Original Article

Taiwan J Ophthalmol 2022;12:415-422

Access this article online

Quick Response Code:

Website:
www.e-tjo.org

DOI:
10.4103/2211-5056.361975

The associations between central serous chorioretinopathy and muscle relaxants: A case–control study

Manish Jain[1,2*], Sunir J. Garg[3], Mohammad Khan[4], Varun Chaudhary[5], Dena Zeraatkar[4,6], Dhanya Kurian[2], Sarath Lal[2]

[1]Department of Ophthalmology, Veer Chandra Singh Garhwali, Government Institute of Medical Sciences and Research, Srinagar, Uttarakhand, India, [2]Department of Ophthalmology, NMC Hospital, Al Ain, United Arab Emirates, [3]Wills Eye Hospital, Thomas Jefferson University, Philadelphia, Pennsylvania, USA, [4]Department of Health Research Methods, Evidence and Impact, McMaster University, [5]Department of Surgery, Division of Ophthalmology, McMaster University, Hamilton, Ontario, Canada, [6]Department of Biomedical Informatics, Harvard Medical School, Boston, Massachusetts, USA

***Address for correspondence:**
Dr. Manish Jain, Department of Ophthalmology, Veer Chandra Singh Garhwali, Government Institute of Medical Sciences and Research, Srinagar - 246 174, Uttarakhand, India.
E-mail: xs2ikr@gmail.com

Submission: 02-08-2022
Accepted: 09-10-2022
Published: 28-11-2022

Abstract:

PURPOSE: To evaluate the role of muscle-relaxants as risk factors for the development of central serous chorioretinopathy (CSC) - the second most common retinopathy in our settings; despite multiple risk factors seen in our patients, 21% were initially labelled as idiopathic.

MATERIALS AND METHODS: Retrospective case-control study at a tertiary hospital in the United Arab Emirates, where we reviewed the medical records of 273 patients with CSC examined between 2010 and 2019 for use of muscle-relaxants including tolperisone/eperisone, carisoprodol and gabapentin/pregabalin within a year of onset/recurrence of the disease. Intake of drugs with known association with CSC (including corticosteroids/sympathomimetics) was also recorded. Two hundred eighty-six subjects with adverse events seen at the same institute during the same study period served as controls. Odds ratios, Chi-Square tests and multivariate logistic regression were carried out to determine any associations with the muscle-relaxants and other pharmacological confounders - corticosteroids/sympathomimetics.

RESULTS: Muscle relaxants may increase the risk of CSC as evident on multivariate regression analysis (OR: 2.55; confidence interval [CI]: 1.208-5.413); the significance was retained on removing the 6 subjects who had corticosteroids/sympathomimetics (OR: 2.30; CI: 1.073–4.939). Univariate analysis yielded an OR of 2.52 for muscle relaxants (CI: 1.2149–5.2276), 2.96 for eperisone/tolperisone (CI: 1.3531–6.5038), and 6.26 for eperisone as an individual agent (CI: 1.8146–21.6252).

CONCLUSION: We found muscle relaxants to be associated factors of CSC regardless of inclusion of corticosteroids/sympathomimetics ($P < 0.05$). Among individual classes of muscle relaxants in this study, only eperisone/tolperisone posed a significant risk ($P < 0.05$). The vascular smooth muscle relaxation could be the possible mechanism that affects the choroidal blood flow and indirectly predisposes to CSC.

Keywords:

Carisoprodol, central serous chorioretinopathy, eperisone, gabapentin, muscle relaxants, pregabalin, tolperisone

Introduction

Central serous chorioretinopathy (CSC) typically presents with a circumscribed serous elevation of the retina often causing distorted vision with decreased visual acuity. While most cases resolve spontaneously, others have a protracted or recurrent course leading to visual loss. Corticosteroid use, psychological stress, hypertension, psychotropic drug use, and type "A" personality traits have all been implicated in causing CSC.[1] Patients with corticosteroid-associated CSC may have changes in mineralocorticoid receptor function.[2] In others, the etiology appears to be choroidal dysfunction, particularly involving choroidal circulation which is under autonomic control.[3-8]

How to cite this article: Jain M, Garg SJ, Khan M, Chaudhary V, Zeraatkar D, Kurian D, *et al*. The associations between central serous chorioretinopathy and muscle relaxants: A case–control study. Taiwan J Ophthalmol 2022;12:415-22.

Autonomic dysfunction such as heart rate variability and sympathetic-parasympathetic imbalance have been reported in CSC.[7,8]

Many drugs associated with CSC have a propensity to modulate the vascular tone or choroidal blood flow (ChBF) through diverse mechanisms that include actions on the autonomic nervous system, as well as on vascular smooth muscles.[4-6,9-16] In our settings, 21% of CSC patients were idiopathic. This prompted us to explore the potential role of other drugs or comorbid conditions in CSC.

