing elective cardiac catheterization (23%).

Figure 1 shows the proportion of study women who were found to have a RLS according to type of stroke and current use of HT. Among patients with a stroke of known cause, the proportion of patients with a RLS was similar in HT users and non-users (14% vs. 20%, $P = 0.40$). In contrast, among patients with a cryptogenic stroke, the proportion of patients found to have a RLS was higher in hormone users compared to non-users (82% vs. 56%, $P = 0.04$) for a prevalence rate ratio of 1.5. All women who were using systemic HT were on oral preparations.

Because the 52 women with a prior history of stroke might have been less likely to have been treated with HT, we repeated the analysis after excluding them. As before, the proportion of women with a RLS was similar between current users and non-users of HT in women with a stroke of known cause (13% vs. 19%, $P = 0.49$), while for women with cryptogenic strokes, more users of HT had a shunt than non-users (79% vs. 53%, $P = 0.06$).

We analyzed the data from each institution separately (Table II) as well as in aggregate. The results at the three institutions that contributed the most patients all showed a trend toward a greater frequency of a RLS in hormone users.

Reference Group: Women Undergoing Elective Cardiac Catheterization

The clinical characteristics of women undergoing elective cardiac catheterization are shown in Table I. Eleven percent had a prior stroke, a prevalence which is similar to the 8.2% prevalence of strokes found in the general female population age 60–79 [15]. Of the 94 patients who had coronary angiograms, 80% had significant coronary artery disease (defined as an obstruction $> 50\%$ in at least one artery).

The proportion of reference women with a RLS was 23% (24% if those with a prior stroke were excluded) with no consistent trend with age (P for trend $= 0.85$) whether those with prior strokes were included or not (Table III). This frequency is comparable to that found

TABLE II. Proportion of Patients with a Right to Left Shunt by Use of Hormone Therapy at Each Institution

	Total strokes, *n*	Total number of strokes with right to left shunt *n/n* (%)	Number of strokes with right to left shunt hormone users *n/n* (%)	Number of strokes with right to left shunt hormone non-users *n/n* (%)	*P* value[a]
Known stroke					
UCLA, CA	99	18/99 (18)	2/19 (11)	16/80 (20)	0.5
Mayo Clinic, AZ	101	21/97 (21)	2/16 (13)	19/81 (23)	0.5
Tufts, MA	66	9/66 (14)	1/8 (13)	8/58 (14)	1
Scripps, CA	13	5/13 (38)	1/1 (100)	4/12 (33)	0.4
Total	275	53/275 (19)	6/44 (14)	47/231 (20)	0.4
Cryptogenic stroke					
UCLA, CA	45	26/45 (58)	10/13 (77)	16/32 (50)	0.2
Mayo Clinic, AZ	23	18/23 (78)	6/7 (86)	12/16 (75)	1
Tufts, MA	16	8/16 (50)	2/2 (100)	6/14 (43)	0.5
Scripps, CA	4	3/4 (75)	0/0 (0)	3/4 (75)	1
Total	88	55/88 (63)	18/22 (82)	37/66 (56)	0.04

[a]Comparison of proportion of right to left shunt in users vs. non-users of hormone therapy.

TABLE III. Frequency of Right to Left Shunt by Age in Reference Patients[a]

Age range (years)	Total patients, *n*	Patients with right to left shunt *n* (%)	*P* value
40–49	25	6 (24)	
50–59	31	5 (16)	
60–69	42	11 (26)	
70–79	22	5 (22)	0.85
80–89	13	3 (23)	
90–99	3	1 (33)	
All	136	31 (23)	

[a]Postmenopausal women undergoing elective cardiac catheterization.

in study women with a stroke of known cause (19%, $P = 0.44$) but significantly less than in study women with cryptogenic strokes (63%, $P < 0.001$).

DISCUSSION

The major finding of this study is that among postmenopausal women with a cryptogenic ischemic stroke, the prevalence of a RLS was 1.5 times more likely in current users than non-users of HT. In contrast, among postmenopausal women with an ischemic stroke of known etiology, the frequency of a RLS was similar in current users and non-users of HT and similar as well to the frequency of a RLS in a reference population of older women.

We found that a RLS was 3.3 times more likely to be present in older postmenopausal women (mean age 70 years) with a cryptogenic stroke compared to patients with a stroke of known etiology. This finding extends to older women prior observations that a RLS may play an important role in the etiology of cryptogenic stroke in younger women [16].

