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ORIGINAL ARTICLE

Cerebral White Matter Disease and Response to Anti-Cholinergic Medication for Overactive Bladder in an Age-Matched Cohort

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Abstract

Objective To determine if the presence of cerebral white matter disease (WMD) affects the response to anti-cholinergic medications.

Materials and Methods This was a retrospective cohort of age-matched patients treated for OAB with anti-cholinergic medications between January 2010 and December 2017. Inclusion criteria were a chief complaint of OAB, never evaluated by a urogynecologist for OAB, treated with a maximum dose for a minimum of 4 weeks, and underwent head computed tomography (CT) within 12 months of starting therapy. Patients with WMD were matched 1:1 by age and number of prior failed antimuscarinics to controls with normal head CTs. Exclusion criteria included incomplete documentation of therapeutic response, non-WMD CT abnormalities, and non-idiopathic OAB. The primary outcome was anti-cholinergic treatment failure. Pairwise analysis between groups was performed using Wilcoxon rank-sum and Fisher's exact test where appropriate. Univariate logistic regression was performed, and any variable that was associated with treatment failure and a p value ≤ 0.2 was included in the multivariable regression analysis.

Results Sixty-eight cases were matched with 68 controls. Patients with WMD were more likely to have undergone hysterectomy (57.4% vs. 41.2%, $p = 0.04$) and to use diuretics (31.1% vs. 19.1%, $p = 0.04$). Patients with WMD were more likely to fail treatment compared with controls (60.7% vs. 29.4%, $p = 0.004$). After adjusting for confounders, WMD was strongly associated with an increased probability of failure (aOR = 7.31, 95% CI: 1.49–12.20). Additional significant risk factors for treatment failure were the previous number of failed medications (aOR = 3.65 per medication, 95% CI: 1.48–9.01) and a rising HbA1c (aOR: 1.39 per 1.0% increase, 95% CI: 1.0–1.91).

Conclusion WMD is independently associated with anti-muscarinic treatment failure in women with overactive bladder symptoms.

Keywords Overactive bladder · White matter disease · Anti-cholinergic

Introduction

Overactive bladder (OAB) is defined by the International Continence Society as urinary urgency, usually accompanied with daytime frequency and/or nocturia, with or without urinary incontinence, and in the absence of urinary tract infection or other detectable disease [1]. OAB affects as many as 17.5 million women in the US, with up to 30–50% of women over the age of 65 years being affected [2]. While the exact pathophysiology of OAB has not yet been ascertained, it is now established that the condition is multifactorial resulting from changes affecting the detrusor, urothelium, levator ani, and nervous system [3–8].

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Recently, attention has been turned to the relationship between white matter disease (WMD) and symptoms of OAB. WMD may be identified and quantified in neuroimaging studies as hypointensities on computed tomography (CT) and hyperintesitities on magnetic resonance imaging (MRI). Previously, WMD was thought to be an incidental finding related to normal aging changes of the brain, but it is now recognized that these findings are associated with vascular dementia and Parkisnonism [9, 10]. Additionally, multiple studies have now demonstrated that WMD is significantly associated with the presence of OAB symptoms, termed vascular incontinence. Sakakibara et al. found that in patients with WMD, the overall prevalence of nocturia was 75%, and detrusor overactivity was found in 82% of patients [11]. Kuchel et al. further determined that the location of white matter changes plays an important role in the development of urinary incontinence symptoms [12].

While the link between WMD and OAB symptoms is now established, the relationship between these brain lesions and response to medication is not known. In continent adults, the supratentorial structures, which are most typically affected by WMD, play a role of inhibiting micturition until a socially appropriate time to void [13]. In the presence of WMD, this inhibitory function may be disrupted, and thus the primary dysfunction in these patients may be neurogenic rather than related to dysfunction at the level of the bladder where anti-cholinergic medications exert their primary effects [14, 15].

There are limited data regarding what clinical factors play a role in the effectiveness of pharmacotherapy to control OAB symptoms [16]. This is true for patients with WMD, and it may be particularly important to understand how these lesions affect the anti-cholinergic response, as it has previously been demonstrated that these patients are at increased risk of central nervous system (CNS) side effects related to anti-cholinergic use [17]. The objective of this study was to determine whether women with WMD who are otherwise neurologically intact have a decreased response to anti-cholinergic medications.