In this article, we explore the potential role of different classes of muscle relaxants including tolperisone/eperisone (class I), carisoprodol (class II), and gabapentin/pregabalin (class III) as independent associated factors for CSC. We included corticosteroids/sympathomimetics in our analysis to mimic the real-life scenario, where concurrent or sequential intake of multiple drugs or risk factors exists, but withdrawal of corticosteroids alone does not lead to remission.[17,18]

Materials and Methods

We obtained the approval from the Institutional Review Board of NMC hospital in Al Ain, UAE for this case–control study (Approval date: May 27th, 2018). The study adhered to the tenets of the Declaration of Helsinki. The medical records of all CSC patients seen over a 10-year period (2010-2019) were explored for past medical history and medications. For our broader epidemiological study, we called the patients if they had missing information.

Participants

The clinical diagnosis of CSC was based on symptoms, such as decreased vision or visual distortion evident as central scotoma with or without metamorphopsia or micropsia. The diagnosis was confirmed by the presence of serous retinal detachment on fundus and optical coherence tomography examinations (3D OCT 2000 Topcon, Corp., Tokyo, Japan, or Spectralis HRA + OCT; Heidelberg Engineering, Heidelberg, Germany). Wherever deemed necessary, we obtained fundus fluorescein angiography to demonstrate active angiographic leakage (TRC-50DX; Topcon Corp., Tokyo, Japan).

Of the 329 patients identified, those with incomplete records, lost to follow-up, or with alternative provisional diagnoses including age-related macular degeneration, diabetic retinopathy, optic disc edema, Vogt–Koyanagi–Harada syndrome, or posterior scleritis were excluded; the remaining 273 patients diagnosed with CSC were included for further analysis [Figure 1]. The presence of recent psychological stress, comorbid conditions, all medications taken within the year preceding the initial diagnosis, or recurrence of CSC was recorded. The period of 1 year was based on a Taiwanese study that looked at the demographic characteristics, comorbidities, and corticosteroid use within 1 year before CSC diagnosis.[19]

Controls

All patients (338) with any systemic adverse drug event (ADE) seen at our hospital and reported to the pharmacovigilance department during the same study period (2010–2019) were reviewed; those with CSC (total 17) were excluded. Subjects below 20 years (28 patients) or over 60 years (7 patients) were also excluded in order to pair the patients with age-matched controls [Figure 1]. The remaining 286 subjects served as controls. UAE has a mobile population with a skewed sex ratio and a high number of immigrants. However, the immigration policies for specific nationalities vary over a period. As controls, the ADE cases were subjected to the same immigration policies over the study period, as the CSC patients. Hence, we believe that both the groups were drawn from the same reference population.

For both the case and control groups, a medication log was generated that included muscle relaxants as well as drugs associated with CSC during the study period.

Drug interactions and clinical pharmacology

Potential drug–drug interactions were explored by direct literature search as well as Medscape (Medscape, New York) drug interaction checker.[20,21] Keywords included muscle relaxants, corticosteroids/sympathomimetics, and other co-medications used by these patients [Table 1].[22] In addition to the mechanism(s) of action, we also looked at adverse events such as orthostatic hypotension and other

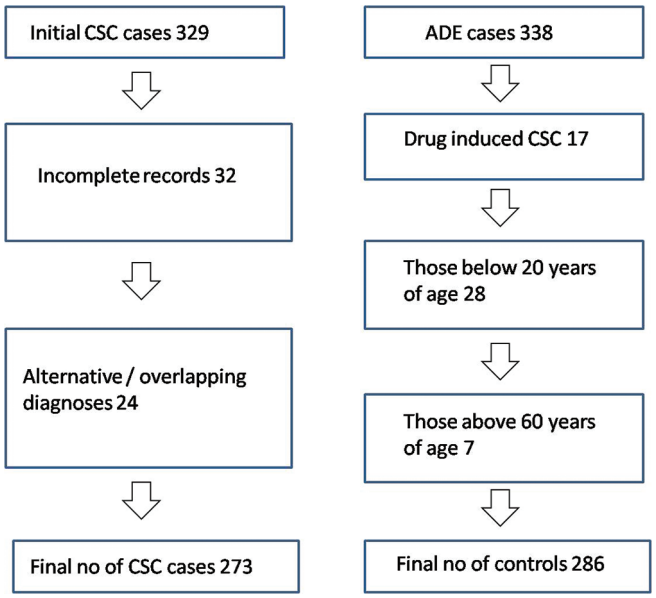

Figure 1: Flow diagram showing the progression to the final number of CSC patients and controls. CSC = Central serous chorioretinopathy

clinical effects that could indicate actions on vascular smooth muscle as these could alter cerebral and choroidal circulation. The most common group of medications taken by our patients was the proton-pump inhibitors. Two patients (patient 19 with eperisone and patient 23 with tolperisone) and one control (patient 8) had taken tramadol, a centrally acting opioid analgesic. Neither proton-pump inhibitors nor tramadol had any interaction with eperisone/tolperisone on our search.[20]