Overall, the study suggests that paradoxical embolism is a potential explanation for how HT might increase the risk of ischemic stroke. This venous based thrombotic mechanism would be compatible with the observation that the risk of both venous thrombosis and ischemic stroke dissipate after discontinuation of HT [17,18] and that, unlike coronary artery disease, the relative risk of ischemic stroke with the use of HT does not increase with age [19]. The mechanism of paradoxical embolism would be in addition to other mechanisms thought to explain how HT causes ischemic stroke, namely by causing thrombosis on an atherosclerotic arterial plaque or within the left atrium of patients in atrial fibrillation.

Several observational studies have led to the general consensus that a paradoxical embolus can cause a stroke [20–23]. Although three recently published randomized controlled trials (CLOSURE I trial [24] which used the STARFlex device and RESPECT [25] and PC [26] trials which used the Amplatzer device) individually failed to find that percutaneous closure of a PFO significantly decreased the rate of events in the closure group by an intention to treat (ITT) analysis, but by a per protocol analysis the RESPECT trial show a 63% reduction in recurrent stroke. In addition, a meta-analysis of the RESPECT and PC Trials shows a statistically significant reduction in recurrent stroke with PFO closure using the Amplatzer PFO device even with an intention to treat analysis [27].

If a RLS enhances the risk of cryptogenic stroke, and, if our hypothesis that HT increases the risk of paradoxical embolism due to increased venous thrombosis is correct, then one would expect HT to increase not just the risk of ischemic stroke generally, but specifically to increase the risk of cryptogenic stroke. In both arms of The Women's Health Initiative, although the distribution of ischemic stroke types according to the TOAST criteria was statistically similar in treated and control subjects [1,2], the category of stroke of

"undetermined origin" showed the largest trend toward an increased risk with HT.

Observational studies have suggested that a modest dose of transdermal estrogen does not appear to increase the risk of venous thrombosis [3] or ischemic stroke [28]. In our study, none of the stroke patients [28] who were using HT were on transdermal preparations.

The clinical impact of the finding that HT appears to modestly increase the risk of cryptogenic stroke depends not only on the relative risk of stroke with HT but also on the absolute risk of ischemic stroke in women with a RLS and the proportion of women using postmenopausal HT. While the absolute risk of ischemic stroke due to a RLS is small [1,2], for the women who suffer this complication the clinical outcome can be devastating. As for the use of HT, at the present time the pendulum of use has swung away from it, but should the pendulum swing back then this small individual risk could translate into a notable population effect. In addition, as our population ages and becomes more obese, the clinical relevance of HT induced ischemic stroke due to paradoxical embolism may become more important because both age [29] and obesity [30] are associated with a substantial increase in the risk of venous thromboembolism.

The recognition that HT may predispose women to ischemic stroke through the mechanism of paradoxical embolism is important because it potentially would be preventable. Women at higher risk for a RLS, for example those with migraine with aura in whom the frequency of PFO is about 50% [31], could be screened for a RLS with a non-invasive test prior to starting therapy and those with a positive test could choose not to take it, especially oral therapy.

A strength of this study is that similar results were found at three separate institutions with different ethnic populations. However, this is an observational study based on a retrospective chart review and thus is only hypothesis-generating. The study could have been subject to many potential biases such as inaccurate recording of HT usage, loss of cases due to fatal stroke, and incomplete capture of RLS data. There were statistical differences in the baseline characteristics of patients with a cryptogenic stroke and an ischemic stroke, and between HT users and non-users. However, these differences would not alter the conclusion because while they could have affected the probability that HT was prescribed, they would not have affected the probability of finding a RLS in those who were or weren't prescribed HT. This is because the use of HT would have been independent of a RLS, the assumption needed for a valid case-only study. In addition, an adequate shunt study was performed only in a minority of cases and so the women included in the study may not have been representative of the entire stroke population from which the cases were drawn. Finally, the number of cases of women with a RLS who were on HT was small. Thus, these results need to be confirmed with a larger database.

SUMMARY

This study provides evidence to support a novel theory on the pathogenesis of HT induced ischemic strokes in postmenopausal women, namely HT in association with a RLS may increase the risk of paradoxical embolism. This hypothesis could be tested in future clinical studies of HT by performing screening studies for a RLS at baseline with a sensitive method, such as a TCD examination.

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