Materials and Methods

This was an Institutional Review Board-approved (IRB#18-00089) retrospective matched cohort of patients who underwent treatment with anti-cholinergic medication for symptoms of overactive bladder within the Division of Urogynecology at a single tertiary care medical center between the dates 1 January 2010 and 31 December 2017.

Patients were identified in the medical record by reviewing prescriptions for one of six anti-cholinergic medications prescribed by members of the Urogynecology Division during the study period: oxybutynin, tolterodine, fesoterodine, trospium, solifenacin, or darifenacin. All medications were administered per os. Eligible patients were identified using additional inclusion criteria: age > 18 years, presenting for the first time to a urogynecologist for bothersome urinary frequency, urgency, urgency incontinence, or nocturia for a minimum of 3 months, no prior history of treatment by a urologist or urogynecologist, treated for a minimum of 4 weeks, and had a record of a follow-up visit to assess medication response. Additionally, patients had to have undergone head computed tomography (CT) scanning within 12 months prior to initiation of anti-cholinergic therapy. Only patients who underwent CT imaging as part of a trauma evaluation for mild head injury and without altered mental status or loss of consciousness were included in the analysis.

Patients were excluded if they had a history of focal deficits on neurologic examinations, impaired cognition or evidence of dementia, prior history of cerebrovascular disease including transient ischemic attacks and evidence of carotid artery stenosis, neurodegenerative conditions such as Parkinson's disease and multiple sclerosis, congenital or traumatic neurologic or urologic disease, history of bladder augmentation, voiding dysfunction as evidenced by a post-void residual ≥ 200 ml, need for intermittent straight catheterization or use of alpha agonist medication to aid in bladder emptying, had chronic pain syndromes, had active psychiatric disorders, or were on medications known to be associated with overactive bladder or interfere with anti-cholinergic medications including opiate analgesics, benzodiazepines, antidepressants, and antipsychotic medications.

Patients were considered to have small vessel ischemic disease if the body or impression of the radiologist's report contained the following terms: "white matter disease," "cerebral atrophy," "generalized atrophy," "microvascular ischemia," "ischemic microangiopathy," "age-related white matter changes," "chronic small vessel ischemia," and "leukoaraiosis." An representative image of WMD findings are shown in Fig. 1. These images were reviewed with a staff radiologist to confirm the findings. If white matter changes were thought to be greater than what would be expected for chronic small vessel ischemia, such as cerebral or carotid artery disease or undiagnosed neurodegenerative disease, patients were excluded from the analysis. Patients with WMD were then matched at a 1:1 ratio by age to patients without evidence of WMD. Similarly, the images of the controls were also reviewed with a staff radiologist to confirm that there was no imaging evidence of WMD (Fig. 2). Patients with CT findings of intracranial hemorrhage, skull fracture, orbital bone fracture, remote or acute ischemic or thrombotic infarct, mass effect, herniation, or a mass lesion were excluded.

Additional variables included in the analysis were body mass index (BMI), diuretic (hydrochlorothiazide, furosemide, or torsemide) use, hemoglobin A1c, parity, race, smoking status, previous pelvic reconstructive surgery and hysterectomy, anterior wall and apical descent, concomitant stress incontinence, post-void residual, menopausal status, type of medication trialed, number of previously failed medications,

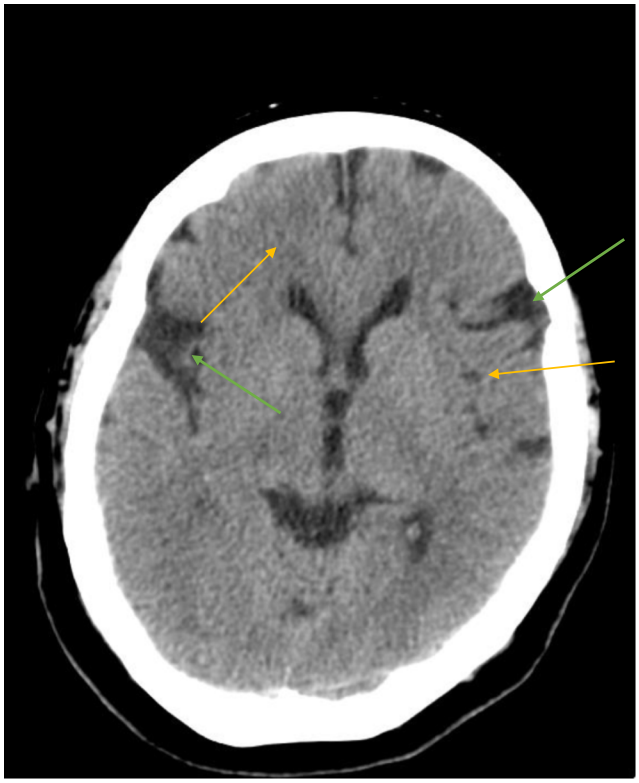

Fig. 1 Unenhanced axial computed tomography image at the level of the cerebellar vermis of a patient with white matter changes (yellow arrows) and cerebral atrophy demonstrated with more prominent cerebral sulci (green arrows)

constipation, number of daytime voids, number of nighttime voids, and number of urgency incontinence episodes.