Statistical tests

A multivariate logistic regression model was used to examine any association between the occurrence of CSC and the intake of muscle relaxants and other pharmacological confounders – corticosteroids/sympathomimetics. Chi-square test was used to determine the significance of predictor variables and associated odds ratios (ORs) of estimates were computed alongside the 95% confidence interval. We repeated the analysis after removing the six subjects who had corticosteroid and/or sympathomimetic prior to the onset of CSC to see if muscle relaxants retained a significant association with CSC. The ORs were calculated for muscle relaxants as a group, and this was followed by the ORs for three classes and individual drugs.

Results

The mean age of the patients was 39.7 ± 7.3 years with age (range: 21 years–59 years). In comparison, the average age of a control was 38.5 ± 9.6 years. The difference between the two groups was not significant ($P = 0.11$). All patients on muscle relaxants were male. All except one were either outdoor workers or had an occupational predisposition for prolonged standing/other strenuous postures such as squatting during fieldwork. One person was on muscle relaxants following a sports injury.

Twenty-five of 273 patients and 11 of 286 controls in the ADE group had muscle relaxants. The timeline of muscle relaxant use (plus corticosteroid/sympathomimetic) in the CSC and the control group ADE is presented in Tables 1 and 2.

Nineteen patients marked as "A" in Table 1 either had no corticosteroids/sympathomimetics, or these were taken only after the diagnosis of CSC (patients 12, 13, 15, and 16), ruling out a primary causative role. Three patients ["B" in Table 1] had at least one of these two classes of drugs before consuming muscle relaxants, while in three additional cases ["C" in Table 1], the exact timeline of corticosteroids/sympathomimetics could not be established as prescriptions originated elsewhere and only the medical history or pills were available. The six cases marked as "B" or "C" were considered confounders for the multivariate analysis.

Among the controls, we had eight cases that had ADE related to muscle relaxants. Only three subjects had an ocular or visual adverse event attributed to muscle relaxants: controls 1 and 3 had allergic manifestations that involved conjunctiva and periorbital edema; control 7 on pregabalin had visual disturbance, but his ocular examination was noncontributory. While looking up at medications within a year, we picked up three additional controls who had muscle relaxants.

The ORs for muscle relaxants, their classes, and individual drugs are summarized in Table 3. As shown, the OR was highest for eperisone (6.26; $P = 0.003$). The OR for muscle relaxants was 2.52 (95% confidence interval [CI]: 1.2149–5.2276; $P = 0.01$). On multivariate analysis, the OR for muscle relaxants was 2.55 (95% CI: 1.208–5.413; $P = 0.01$). On removing the six confounders, the OR (2.30) was still significant (95% CI: 1.073–4.939; $P = 0.02$). Table 4 summarizes the results of the regression analysis with and without the confounding drugs.

Discussion

CSC can cause mild-to-moderate vision loss in younger patients, and its etiology is not well understood. While corticosteroid use, stress, and a type A personality have been implicated in some patients, in many others, there is no identifiable cause. The current study suggests that for some patients, muscle relaxants may be a predisposing factor.

All 25 subjects who used muscle relaxants were male, which reflects the skewed gender ratio in the UAE due to a large number of immigrants, specifically men who perform manual labor.[7] Some occupations had predilection for male recruitment and their outdoor work may have increased the use of nasal corticosteroids/sympathomimetics in allergic rhinitis or of muscle relaxants due to strenuous activities or painful musculoskeletal conditions.

The three classes of muscle relaxants operate either through the voltage-gated channels (eperisone and tolperisone), or GABAergic pathways (carisoprodol, gabapentin, and pregabalin). Tolperisone and eperisone are centrally acting muscle relaxants that act at the reticular formation in the brain stem by blocking voltage-gated sodium and calcium channels. They inhibit spinal reflexes predominantly by a presynaptic inhibition of neurotransmitter release.[23] These drugs relax both the skeletal muscles and vascular smooth muscle. They affect vascular smooth muscles through blockade of adrenergic alpha-receptors.[21,23,24] Hypotension is a known adverse effect. They do not exhibit somnolence on withdrawal unlike carisoprodol which has an active metabolite meprobamate.

