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Gender and hormonal influences in reversible cerebral vasoconstriction syndrome

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Abstract

Introduction: The reversible cerebral vasoconstriction syndromes, including postpartum angiopathy, have been characterized over the last decade. Women are predominantly affected. Some studies suggest that postpartum angiopathy carries a worse prognosis.

Patients and methods: We compared the clinical, neuroimaging, and angiographic features of 36 men, 110 non-pregnant women and 16 postpartum women included in our single-center cohort of patients with reversible cerebral vasoconstriction syndromes encountered from 1998 to 2016.

Results: As compared to men, non-pregnant women were older (48 ± 11 vs. 34 ± 13 years, $p < 0.001$), had more underlying migraine (49% vs. 19%, $p = 0.002$), depression (53% vs. 14%, $p < 0.001$) and serotonergic antidepressant use (45% vs. 11%, $p < 0.001$), developed more clinical worsening (18% vs. 3%, $p = 0.022$), more infarcts (39% vs. 20%, $p = 0.031$) and worse angiographic severity scores (23 ± 14 vs. 10.9 ± 10.3, $p < 0.001$), but had similar discharge outcomes (modified Rankin scale scores 0–3, 90% vs. 91%, $p = 0.768$). Sexual activity was an important trigger in men (22% vs. 4%, $p = 0.002$). As compared to non-pregnant women, postpartum angiopathy patients were younger (33 ± 6 years, $p < 0.001$) and had less vasoconstrictive drug exposure (25% vs. 67%, $p = 0.002$) but showed similar clinical, radiological and angiographic findings and similar discharge outcomes (modified Rankin scale scores 0–3 in 94%, $p = 0.633$). There were no significant differences between pre- and post-menopausal women, or those with and without hysterectomy.

Discussion/Conclusion: The observed gender differences in reversible cerebral vasoconstriction syndromes may result from hormonal or non-hormonal factors. Hormonal imbalances may trigger reversible cerebral vasoconstriction syndromes. Given the absence of significant differences in the female subgroups, hormonal factors do not appear to significantly affect the course or outcome of reversible cerebral vasoconstriction syndromes.

Keywords

Thunderclap headache, headache associated with sexual activity, oestrogen, progesterone, vasoconstriction, stroke, posterior reversible leukoencephalopathy syndrome

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Introduction

The cardinal features of the reversible cerebral vasoconstriction syndromes (RCVS) are reversible angiographic narrowing of multiple medium-sized cerebral arteries, and recurrent sudden-onset severe headaches.[1–6] Some patients develop seizures or focal neurological deficits from ischemic or hemorrhagic strokes. Multiple cohort studies have shown that RCVS predominantly affects women with a female:male ratio ranging from approximately 2:1 to 10:1.[3–7] Postpartum angiopathy (PPA) is a prototype RCVS condition that usually occurs within two weeks after delivery.[8,9] The pathophysiology of RCVS is unknown. An important role for female reproductive hormones is suggested by the higher occurrence in woman, onset soon after childbirth, association with female-preponderant conditions like depression and migraine, and case reports

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suggesting a triggering effect of oral contraceptive pills (OCPs), hormonal treatment and surgical hysterectomy with salpingo-oopherectomy.[10–12] There may be gender differences in phenotype and outcomes. For example, in a prior study of 67 RCVS patients (43 women and 24 men), women were significantly older, had more severe focal deficits and more abnormalities on brain magnetic resonance imaging.[3] Further, PPA may have worse outcome than the other conditions included under the umbrella of RCVS.[13,14]

In this study, we compared the clinical, imaging and angiographic features of men and women with RCVS. For the first time, we compared the features in pregnant vs. non-pregnant women, and explored the role of hormonal influences on RCVS risk and progression.