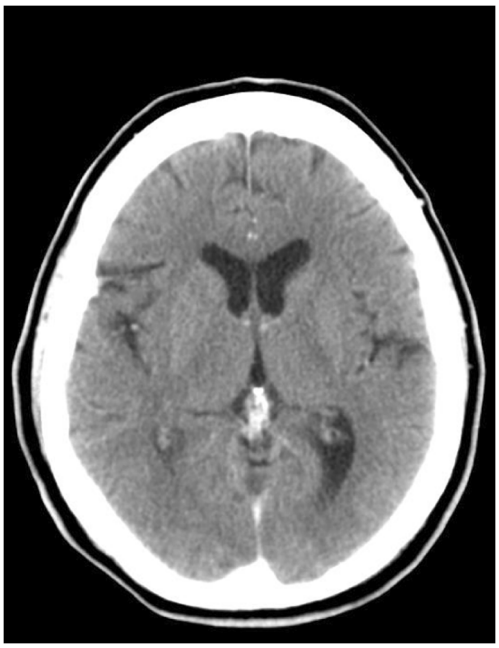

Figure 2 Unenhanced axial computed tomography image at the level of the cerebellar vermis of a patient without white matter changes or cerebral atrophy

The primary outcome was subjective failure of an anticholinergic treatment, defined as the patient reporting no or minimal improvement after a minimum of 4 weeks on the maximum dose of the prescribed medication. Maximum dose was defined as the maximum allowable dose by the drug manufacturer. Patients had to have explicit documentation of medication adherence, evidence that the prescription was filled in the electronic chart, and treatment response in the medical record to be included in the analysis. Patients were assumed to be adherent to therapy if they responded "no" to the question of whether or not they skipped any medication doses; if they reported being forgetful about taking medication or reported that they had periods of stopping and resuming treatment they were excluded for non-adherence. Pairwise analysis between groups was performed using the Wilcoxon rank-sum test and Fisher's exact test where appropriate. Univariate logistic regression was performed, and any variable that was associated with treatment failure and $p \leq 0.2$ was included in the multivariable regression analysis. All statistical analysis was performed using STATA version 14.1 (Stata Corp., College Station, TX).

This study had Institutional Review Board approval (IRB no. IRB18-00089).

Results A total 2177 charts were reviewed with 233 patients having had a CT scan within 12 months of being treated with anti-cholinergic medications. Of these, 12 were excluded for a finding of remote infarct, and 31 were excluded for missing information, elevated PVR, and presence of one of the excluding comorbidities. Of the remainder, 68 patients with cerebral WMD met all criteria for inclusion and were matched by age with 68 who did not have CT evidence of WMD. Table 1 lists the patient demographics at the time of treatment initiation, stratified by those with and without WMD. The two cohorts differed in diuretic use with patients with WMD being more likely to be using a diuretic at the time of treatment compared with the control group (31.1% vs. 19.1%, $p = 0.04$) and patients with WMD being more likely to have undergone a hysterectomy (57.4% vs. 41.2%, $p = 0.04$), but there were no differences in rates of incontinence or pelvic organ prolapse surgery. The median age of the cohort was 59 (IQR: 52–68) years. The median BMI was 33.9 (IQR: 28.9–39.2) kg/m^2, and 30.1% of the patients were diabetic with a median HbA1c of 6.6 (IQR: 5.6–8.1%). The median number of deliveries was 2, and 36.0% were smokers.

The groups did not differ in number of daytime voids ($p = 0.27$), nocturia episodes ($p = 0.35$), and urgency incontinence episodes ($p = 0.09$) (Tables 2 and 3). The median number of previously tried medications was 0 (IQR: 0–1) medications ($p = 0.23$). The median PVR was 13 ml (IQR: 0–35) in the WMD group and 16 ml (IQR: 0–32) in the control group ($p = 0.92$). The majority of patients in both groups, 80.3% and 77.9%, were postmenopausal ($p = 0.74$).