Table 1: Muscle relaxants and other co-medications' intake by central serous chorioretinopathy patients

Timeline pattern*	Age	Muscle relaxant used	Indication and comorbid conditions	Co-medication (s)	Dose	Interval between drug (s) intake and CSC onset	Laterality
A	50	Eperisone	Sacroiliitis (fall)	Diclofenac	Eperisone 50 mg tid for 10 days	49 days	Unilateral
A	43	Eperisone	Paravertebral spasm	Aceclofenac	Eperisone 50 mg bid for 15 days	61 days	Unilateral
A	43	Eperisone	Hyperlipidemia Backache	Atorvastatin, diclofenac, etoricoxib	Eperisone 50 mg tid for 10 days	56 days	Unilateral
A	43	Eperisone	Diabetes Hypertension Lumbago	Metformin, glimepiride, losartan, olmesartan, amlodipine, telmisartan, rosuvastatin	Eperisone 50 mg tid for 14 days	61 days	Bilateral simultaneous
A	46	Eperisone	Lumbar spondylosis	NSAIDs (diclofenac, celecoxib, ketoprofen)	Eperisone 50 m tid 15 days	68 days	Unilateral
A	42	Eperisone	Backache	-	Eperisone 50 mg bid 14 days	59 days	Unilateral
A	45	Eperisone	Migraine, allergic rhinitis, cervical spondylosis	-	Eperisone 50 mg tid for 21 days	53 days	Unilateral
A	35	Eperisone	Paravertebral spasm Dyspepsia	Lansoprazole	Eperisone 50 mg tid for 10 days	52 days	Unilateral
A	40	Eperisone	Lumbar spondylosis Hypertension	Perindopril and indapamide	Eperisone 50 mg tid 28 days	69 days	Unilateral
A	39	Eperisone	Cervical spondylosis Gout Urticaria	Aceclofenac, ketoprofen gel Allopurinol Loratadine	Eperisone 50 mg tid for 21 days Gabapentin 300 mg OD for 14 days	52 days	Unilateral
A	50	Eperisone	Planter fasciitis Peptic ulcer	Chlordiazepoxide and clidinium Pantoprazole	Eperisone 50 mg bid for 21 days	78 days (delayed referral; symptoms appeared on day 22)	Unilateral
A	58	Tolperisone	Backache and myalgia Allergic rhinitis	Diclofenac, ketoprofen Mometasone 50 mcg bid for 5 days	Tolperisone 150 mg tid for 21 days	50 days	Unilateral No exacerbation
A	45	Tolperisone	Cervical spondylosis Acute pharyngitis Reflux esophagitis	Xylometazoline Esomeprazole	Tolperisone 150 mg tid for 14 days	56 days	Unilateral No exacerbation
A	35	Tolperisone	Low back ache GERD	Diclofenac, ketoprofen gel Pantoprazole	Tolperisone 150 mg bid for 14 days	Recurrence after 6 days	Bilateral simultaneous
A	39	Tolperisone	Lumbago/neuralgia Hypertension Hyperlipidemia GERD Rhinitis Dermatitis	Etoricoxib, diclofenac, ibuprofen, fenofibrate, bromhexine, loratadine, mometasone, fluticasone	Tolperisone 150 mg bid 14 days=4.2 g	54 days	Unilateral
A	33	Tolperisone	Lumber spondylosis Allergic rhinitis Otitis media	Naproxen Oral loratadine and pseudoephedrine combination; injection dexamethasone; xylometazoline, beclomethasone dipropionate 100 mcg per dose-2 puffs a day, dexamethasone ear drop ciprofloxacin + hydrocortisone ear drops for 5 days with mometasone furoate 50 mcg/dose nasal spray bid 30 days	Tolperisone 150 mg bid 19 days; followed by naproxen Later had gabapentin 300 mg bid for 50 days	51 days	Unilateral Unrelenting course over 27 months

Contd...

Table 1: Contd...

Timeline pattern*	Age	Muscle relaxant used	Indication and comorbid conditions	Co-medication (s)	Dose	Interval between drug (s) intake and CSC onset	Laterality
A	37	Carisoprodol	Backache	Paracetamol	Carisoprodol 250 mg tid for 3 weeks	52 days	Unilateral
A	41	Eperisone	Paravertebral spasm	-	Eperisone 50 mg tid 14 days	Recurrence after 35 days	Unilateral recurrence
A	33	Eperisone	Sprain/sports injury	Diclofenac	Eperisone 50 mg tid for 14 days	38 days	Unilateral
B	39	Eperisone	Acute pharyngitis Cervical spondylosis Perianal abscess	Pseudoephedrine, loratadine, celecoxib, eperisone, diclofenac, ketoprofen, tramadol, augmentin; ciprofloxacin	Eperisone 50 mg tid for 10 days	Post pseudoephedrine 64 days Post eperisone 28 days	Bilateral simultaneous
B	42	Eperisone	Hypertension Contact-dermatitis Gastritis Myalgia Epicondylitis Hemorrhoids	Losartan Mometasone furoate Omeprazole, lignocaine	Eperisone 50 mg bid for 28 days with interruption between therapy	Post mometasone 58 days Post eperisone 34 days	Unilateral
B	35	Eperisone	Allergic rhinitis Sinusitis Bronchitis Asthma Lumbar radiculitis	Xylometazoline 0.1 nasal spray, budesonide 160 mcg plus formoterol fumarate dihydrate 4.5 mcg; fluticasone 50 mcg	Eperisone 50 mg bid for 7 days=0.7 g	Post xylometazoline and budesonide 51 days Post eperisone 28 days	Unilateral
C	45	Eperisone	Epistaxis *Helicobacter pylori* Lumbago Gouty arthritis Conjunctival hyperemia	Xylometazoline Lansoprazole Etoricoxib Naphazoline	Eperisone 50 mg bid 14 days	Timeline with respect to xylometazoline not determined Post eperisone 26 days	Unilateral
C	36	Tolperisone	Sciatica	Tramadol, diclofenac, naproxen, dexamethasone IM 8 mg once	Tolperisone 150 mg tid multiple times (total 56 days)=25.2 g	All these drugs fairly close together and CSC appeared around 10 months later	Unilateral
C	49	Tolperisone	Allergic rhinitis Calcaneal spur Spondylosis Planter fasciitis Gout	Budesonide 64 mcg intranasal for 30 days Corticosteroid in heel and left thumb: Led to recurrence in the other eye Allopurinol	Tolperisone 150 mg tid for 10 days	Timeline with respect to budesonide not determined Post tolperisone 48 days	Bilateral sequential