Methods

We analysed 162 patients with RCVS encountered at Massachusetts General Hospital from 1998 to 2016. The methods for diagnosis and the details of clinical, imaging and angiographic data collection have been previously published.[5] Briefly, the diagnosis was confirmed by documenting vasoconstriction reversibility in 128 patients, and 30 patients had recurrent thunderclap headaches with segmental cerebral artery narrowing and a self-limited clinical course without recurrences, which is typical for RCVS. The final four patients had typical clinical presentations but died from RCVS complications. Two had normal cerebral arteries (no inflammation) on autopsy and two had immediate angiographic resolution upon intra-arterial vasodilator infusion, consistent with RCVS. Demographics, triggers, medical history, neurological deficits, daily clinical events and laboratory results were extracted from medical records as previously described. Given the focus on gender and hormonal influences in this study, we extracted additional data on menopausal status (post-menopausal and pre-/peri-menopausal), oral contraceptive use, use of other oestrogen–progesterone-containing compounds, gynaecological procedures (hysterectomy–oopherectomy). In the subset with PPA, we extracted data on the timing and type of delivery, type of anaesthesia and complications relevant to RCVS (eclampsia; haemolysis, elevated liver enzyme levels and low platelet levels or the HELLP syndrome; and the posterior reversible leukoencephalopathy syndrome or PRES[15]) during current and prior pregnancies.

Clinical worsening was defined as the development of new persistent focal or cognitive deficits, or abrupt worsening of existing deficits. Expected evolution of baseline deficits, recurrent thunderclap headache and transient neurological spells (including seizures) with prompt return to baseline function, were not included. Radiological lesions types were classified as infarction, intracerebral haemorrhage, convexal subarachnoid haemorrhage (cSAH), or vasogenic oedema (i.e. lesions consistent with PRES). Digital subtraction cerebral angiogram (DSA), computed tomography angiogram (CTA) and magnetic resonance angiogram (MRA) were analysed to determine the site of arterial involvement. Vasoconstriction severity scores were derived from analysis of DSA and CTA (but not MRA) as previously described.[5]

Data were analysed using the Chi square, Fisher Exact test, Student t test or Mann-Whitney U test, as appropriate. A value of $p < 0.05$ was considered significant. Data are presented as percentages or mean and standard deviation. SPSS version 21 was used for analyses. The study was approved by our Institutional Human Research Committee.

Results

The overall mean age was 44 ± 13 years. There were 126 (78%) women including 16 (10%) PPA cases. Table 1 shows a comparison of features between men and non-pregnant women, and between non-pregnant women and PPA.

Men were significantly younger than non-pregnant women, none were Hispanic, and they had a significantly higher rate of RCVS associated with sexual activity (Table 1). Non-pregnant women had significantly higher rates of serotonergic antidepressant use, underlying depression and migraine. There were no significant differences in the number of triggers (data not shown). There were no significant differences in baseline features such as thunderclap headache or elevated admission blood pressures. However, non-pregnant women tended to have more focal neurological deficits (43% vs. 25%, $p = 0.058$; mainly hemiparesis/aphasia, 31% versus 17% in men, $p = 0.096$), more clinical worsening (18% vs. 3%, $p = 0.022$), more lesions on baseline as well as follow-up brain imaging and a higher length of stay, suggesting a higher complication rate. On brain imaging (Table 2), non-pregnant women had significantly more infarcts, tended to have more PRES lesions and had over twice the rate of parenchymal haemorrhages (though not statistically significant). There was no difference in the rate of cSAH or sulcal hyperintensities on fluid-attenuated inversion recovery MR images (i.e. the FLAIR dot sign, which reflects slow flow in dilated cortical arteries[16,17]). While most patients had the typical watershed-distribution bilateral hemispheric infarcts, the presence of deep grey/brainstem infarcts was notably higher in men (43% vs. 7%, $p = 0.029$). There were no significant differences in the discharge modified Rankin's scale (mRS) scores or mortality rates.

Table 1. Clinical and laboratory features.

