Associations Between Topical Ophthalmic Corticosteroids and Central Serous Chorioretinopathy: A Taiwanese Population-Based Study

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Purpose. To investigate the association between central serous chorioretinopathy (CSCR) and topical ophthalmic corticosteroid use.

Methods. Data were collected from the Longitudinal Health Insurance Database 2000, containing randomly selected medical claim data from 23 million residents in Taiwan. The study cohort comprised all patients diagnosed with CSCR between January 2001 and December 2010 ($n = 2921$) with a control group of patients ($n = 17,526$) matched to study patients according to age, sex, geographic region, and date of index medical care. Demographic characteristics, comorbidities, and corticosteroid use (topical ophthalmic, oral, nasal spray, injected, and inhaled) within 1 year before CSCR diagnosis were examined using univariate logistic regression. Student's *t*-test was used for continuous variables. Adjusted logistic regression was used to compare the odds ratio (OR) of the prognosis of CSCR patients with that of controls.

Results. In CSCR patients, we observed an increased prevalence of topical ophthalmic corticosteroid use (OR 6.328, 95% confidence interval [CI] 5.786–6.921, $P < 0.0001$). After adjusting for age, sex, geographic location of the patient's residence, hypertension, diabetes mellitus, hyperlipidemia, chronic renal disease, peptic ulcer, psychiatric disease, allergic respiratory disease, coronary artery disease, and corticosteroid use, conditional logistic regression analysis showed that CSCR patients were more likely to have used topical ophthalmic corticosteroids recently than the controls (OR 6.036, 95% CI 5.512–6.610, $P < 0.0001$).

Conclusions. Results strongly support an association between recent topical ophthalmic corticosteroid use and CSCR. Thus, patients who require ophthalmic corticosteroids should be advised of the associated risk of developing CSCR.

Keywords: central serous chorioretinopathy, Taiwanese population, mode of steroid administration

Central serous chorioretinopathy (CSCR) is an idiopathic and multifactorial chorioretinal disorder, characterized by detachment of the retinal neuroepithelium from the pigment epithelium with accumulation of fluid in the macular region, which may be related to increased permeability from choriocapillaries or impaired function of the RPE.[1–4] The condition mainly affects young and middle-aged adults, primarily men. Patients often present with a sudden, mild reduction in visual acuity, micropsia, metamorphopsia, and defects in the center of the visual field. Clinically, CSCR can develop acutely and often resolves spontaneously within 3 to 6 months.[5] Within the first year, recurrent episodes often occur. Central serous chorioretinopathy also can present chronically, with distinctive RPE changes, persistent shallow retinal detachment, and visual impairment.[4–7] An improved understanding of CSCR has changed the notion that it is a benign condition affecting young men that resolves almost completely. Central serous chorioretinopathy shows a spectrum of presentations with diffused retinal dysfunction, and is a common cause of visual impairment.[5]

The pathophysiology of CSCR is poorly understood, but alterations in choroidal circulation and RPE function have been hypothesized to play a role, following improvements in imaging techniques, such as fluorescein angiography, optical coherence tomography, indocyanine green angiography,[8] and fundus autofluorescence.[9] Although the etiology and triggering factors

of CSCR are not clearly understood, the condition is commonly associated with the use of systemic or topical corticosteroids.[10,11] Corticosteroids may contribute to these changes by virtue of their propensity to increase platelet aggregation, and may favor conditions promoting microthrombus formation and increased blood viscosity, thus altering choroidal microcirculation.[4] The effects of long-term use of corticosteroids include increased hyperpermeability and induced choriocapillary fragility, although they reduce vessel permeability with short-term use.[12–14] In addition, recently a mechanism has been proposed by which corticosteroids contribute to choriocapillary hyperpermeablity by interacting with the mineralocorticoid receptor (MR).[15,16] Furthermore, corticosteroids induce a nonapoptotic, caspase-independent form of cell death related to paraptosis in RPE cells, which constitute the outer blood-retinal barrier, leading to accumulation of subretinal fluid.[14,17]

In fact, the condition has been associated with corticosteroid use through almost all routes of administration. In previous publications, corticosteroid administration through multiple routes was implicated in the development of acute exudative changes in CSCR. These include oral,[11,18] intravenous,[13] epidural,[19,20] intra-articular,[21] and even, most recently, intranasally administered[22,23] and inhaled[24] corticosteroids. Numerous other risk factors, including alcohol and tobacco intake, untreated hypertension, allergic airway disease,[11,23] and *Helicobacter pylori* infection,[25,26] also have been implicated as possible causes of CSCR. It is crucial to identify and clarify risk factors, especially significant risk factors, such as corticosteroids, to prevent further vision impairment.