*The timeline patterns segregated the confounders (A) from others (B and C). The smallest doses (eperisone: 0.7 g or 50 mg bid for 7 days; tolperisone: 4.2 g or 150 mg bid for 14 days), highest cumulative doses (eperisone: 4.2 g; tolperisone: 25.2 g), smallest interval between drug intake and onset of CSC (eperisone: 26 days with other drugs, 49 days when used alone and 35 days for recurrence; tolperisone: 48 days with other drugs, 50 days when used alone and 6 days for recurrence), and the longest interval (eperisone: 78 days; tolperisone 10 months) are highlighted. Carisoprodol had a single user. Case number 16 was unique with the most diverse drug exposures that included muscle relaxant tolperisone, corticosteroids, sympathomimetics, and gabapentin and had an unrelenting course at 27 months when last seen. A=Nonconfounders (corticosteroids or sympathomimetics either not taken or taken after the onset of CSC with muscle relaxant), B=Corticosteroids or sympathomimetics taken before muscle relaxant, C=Exact timeline of muscle relaxant and corticosteroids or sympathomimetics not known; for the regression analysis, these additional drugs were considered to have been taken prior to muscle relaxant. CSC=Central serous chorioretinopathy, GERD=Gastrointestinal reflux disease, NSAIDs=Nonsteroidal anti-inflammatory drugs

Carisoprodol is a GABAergic central nervous system depressant that acts as a sedative and skeletal muscle relaxant.[25] It interrupts the neuronal communication within the reticular formation and spinal cord. Reflex tachycardia is a known adverse effect. Gabapentin and pregabalin have an affinity for alpha2-delta protein, an auxiliary subunit of voltage-gated calcium channels, and it modulates GABA and glutamate synthesis.[26]

Tolperisone and eperisone cause dilatation of basilar artery in guinea pigs.[27] Eperisone reverts the vasoconstrictive actions of norepinephrine, serotonin, and acetylcholine.[28] Tsokolas *et al*. described a case of vitreous hemorrhage ascribed to tolperisone.[29] Carisoprodol, gabapentin, and pregabalin have diverse cardiorespiratory, vasodilatory, and visual effects mediated through GABAergic pathways.[29-32] Doğan *et al*. have recently reported two cases of CSC with

Table 2: Adverse drug event cases (controls) and their intake of muscle relaxants at the time of event or within a year

Age and sex	Drug and co-medication at the time of ADE	Adverse event	Muscle relaxant as previous medication	Corticosteroids or sympathomimetics within a year
49 male	Tolperisone 150 mg OD	Pruritus, dyspnea, circulatory collapse, ocular hyperemia, and dizziness	-	-
34 male	Tolperisone 150 mg BID; celecoxib	Urticaria	-	-
24 male	Tolperisone 150 mg	Periorbital edema, facial puffiness, and erythema	-	-
42 male	Tolperisone 150 mg BID+2.5% gel T.I.D; paracetamol	Numbness and swelling over face	-	-
48 male	Eperisone 50 mg OD	Pruritus	-	-
35 male	Carisoprodol 75 mg; diclofenac 50 mg	Erythema, pruritus, headache, dizziness, and vomiting	-	-
37 female	Pregabalin	Blurring of vision, dizziness, fatigue, dyskinesia, irritability, phonophobia, and tinnitus	-	-
46 female	Injection tramadol+tolperisone 150 mg	Urticaria	-	Nasal fluticasone and xylometazoline
32 female	Ceftriaxone	Pruritus	Eperisone 50 mg	-
39 male	Naproxen	Bilateral lid edema	Tolperisone 150 mg	Triamcinolone injection
40 male	Diclofenac	Rashes	Eperisone 50 mg	Beclomethasone dipropionate