Table 1 Patient demographics stratified by presence of white matter disease

	White matter disease (n = 68)	Control (n = 68)	p
Age (years), median (IQR*)	61 (52–69)	58 (51–63)	0.67
Body mass index (kg/m²), median (IQR)	33.7 (28.9–39.3)	34.6(27.9–39.2)	0.98
Postmenopausal status	55(80.3)	53(77.9)	0.74
Current diuretic use	21(31.1)	13(19.1)	0.04
Diabetes	22(32.8)	19(27.9)	0.55
Hemglobin A1c (%) median (IQR)	6.7 (5.7–8.2)	6.5(5.6–8.0)	0.29
Parity, median (IQR)	2 (1–3)	2 (1–3)	0.95
Race			0.25
Caucasian	37(54.1)	30(44.1)	--
African American	22(32.8)	26(38.2)	--
Hispanic	6(8.2)	10(14.7)	--
Other	0(0.0)	2(2.9)	--
Current Smoker	27(39.3)	22(32.4)	0.4
Constipation	18(26.2)	17 (25.0)	0.97
Post-void residual (ml), median (IQR)	13 (0–5)	16 (0–32)	0.92
Prior hysterectomy	39(57.4)	28(41.2)	0.04
Prior sling procedure	15(22.1)	10(14.7)	0.23
Prior apical reconstruction with mesh	0(0.0)	1(1.6)	0.72
Prior apical reconstruction without mesh	8(11.7)	9(13.1)	0.59
Non-apical repair	14(21.3)	12(17.6)	0.18

*IQR: interquartile range

There were no differences in the type of medication prescribed for patients in either group, with oxybutynin and tolterodine being the most common medications, started for 41.2% and 18.6% of patients, respectively. Patients with WMD were significantly more likely to fail anti-cholinergic medication compared with controls (60.7% vs. 29.4%, p = 0.004), with a median follow-up of 98 days for both groups.

After adjusting for HbA1c, the number of previously failed medications, urinary frequency, nocturia and incontinence episodes, and diuretic use, WMD was independently associated

Table 2 Symptom severity and medication trialed stratified by presence of white matter disease

	White matter disease (n = 68)	Control (n = 68)	p
Number of previous failed medications, median (IQR)	0 (0–1)	0 (0–1)	0.23
No. of daily incontinence episodes, median (IQR)	2 (1–4)	1 (1–3)	0.09
No. of daytime voids, median (IQR)	12 (10–15)	12 (10–15)	0.27
No. of nighttime voids, median (IQR)	3 (2–4)	3 (2–4)	0.35
Complaint of stress incontinence	45(65.6)	44(64.7)	0.92
Ba, median (IQR)	-3 (-3 to -2)	-3 (-3 to -2)	0.5
C, median (IQR)	-8 (-8 to -7)	-8 (-8 to -7)	0.64
Medication trialed	--	--	0.21
Oxybutynin	30(44.1)	26(38.2)	--
Trospium	10 (14.7)	8(11.8)	--
Tolterodine	9(13.2)	15(22.1)	--
Fesoterodine	1(1.5)	4(5.9)	--
Solifenacin	9(13.2)	7(10.3)	--
Darifenacin	2(2.9)	8(11.8)	--
Failed treatment	41(60.7)	20(29.4)	0.004
Mean follow-up time (days), median (IQR)	98 (91–123)	98 (89–121)	0.77

*IQR: interquartile range

Table 3 Independent risk factors predictive of anti-cholinergic treatment failure

	Adjusted odds ratio	95% confidence interval
White matter disease	7.31	1.49–12.20
Previously failed medication per one medication	3.65	1.48–9.01
Hemoglobin A1c (per 1.0% increase)	1.39	1.02–1.91

with a markedly increased risk of medication failure (aOR = 7.31, 95% CI: 1.49–12.20), (Table 3). Additional significant risk factors for treatment failure were previous number of failed medications (aOR = 3.65 per medication, 95% CI: 1.48–9.01) and a rising HbA1c (aOR: 1.39 per 1.0% increase, 95% CI: 1.0–1.91).