Evidently, corticosteroids use is associated with CSCR by way of contributing to choriocapillaris, or RPE pathologic changes. However, most previous reports have focused on the use of systemic corticosteroids administered via the oral route, and their significance is limited because they were small-scale studies, case series, or case reports. There have been only a few reports to date of corticosteroids use via other routes, such as epidural injection, intra-articular injection, nasal spray, and inhalation, being associated with CSCR, and all are case reports. To our knowledge, there have been no reports investigating a link between the use of ophthalmic corticosteroids and CSCR, even though topical ophthalmic administration is the most direct route of corticosteroid administration for ocular absorption. Using a nationwide population-based dataset, we performed a case-controlled study to evaluate the association between recent topical ophthalmic corticosteroids use and CSCR in Taiwan.

Methods

Database

Since March 1, 1995, the Taiwan National Health Insurance (NHI) program has offered comprehensive medical care to all Taiwanese residents. More than 98% of the Taiwanese population (22.6 million members) have been included in this program since 2007. The NHI Research Database (NHIRD) provides encrypted patient identification numbers together with information on patients' dates of birth, sex, and dates of admission and discharge. It also incorporates the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes for diagnoses and procedures, prescription items, and costs covered by NHI. The Longitudinal Health Insurance Database 2000 (LHID2000), a part of the NHIRD, contains all claims data from 1996 to 2011 on 1 million beneficiaries who were randomly and systematically assigned to the database in 2000. No significant differences in age, sex, or average insured payroll-related premiums exist between the sampled group in the LHID2000 and all NHI enrollees.

Selection of Patients and Variables

This population-based case-controlled study included all LHID2000 patients diagnosed with CSCR (ICD-9-CM code 362.41) who received ambulatory (including emergency) or inpatient care from January 2001 to December 2010 (n = 2921). The controls (n = 17,526; six patients for each CSCR patient) were patients drawn from the dataset who had not been diagnosed with CSCR, and were matched with the study patients with regard to sex, age, geographic region, and index date via propensity scores. To reduce selection bias, we used propensity score matching because it enables grouping of the numerous confounding covariates in an observational study with this number of variables. The index date for the CSCR patients was the date of their initial diagnosis, and the index date for the control patients was created based on the index date of the CSCR patients. To ensure that the selected CSCR cases represented new episodes, patients diagnosed with CSCR in ambulatory care before January 2001 were excluded. In addition, to eliminate possible causes of RPE leaks other than CSCR, we excluded patients who had ever been diagnosed with any of the following conditions before enrollment: malignant neoplasm of the choroid (ICD-9-CM code 190.6), degenerative myopia (ICD-9-CM code 360.21), hemorrhagic RPE detachment (ICD-9-CM code 362.43), exudative AMD (ICD-9-CM code 362.52), macular hole (ICD-9-CM code 362.54), hereditary retinal dystrophies (ICD-9-CM code 362.7x), focal chorioretinitis (ICD-9-CM code 363.0x), disseminated chorioretinitis (ICD-9-CM code 363.1x), Harada's disease (ICD-9-CM code 363.22), and angioid streak (ICD-9-CM code 363.43).

To determine the medical comorbidities for CSCR based on previously reported risk factors, we recorded conditions such as diabetes mellitus (ICD-9-CM code 250), hyperlipidemia (ICD-9-CM code 272), hypertension (ICD-9-CM codes 401–405), chronic renal diseases (chronic glomerulonephritis: ICD-9-CM code 582, nephritis and nephropathy: ICD-9-CM code 583, acute renal failure: ICD-9-CM code 584, chronic kidney disease: ICD-9-CM code 585, renal failure: ICD-9-CM code 586, and disorders resulting from impaired renal function: ICD-9-CM code 588), peptic ulcer (ICD-9-CM codes 531–534), psychiatric diseases (drug-induced mental disorders: ICD-9-CM code 292; transient mental disorders: ICD-9-CM code 293; persistent mental disorders: ICD-9-CM code 294; schizophrenic disorders: ICD-9-CM code 295; episodic mood disorders: ICD-9-CM code 296; delusional disorders: ICD-9-CM code 297; nonorganic psychoses: ICD-9-CM code 298; pervasive developmental disorders: ICD-9-CM code 299; anxiety, dissociative, and somatoform disorders: ICD-9-CM code 300; personality disorders: ICD-9-CM code 301; sexual and gender identity disorders: ICD-9-CM code 302; drug dependence: ICD-9-CM code 304; nondependent abuse of drugs: ICD-9-CM code 305; physiological malfunction arising from mental factors: ICD-9-CM code 306; special symptoms: ICD-9-CM code 307; acute reaction to stress: ICD-9-CM code 308; adjustment reaction: ICD-9-CM code 309; and depressive disorder: ICD-9-CM code 311), allergic respiratory diseases (allergic rhinitis: ICD-9-CM code 477, and asthma: ICD-9-CM code 493), coronary artery disease (ICD-9-CM code 410-414), and corticosteroids administered, including cortisone, hydrocortisone, prednisolone, methylprednisolone, triamcinolone, betamethasone, and dexamethasone by various routes according to their formulations, including topical ophthalmic, oral, nasal spray, injected, and inhaled corticosteroids. These risk factors were identified based on an ICD-9-CM code being recorded within the 12