ADE=Adverse drug event

Table 3: Odds ratios for individual muscle relaxants (univariate analysis)

Class	Class of MR	CSC patients	Controls	OR	95% CI	*P*
I	Eperisone + tolperisone	24	9	2.96	1.3531-6.5038	0.006
	Eperisone	17	3	6.26	1.8146-21.6252	0.003
	Tolperisone	7	6	1.22	0.4075-3.7015	0.7
II	Carisoprodol	1	1	1.04	0.0652-16.8360	0.97
III	Gabapentin/pregabalin	2	1	2.1	0.1896-23.3307	0.54
All	All MR	25	11	2.52	1.2149-5.2276	0.01

MR=Muscle relaxants, CSC=Central serous chorioretinopathy, OR=Odds ratio, CI=Confidence interval

Table 4: Logistic regression analysis

Variable	β	SE	χ^2 value	*P*	OR	95% CI	
						Lower	Upper
A. Confounders retained							
Intercept	−0.2265	0.1022	−2.217	0.0266	0.797	0.649	0.978
Corticosteroids	0.3361	0.236	1.424	0.1543	1.399	0.872	2.243
MR	0.9389	0.375	2.503	0.0123	2.557	1.208	5.413
Sympathomimetics	0.3109	0.333	0.934	0.3504	1.364	0.701	2.656
B. Six confounders removed							
Intercept	−0.2255	0.1022	−2.206	0.0274	0.798	0.651	0.979
Corticosteroids	0.2809	0.2421	1.16	0.2429	1.324	0.816	2.149
MR	0.8339	0.3817	2.185	0.0289	2.302	1.073	4.939
Sympathomimetics	0.3328	0.3415	0.975	0.3297	1.395	0.705	2.762

OR=Odds ratio, CI=Confidence interval, SE=Standard error, MR=Muscle relaxants

pregabalin as a probable cause.[33] *In vitro* studies involving the isolated basilar artery of rabbit show vascular smooth muscle relaxation in response to GABA.[32] Gabapentin causes diverse ADEs such as somnolence, dizziness, headache, nausea, blurred vision, diplopia, altered color vision, macular edema, serous detachment, reversible visual field constrictions, and electrophysiological alterations.[33-36] Another GABA analog, γ-vinyl GABA (vigabatrin), reduces the pulsatile ocular blood and pulse amplitude when used for epilepsy.[32] Pregabalin and gabapentin are structurally and functionally similar and reduce the synaptic release of many neurotransmitters.[26] A recent meta-analysis reports diplopia, blurred vision, and amblyopia with

these drugs.[37] Previously, a role of serotonin, dopamine, and melatonin has been demonstrated in CSC,[12,38,39] while GABA has a role in the circadian rhythm and obstructive sleep apnea.[40]

Regulation of ChBF is complex and extends beyond the adrenergic pathways.[41-43] The sympathetic system employs adrenergic neurotransmitters and neuropeptide P, while the parasympathetic system uses vasoactive intestinal polypeptide, acetylcholine, and neuronal nitric oxide synthase.[6] Some of these affect the release of other neurotransmitters.[26] The presence of intrinsic choroidal neurons and other contractile cells provides additional mechanisms of ChBF control.[6,44] The exact mechanism through which muscle relaxants may alter the ChBF remains conjectural but is likely to be mediated through their actions on vascular smooth muscles. Occasionally, drugs that do not cause significant hypotension *per se* may cause profound hypotension following drug interactions.[45]

Conclusion

In conclusion, our data suggest that muscle relaxants, especially eperisone and tolperisone, may be associated with predisposing factors for CSC regardless of consumption of drugs such as corticosteroids and sympathomimetics. There is a caveat: CSC has a known association with type A personality. People with type A personality are prone to stress, muscular tension and myofascial pain, and then need for muscle relaxant use. Compared to other potential controls, our choice of ADE subjects as controls may have some disadvantages: some of these might have had other systemic comorbidities that could have confounded the results. We do not have data on how well the groups were matched, especially with regard to ethnic origin, nor do we have specific data regarding other health concerns, presence of stress, or personality type. There were no female CSC patients that met the inclusion criteria. Additionally, the prevalence of muscle relaxant use is unknown, and often due to logistics and financial reasons, fluorescein angiography and repeat OCTs were not regularly obtained. However, this was the most complete set of accessible data available for controls at our institution.

The strength of the study is the inclusion of morbid conditions, medications, their interactions, and occupational and physiological background. More importantly, our observations open the possibility that other vasoactive drugs could contribute to CSC and this should be asked about on medical history. Further studies are needed to validate the effect of muscle relaxants on ChBF in other geographical areas and ethnic groups. Imaging techniques such as laser Doppler flowmetry and enhanced depth imaging could also be used to delineate choroidal vascular changes in response to vasoactive medications.