Variable	Group A (n = 36)	Group B (n = 110)	Group C (n = 16)	P A vs. B	P B vs. C
Age in years (mean, SD)	34 ± 13	48 ± 11	33 ± 6	<**0.001**	<**0.001**
Caucasian	83%	74%	56%	0.110	**0.021**
Hispanic	0%	14%	38%	**0.022**	**0.028**
Trigger/associated condition					
Vasoconstrictive drugs	53%	67%	25%	0.162	**0.002**
Serotonergic antidepressants	11%	45%	19%	<**0.001**	**0.050**
Illicit drugs	31%	20%	0%	0.189	**0.049**
Orgasmic/sexual	22%	4%	0%	**0.002**	0.438
Prior depression	14%	53%	25%	<**0.001**	**0.038**
Prior migraine	19%	49%	31%	**0.002**	0.181
History of hypertension	33%	36%	50%	0.742	0.294
Clinical					
Thunderclap headache at onset	94%	88%	75%	0.232	0.190
Admission blood pressure > 140/90	36%	48%	75%	0.207	**0.045**
Systolic	148 ± 35	150 ± 35	161 ± 35	0.757	0.262
Diastolic	83 ± 16	82 ± 16	94 ± 16	0.672	**0.005**
Focal neurological sign(s)	25%	43%	50%	0.058	0.584
Seizures	11%	13%	31%	0.798	0.053
Treatment and course					
Immunosuppressive therapy	17%	34%	6%	0.060	**0.026**
Calcium channel blocker therapy	50%	58%	20%	0.390	0.537
Clinical worsening	3%	18%	13%	**0.022**	0.576
Length of stay (first admission, days)	6 ± 7	10 ± 9	10 ± 5	**0.012**	0.913
Discharge mRS score (mean)	0.6 ± 1.4	0.8 ± 1.5	0.6 ± 1.5	0.614	0.633
mRS score 0–3	91%	90%	94%	0.768	0.633
mRS score 6 (death)	3%	2%	6%	0.725	0.277

Note: Group A, men; Group B, non-pregnant women; Group C, postpartum angiopathy. Bold indicates statistically significant P values.
mRS: modified Rankin scale.

Among non-pregnant women, 27 were pre-menopausal and 20 were post-menopausal; menopausal information was not documented in 63 patients. There were no significant differences in the mean vasoconstriction severity scores between pre- and post-menopausal women ($p = 0.3$), or in women with and without hysterectomy/oopherectomy ($p = 0.595$). Unfortunately, information on oral contraceptive use was documented in only 33 patients, with only four active users.

As compared to non-pregnant women, the PPA group was significantly younger, with significantly more Hispanics and lower rates of exposure to serotonergic antidepressants and illicit vasoconstrictive drugs such as marijuana and ecstasy (Table 1). The PPA group had less depression. The rate of onset thunderclap headache was numerically lower in PPA patients. There were no significant differences in the rate of focal neurological deficits, rate of seizures, mean length of stay, or discharge mRS scores.

Of the 16 PPA cases, three had preterm deliveries, one early-term, 10 full-term and two post-term. The PPA group had significantly higher admission blood pressures than non-pregnant women or men. Five of these patients developed preeclampsia/eclampsia and one developed the HELLP syndrome. This was the first delivery for five women, four had one prior delivery and seven had multiple prior deliveries. However, no prior pregnancy in any patient was complicated by toxemia, HELLP or PPA. Ten women underwent spontaneous vaginal delivery and six underwent C-sections. Epidural anaesthesia was administered in all 10 patients in whom this information was available. The onset of PPA (first symptom, usually TCH) was 2.5 ± 2 days (five women had onset on day 1, two on day 2, two on day 4, four on day 7, and one each on days 5, 8 and 10 after delivery).

Table 2. Brain imaging and angiographic features.