months preceding the index date, and ascertained by at least three clinical visits.

The research adhered to the tenets of the Declaration of Helsinki, and was exempted from review by the institutional review board of the Chi Mei Medical Center, Tainan.

Statistical Analysis

The software SAS 9.3.1 for Windows (SAS Institute, Inc., Cary, NC, USA) was used in this study. Demographic characteristics, such as age-group, sex, and geographic region, were analyzed using χ^2 tests, and Student's *t*-test was used for continuous variables. In addition, we compared the recent use of corticosteroids via various routes, and previously reported comorbidities (hypertension, diabetes mellitus, hyperlipidemia, chronic renal disease, peptic ulcer, psychiatric disease, and allergic respiratory disease) in the CSCR patients and the controls by using χ^2 tests. Conditional logistic regression (conditional on age, sex, geographic region, and index date) was used to compute the odds ratio (OR) for recent corticosteroid use via various routes between the CSCR patients and the controls, after adjusting for previously reported comorbidities and different routes of corticosteroid use. The level of significance was set at P less than 0.05.

Results

Demographic Data

After ineligible patients were excluded, 2921 CSCR patients and 17,526 age, sex, and geographic region–matched controls who had used medical care services covered by NHI between 2001 and 2010 were analyzed. The mean ages of the CSCR patients and the controls were 42.26 (SD 14.57) and 42.34 (SD 14.35) years respectively (Table 1). Of the 2921 patients with CSCR, 289 (9.89%) were younger than 25 years, 2069 (70.84%) were aged 25 to 54 years, 320 (10.96%) were aged 55 to 64 years, and 243 (8.32%) were aged 65 years or older. With regard to the sex distribution of the 2921 CSCR patients, 1673 (57.27%) were men and 1248 (42.73%) were women. With regard to geographic distribution, the most common region of residence of the patients diagnosed with CSCR was central Taiwan (1218; 41.70%), followed by the northern (1024; 35.06%), southern (613; 20.99%), and eastern regions (66; 2.26%).

Associated Risk Factors

Corticosteroid use via various routes within 1 year before the index date of CSCR diagnosis was examined by using univariate logistic regression (Table 2). Topical ophthalmic corticosteroid use was present in 1373 CSCR patients (47.00%) and 2227 controls (12.71%) (OR 6.328, 95% confidence interval [CI] 5.786–6.921, $P < 0.0001$). With regard to other routes of corticosteroid use, 23.01% of the CSCR patients and 15.65% of the controls used oral corticosteroids (OR 1.620, 95% CI 1.472–1.783, $P < 0.0001$), nasal spray corticosteroids were used by 3.01% of the CSCR patients and 1.65% of controls (OR 1.858, 95% CI 1.458–2.369, $P < 0.0001$), and injected corticosteroids were used by 8.80% of the CSCR patients and 5.52% of controls (OR 1.666, 95% CI 1.441–1.927, $P < 0.0001$). Inhaled corticosteroids use was present in 21 CSCR patients (0.72%) and 95 controls (0.54%), and was not a significant risk factor for CSCR (OR 1.330, 95% CI 0.827–2.139, $P = 0.2395$) (Table 2).

Previously reported comorbidities were also examined using univariate logistic regression (Table 2). As expected, the patients with CSCR exhibited a higher prevalence of several medical comorbidities than the controls. These comorbidities were hypertension (OR 1.451, 95% CI 1.265–1.664, $P < 0.0001$), diabetes mellitus (OR 1.427, 95% CI 1.195–1.703, $P < 0.0001$), hyperlipidemia (OR 1.484, 95% CI 1.232–1.787, $P < 0.0001$), chronic renal disease (OR 1.877, 95% CI 1.303–2.705, $P = 0.0007$), peptic ulcer (OR 1.728, 95% CI 1.441–2.072, $P < 0.0001$), psychiatric disease (OR 1.417, 95% CI 1.193–1.683, $P < 0.0001$), allergic respiratory disease (OR 1.727, 95% CI 1.427–2.089, $P < 0.0001$), and coronary heart disease (OR 1.649, 95% CI 1.314–2.069, $P < 0.0001$).