Acknowledgement

The authors acknowledge the contribution of Dr. Jay Chhablani, University of Pittsburgh, UPMC Eye Center, PA, USA through his valuable comments.

Financial support and sponsorship

Nil.

Conflicts of interest

The authors declare that there are no conflicts of interest of this paper.

References

1. Liu B, Deng T, Zhang J. Risk factors for central serous chorioretinopathy: A systematic review and meta-analysis. Retina 2016;36:9-19.
2. Zhao M, Célérier I, Bousquet E, Jeanny JC, Jonet L, Savoldelli M, *et al.* Mineralocorticoid receptor is involved in rat and human ocular chorioretinopathy. J Clin Invest 2012;122:2672-9.
3. Prünte C. Indocyanine green angiographic findings in central serous chorioretinopathy. Int Ophthalmol 1995;19:77-82.
4. Bill A, Nilsson SF. Control of ocular blood flow. J Cardiovasc Pharmacol 1985;7 Suppl 3:S96-102.
5. Reiner A, Fitzgerald ME, Del Mar N, Li C. Neural control of choroidal blood flow. Prog Retin Eye Res 2018;64:96-130.
6. McDougal DH, Gamlin PD. Autonomic control of the eye. Compr Physiol 2015;5:439-73.
7. Tewari HK, Gadia R, Kumar D, Venkatesh P, Garg SP. Sympathetic-parasympathetic activity and reactivity in central serous chorioretinopathy: A case-control study. Invest Ophthalmol Vis Sci 2006;47:3474-8.
8. Nathaniel Roybal C, Sledz E, Elshatory Y, Zhang L, Almeida DR, Chin EK, *et al.* Dysfunctional autonomic regulation of the choroid in central serous chorioretinopathy. Retina 2018;38:1205-10.
9. Michael JC, Pak J, Pulido J, de Venecia G. Central serous chorioretinopathy associated with administration of sympathomimetic agents. Am J Ophthalmol 2003;136:182-5.
10. Haimovici R, Gragoudas ES, Duker JS, Sjaarda RN, Eliott D. Central serous chorioretinopathy associated with inhaled or intranasal corticosteroids. Ophthalmology 1997;104:1653-60.
11. Fraunfelder FW, Fraunfelder FT. Central serous chorioretinopathy associated with sildenafil. Retina 2008;28:606-9.
12. Jain M. Quetiapine associated central serous chorioretinopathy: Implicit role of serotonin and dopamine pathways. Indian J Ophthalmol 2019;67:292-4.
13. Jain M, Nevin RL, Ahmed I. Mefloquine-associated dizziness, diplopia, and central serous chorioretinopathy: A case report. J Med Case Rep 2016;10:305.
14. Kisma N, Loukianou E, Pal B. Central serous chorioretinopathy associated with desmopressin nasal spray: Causality or unfortunate association. Case Rep Ophthalmol 2018;9:120-5.
15. Brill D, Albert D, Fields T, Mikkilineni S, Crandall D, Gao H. Ciliochoroidal effusion syndrome with central serous-like chorioretinopathy and secondary angle closure following exogenous testosterone use. Am J Ophthalmol Case Rep 2019;15:100482.
16. Venkatesh R, Pereira A, Jain K, Yadav NK. Minoxidil induced central serous chorioretinopathy treated with oral eplerenone – A case report. BMC Ophthalmol 2020;20:219.