Variable	Group A (n = 36)	Group B (n = 110)	Group C (n = 16)	P A vs. B	P B vs. C
Initial brain imaging					
Abnormal	53%	74%	81%	**0.019**	0.513
Infarct	17%	32%	25%	0.134	0.682
Parenchymal haemorrhage	6%	14%	19%	0.232	0.510
Convexal SAH	33%	35%	25%	0.817	0.410
Vasogenic edema (PRES)	14%	27%	44%	0.103	0.176
Final brain Imaging					
Abnormal	53%	82%	81%	**0.001**	0.956
Infarct	20%	39%[c]	25%	**0.031**	0.408
Parenchymal haemorrhage	6%	14%	25%	0.189	0.235
Convexal SAH	33%	41%	31%	0.419	0.461
Vasogenic oedema (PRES)	14%	29%	50%	0.069	0.093
Onset to angiography (days)	6.3 ± 5.9	7.5 ± 6.1	6.7 ± 4.5	0.298	0.706
Artery involved					
Intracranial ICA	8%	17%	25%	0.205	0.466
Middle cerebral artery	78%	90%	94%	0.084	0.700
Anterior cerebral artery	67%	90%	75%	**0.001**	0.061
Posterior cerebral artery	56%	85%	88%	**0.001**	0.817
Vertebral or basilar arteries	44%	48%	56%	0.764	0.659
SCA/AICA/PICA	22%	65%	38%	<**0.001**	**0.034**
Extracranial ICA or vertebral	6%	7%	13%	0.742	0.615
Arterial segment involvement					
Proximal segment[a]	86%	82%	88%	0.777	0.874
Middle segment[a]	77%	95%	100%	**0.022**	0.437
Smaller distal branches	77%	91%	88%	0.264	0.895
Angiographic appearance					
Sausaging	46%	77%	38%	**0.002**	**0.019**
Segmental dilatation	23%	56%	63%	**0.004**	0.821
Cervical artery dissection	6%	8%	19%	**0.604**	0.178
Vasoconstriction severity score	10.9 ± 10.3	23 ± 14	23 ± 18	<**0.001**	0.977

Note: Group A, men; Group B, non-pregnant women; Group C, postpartum angiopathy.
SAH: subarachnoid haemorrhage; PRES: posterior reversible leukoencephalopathy syndrome; ICA: internal carotid artery; SCA, AICA and PICA: superior, anterior–inferior and posterior–inferior cerebellar arteries.
[a]Proximal arterial segments include the terminal ICA, the first-order branches of the anterior, middle and posterior cerebral arteries, and the intracranial vertebral and basilar arteries. Middle segments include the second-order branches of the anterior, middle and posterior cerebral arteries and the SCA, AICA and PICA. Bold indicates statistically significant P values.

A comparison of cerebral angiographic findings is shown in Table 2. There were no significant differences in the angiographic features of non-pregnant women and PPA cases. As compared to these two groups, men had less severe arterial narrowing as reflected by significantly lower vasoconstriction severity scores and lesser involvement of the second-order intracranial arteries. In addition, the morphological features were less typical in men; for example, the 'sausage-on-a-string' appearance and segmental dilatation was less frequently observed in men as compared to non-pregnant women (46% vs. 77%, p = 0.002 and 23% v. 56%, p = 0.004, respectively).

Discussion

Our study shows that women with RCVS are older than men, have a higher frequency of triggers and underlying conditions such as migraine and depression, and develop more severe manifestations as reflected by the higher frequency of clinical and radiological worsening, more severe and widespread vasoconstriction, and longer duration of hospitalization. However, discharge mRS scores are invariably excellent in both men and women. Although PPA cases differed in some respects from non-pregnant women (younger age, less exposure to drugs and medications, more hypertension,

seizures and PRES), these differences are not unexpected and the other clinical, radiological and angiographic findings including discharge outcomes were similar, suggesting that parturition itself does not affect the course or outcome although it remains an important trigger for PPA.