Discussion

The brain plays an important role in normal micturition, with suprapontine structures being primarily involved in voluntary initiation of voiding [18, 19]. Multiple studies have described that lesions above the brainstem typically result in decreased inhibition and an overexaggerated but normal micturition reflex, leading to symptoms of an overactive bladder [20, 21]. White matter changes noted on CT as areas of hypodensity, previously thought to be non-pathologic age-related changes, occur as a result of demyelination and axonal loss, which may be due to chronic ischemia related to cerebral small vessel disease or hypoperfusion due to blood-brain barrier inflammation and amyloid angiopathy [22–24].

Regardless of the etiology of these changes, researchers have been able to implicate WMD as a causal factor in the development of OAB [8, 12, 25].

Our age-matched cohort study demonstrates that patients with evidence of WMD on CT and without any gross neurologic symptoms are twice as likely to fail a trial of anti-cholinergic therapy as patients without CT evidence of WMD. The impact of WMD on treatment response persisted even after adjusting for possible confounders on logistic regression. This may be because in patients with WMD a large component of their OAB symptoms is related, at least in part, to some degree of disinhibition of the micturition reflex rather than dysfunction at the detrusor level where anti-cholinergic medications exert their primary therapeutic effect [7, 13, 14].

Sakakibara previously demonstrated that anti-cholinergics, or at least tolterodine, may exert some of their therapeutic effects in the brain itself [26]. However, the study was limited to a very small number of patients and did not comment on the presence of white matter changes or cerebral atrophy in these patients, and it is possible that patients with WMD may have a less healthy brain "substrate" on which anti-cholinergics may exert their neurologic effect.

Our findings may also be related to the fact that WMD is thought to arise in part in patients with atherosclerotic disease, which is systemic. Atherosclerosis affects the bladder vasculature leading to chronic ischemia causing nerve and muscle damage, which can result in OAB symptoms that may not be as responsive to anti-cholinergic therapy [5, 27].

While WMD was the strongest predictor of treatment failure in this cohort, several additional independent risk factors for failure were identified. These included an increasing hemoglobin A1c level and the number of prior medication failures. The odds of failure were almost four fold for each additional failed medication. This is consistent with prior studies that have suggested that prior anti-cholinergic therapy is associated with a decreased response to treatment with another anti-cholinergic medication [28].

Several studies have evaluated the impact of diabetes on treatment response, with Schneider et al. finding a statistically significant decrease in treatment response to darifenacin in diabetics. Conversely, Choi et al. did not find any difference in response to solifenacin between diabetics and non-diabetics [29, 30]. However, neither study included hemoglobin A1c in their analysis. It is plausible that a higher hemoglobin A1c level would be associated with a greater degree of neuropathy and muscular injury and that this particular mechanism of pathogenesis would be associated with a lesser response to anti-cholinergic effects.

The main strengths of this study are that it is the first to report on the impact of WMD on treatment response and that subjects were matched by age, as both WMD and OAB tend to increase with age. However, our results must also be interpreted in the context of several important limitations. First, the retrospective design of the study makes it prone to input errors. The study also relied on a subjective report of successful treatment; however, it is the subjective response that will likely be more important to the patient and determine whether she will choose another treatment option. Additionally, the retrospective design did not allow for a determination of treatment adherence; per review of the notes patients reported taking the medications as prescribed for a minimum of 4 weeks.

The use of CT images rather than magnetic resonance imaging (MRI) also represents a potential confounder as MRI detects WMD with more sensitivy than CT scans, leading to a lower detection rate of more subtle changes.

We were also not able to quantify the severity of WMD as a classification system only exists for MRI. However, this would lead to an underestimation rather than overestimation of the impact of WMD on treatment response. Additionally, all CT images were carefully reviewed with a staff neuro-radiologist to avoid placement of patients with subtle WMD into the control group and to exclude patients in whom WMD was felt to be more severe than would be expected from chronic small vessel ischemia and aging.

Another limitation is that we were not able to perform analyses on whether one medication is superior to others, given the small number of medications prescribed other than oxybutynin; however, one would not expect a substantial difference in these patients as the mechanism of disease would still be neurogenic rather than myogenic. Finally, we were not able to account for every comorbidity and pharmacologic variable which may affect treatment response, such as frailty, use of angiotensin-converting enzyme inhibitors, and polypharmacy.

In summary, WMDs are associated with greater than sevenfold odds of failing anti-cholinergic medications. Clinicians should take these findings into account when considering a trial of an anti-cholinergic. These findings also warrant further investigation with prospective trials evaluating CNS function and treatment response in patients with and without WMD.

Compliance with ethical standards

Conflict of interest The authors report no conflicts of interest.

Financial Disclosures The authors report no relevant financial disclosures.

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