17. Jain M, Kurian D, Lal S, Biswas J, Pathak K. Clinical profile and risk factors of central serous chorioretinopathy in Al-Ain, United Arab Emirates. New Emirates Med J 2022;3:e280422204222. [doi: 10.2174/03666220428133215].
18. Alsberge JB, Lee DY, Jumper JM. Central serous chorioretinopathy associated with Adderall (dextroamphetamine-amphetamine) and topical steroid use. Am J Ophthalmol Case Rep 2022;26:101482.
19. Chang YS, Weng SF, Chang C, Wang JJ, Wang JY, Jan RL. Associations between topical ophthalmic corticosteroids and central serous chorioretinopathy: A taiwanese population-based study. Invest Ophthalmol Vis Sci 2015;56:4083-9.
20. Available from: https://reference.medscape.com/drug-interactionchecker. [Last accessed on 2022 Apr 26].
21. Kim MJ, Lim HS, Noh YH, Kim YH, Choi HY, Park KM, *et al.* Pharmacokinetic interactions between eperisone hydrochloride and aceclofenac: A randomized, open-label, crossover study of healthy Korean men. Clin Ther 2013;35:1528-35.
22. Tittl MK, Spaide RF, Wong D, Pilotto E, Yannuzzi LA, Fisher YL, *et al.* Systemic findings associated with central serous chorioretinopathy. Am J Ophthalmol 1999;128:63-8.
23. Kocsis P, Farkas S, Fodor L, Bielik N, Thán M, Kolok S, *et al.* Tolperisone-type drugs inhibit spinal reflexes via blockade of voltage-gated sodium and calcium channels. J Pharmacol Exp Ther 2005;315:1237-46.
24. Furuta Y, Yoshikawa A. Reversible adrenergic alpha-receptor blocking action of 2,4'-dimethyl-3-piperidino-propiophenone (tolperisone). Jpn J Pharmacol 1976;26:543-50.
25. Bramness JG, Mørland J, Sørlid HK, Rudberg N, Jacobsen D. Carisoprodol intoxications and serotonergic features. Clin Toxicol (Phila) 2005;43:39-45.
26. Taylor CP, Angelotti T, Fauman E. Pharmacology and mechanism of action of pregabalin: The calcium channel alpha2-delta (alpha2-delta) subunit as a target for antiepileptic drug discovery. Epilepsy Res 2007;73:137-50.
27. Fujioka M, Kuriyama H. Eperisone, an antispastic agent, possesses vasodilating actions on the guinea-pig basilar artery. J Pharmacol Exp Ther 1985;235:757-63.
28. Inoue S, Bian K, Okamura T, Okunishi H, Toda N. Mechanisms of action of eperisone on isolated dog saphenous arteries and veins. Jpn J Pharmacol 1989;50:271-82.
29. Tsokolas G, Almuhtaseb H, Hanifudin A, Lotery A. Tolperisone, a centrally-acting muscle relaxant: A possible cause of macular haemorrhage. Eye (Lond) 2020;34:1380-1.
30. Anwar N, Mason DF. Two actions of gamma-aminobutyric acid on the responses of the isolated basilar artery from the rabbit. Br J Pharmacol 1982;75:177-81.
31. Hosking SL, Roff Hilton EJ, Embleton SJ, Gupta AK. Epilepsy patients treated with vigabatrin exhibit reduced ocular blood flow. Br J Ophthalmol 2003;87:96-100.
32. Herranz JL, Sol JM, Hernández G. Gabapentin used in 559 patients with partial seizures. A multicenter observation study. Spanish Gabapentin Work Group. Rev Neurol 2000;30:1141-5.
33. Doğan YE, Kurt Oktay KN, Buyru Özkurt Y, Aktaş İ. Pregabalin as a probable cause of central serous chorioretinopathy: Two case reports. Turk J Phys Med Rehabil 2021;67:530-3.
34. Steinhoff BJ, Freudenthaler N, Paulus W. The influence of established and new antiepileptic drugs on visual perception. 1. A placebo-controlled, double-blind, single-dose study in healthy volunteers. Epilepsy Res 1997;29:35-47.
35. Kim JY, Kim DG, Kim SH, Kwon OW, Kim SH, You YS. Macular Edema after Gabapentin. Korean J Ophthalmol 2016;30:153-5.
36. Bekkelund SI, Lilleng H, Tønseth S. Gabapentin may cause reversible visual field constriction. BMJ 2006;332:1193.
37. Zaccara G, Gangemi P, Perucca P, Specchio L. The adverse event profile of pregabalin: A systematic review and meta-analysis of randomized controlled trials. Epilepsia 2011;52:826-36.
38. Gramajo AL, Marquez GE, Torres VE, Juárez CP, Rosenstein RE, Luna JD, *et al.* Therapeutic benefit of melatonin in refractory central serous chorioretinopathy. Eye (Lond) 2015;29:1036-45.
39. Pandolfo G, Genovese G, Bruno A, Palumbo D, Poli U, Gangemi S, *et al.* Sharing the same perspective. Mental disorders and central serous chorioretinopathy: A systematic review of evidence from 2010 to 2020. Biomedicines 2021;9:1067.
40. Macey PM, Sarma MK, Nagarajan R, Aysola R, Siegel JM, Harper RM, *et al.* Obstructive sleep apnea is associated with low GABA and high glutamate in the insular cortex. J Sleep Res 2016;25:390-4.
41. Bujarborua D, Borooah S, Dhillon B. Getting serious with retinopathy: Approaching an integrated hypothesis for central serous chorioretinopathy. Med Hypotheses 2013;81:268-73.
42. Reghunandanan V, Reghunandanan R. Neurotransmitters of the suprachiasmatic nuclei. J Circadian Rhythms 2006;4:2.
43. Korshunov KS, Blakemore LJ, Trombley PQ. Dopamine: A modulator of circadian rhythms in the central nervous system. Front Cell Neurosci 2017;11:91.
44. Poukens V, Glasgow BJ, Demer JL. Nonvascular contractile cells in sclera and choroid of humans and monkeys. Invest Ophthalmol Vis Sci 1998;39:1765-74.
45. Chauhan G, Gupta K, Nayar P. Severe hypotension during general anesthesia in a patient on chronic high-dose Tamsulosin therapy. Anesth Essays Res 2013;7:285-6.