Our results provide an opportunity to consider whether gender differences in RCVS are explained by hormonal influences, or other genetic, molecular or biological factors. There is sufficient evidence to implicate female reproductive hormones in *triggering* RCVS. Women clearly have a lower threshold for RCVS.[3–7] The onset of RCVS is associated with pregnancy, OCPs, hormonal treatments and ovarian manipulation.[8–12] Extensive evidence supports a role for oestrogens in migraine,[18] which may be a risk factor for RCVS. Female hormones are implicated in altered blood–brain barrier permeability and eclampsia–PRES, which shares features with PPA. Finally, preclinical studies have shown that cerebral arteries express specific receptors for gonadal hormones, and that oestrogen inhibits central sympathomimetic activity and reduces cerebral vascular tone via its effects on endothelial nitric oxide, prostanoid and other molecular pathways.[19–21] Hence, the risk for PPA may suddenly increase with the precipitous fall in oestrogen levels after delivery. Non-hormonal factors such as placental growth factor (PlGF) and soluble PlGF receptor (sFlt-1) may also play a role in triggering PPA.[22]

In contrast, the lack of differences between the various female subgroups (non-pregnant women, PPA, pre- and post-menopausal, pre- and post-hysterectomy), and our prior analysis showing no significant phenotypic differences between PPA and other trigger-based RCVS subgroups,[4] suggests a less important role of female hormones on the *course* or *severity* of RCVS. Indeed, preliminary analysis of our cohort suggests that gender is not an independent predictor of clinical, radiological or angiographic worsening or poor discharge outcome (unpublished data). We acknowledge that our interpretation is limited by relatively small patient numbers and the retrospective nature of our studies. Further research is needed to understand whether the numerous non-hormonal molecular and biological factors (oxidative stress, prostaglandins, endothelial progenitor cells, endothelin, and others[1,6,23,24]) implicated in RCVS play a triggering role or whether they influence its severity/progression.

While the oestrogen–progesterone axis probably has an important role in triggering RCVS in women, different factors may be implicated in men. We noted an association between sexual activity and RCVS in men (Table 1). Similarly, male prevalence has been documented in primary headache associated with sexual activity[25] which is an RCVS-spectrum disorder.[26] Changes in the levels of sympathomimetic amines, prolactin and oxytocin occur around the time of sexual orgasm[27] and may play a role in triggering RCVS in men. Illicit drugs with predominantly sympathomimetic effects may be more relevant as triggers in men, while the higher prevalence of underlying depression, migraine, and antidepressant exposure suggests that serotonergic triggers may play a greater role in women. Finally, ethnicity may be important given the absence of Hispanic men in our cohort.

The strengths of our study include the relatively large numbers as compared to prior studies and the detailed analysis of imaging and angiographic data. The comparison of men, non-pregnant women and PPA is novel. We provide new information about prior pregnancy-related complications in PPA cases and consider the role of menopause and gynaecological surgery. The main limitation is the retrospective nature of the study and the lack of information on variables such as menopause and OCP use. Our results extend the results of Ducros et al.[3] showing differences in age, exposures and imaging findings between men and women. Unlike that study, we did not find a higher incidence of dissection in women. Further, our findings do not support the notion that PPA carries a worse prognosis.[13,14] It is unknown whether long-term outcomes such as chronic headache, quality of life and depression differ between men and women.[28] We hope the insights gained from this study will stimulate further research on the role of gender and hormonal factors on the risk and outcome after RCVS and other cerebrovascular disorders.

Authors' contributions

ABS and MAT conceived and designed the study, analysed the data, drafted the text, and prepared the Figures. All authors participated in data acquisition, data interpretation, critical revisions to the manuscript, and have approved the final version.

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Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Singhal has served as a medical expert witness and has received honoraria from the American Academy of Neurology, Medlink, Inc., and UptoDate. Topcuoglu and McKee have no relevant disclosures.

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Informed consent

Not applicable.

Ethical approval

This study was approved by Partners Human Research Committee.

Guarantor

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