Table 3 shows the adjusted ORs of corticosteroid use via various routes of administration, and comorbidities, between the CSCR patients and the controls after adjustment for age, sex, geographic location of the patient's residence, hypertension, diabetes, hyperlipidemia, chronic renal disease, peptic ulcer, psychiatric disease, allergic respiratory disease, coronary artery disease, and the different routes of corticosteroid use. The OR for CSCR patients who had previously used topical ophthalmic corticosteroids was 6.036 (95% CI 5.512–6.610, $P < 0.0001$) compared with controls after adjustment for other confounding factors. Besides topical ophthalmic corticosteroid use, oral corticosteroid use (OR 1.222, 95% CI 1.097–1.361, $P = 0.0003$), nasal spray corticosteroid use (OR 1.374, 95% CI 1.038–1.817, $P = 0.0258$), and injected corticosteroid use (OR 1.177, 95% CI 1.000–1.386, $P = 0.0496$) remained significant risk factors after conditional logistic regression was conducted. Inhaled corticosteroids persistently exhibited no significant association with CSCR, despite adjustment for corticosteroids via other routes, and comorbidities (OR 0.786, 95% CI 0.463–1.337, $P = 0.3427$) (Table 3).

Of the medical comorbidities analyzed, only peptic ulcer (OR 1.366, 95% CI 1.116–1.673, $P = 0.0025$) and coronary artery disease (OR 1.320, 95% CI 1.016–1.716, $P = 0.0378$) remained significant risk factors after conditional logistic regression was conducted (Table 3). Other comorbidities, such as hypertension, diabetes mellitus, hyperlipidemia, chronic renal disease, psychiatric disease, and allergic respiratory disease, were not significant risk factors for CSCR after adjustment for other confounding factors (Table 3).

Table 1. Baseline Characteristics of CSCR Patients and Comparison Group Patients After Propensity Score Matching

	CSCR, $n = 2921$ *n* (%)	Comparison, $n = 17{,}526$ *n* (%)	*P*
Age, y, mean ± SD	42.26 ± 14.57	42.34 ± 14.35	0.7905*
Age, y			
<25	289 (9.89)	1663 (9.49)	0.8543†
25–34	705 (24.14)	4168 (23.78)	
35–44	822 (28.14)	4976 (28.39)	
45–54	542 (18.56)	3383 (19.30)	
55–64	320 (10.96)	1951 (11.13)	
≥65	243 (8.32)	1385 (7.90)	
Sex			
Female	1248 (42.73)	7445 (42.48)	0.8039†
Male	1673 (57.27)	10081 (57.52)	
Geographic region			
Northern	1024 (35.06)	6144 (35.06)	0.8789†
Central	1218 (41.70)	7264 (41.45)	
Southern	613 (20.99)	3678 (20.99)	
Eastern	66 (2.26)	440 (2.51)	

* Student's *t*-test.
† χ^2 test.

Table 2. Odds Ratios Obtained by Univariate Logistic Regression for Recent Corticosteroid Use Between CSCR Patients and Controls

	CSCR, $n = 2921$	Comparison, $n = 17{,}526$		
	n (%)	*n* (%)	Crude OR (95% CI)	*P*
Corticosteroid use				
Ophthalmic agent	1373 (47.00)	2227 (12.71)	6.328 (5.786–6.921)	<0.0001
Oral	672 (23.01)	2742 (15.65)	1.620 (1.472–1.783)	<0.0001
Nasal spray	88 (3.01)	289 (1.65)	1.858 (1.458–2.369)	<0.0001
Injection	257 (8.80)	968 (5.52)	1.666 (1.441–1.927)	<0.0001
Inhaler	21 (0.72)	95 (0.54)	1.330 (0.827–2.139)	0.2395
Comorbidity				
Hypertension	347 (11.88)	1582 (9.03)	1.451 (1.265–1.664)	<0.0001
Diabetes mellitus	175 (5.99)	770 (4.39)	1.427 (1.195–1.703)	0.0001
Hyperlipidemia	153 (5.24)	641 (3.66)	1.484 (1.232–1.787)	<0.0001
Chronic renal disease	39 (1.34)	127 (0.72)	1.877 (1.303–2.705)	0.0007
Peptic ulcer	162 (5.55)	584 (3.33)	1.728 (1.441–2.072)	<0.0001
Psychiatric disease	174 (5.96)	756 (4.31)	1.417 (1.193–1.683)	<0.0001
Allergic respiratory disease	143 (4.90)	509 (2.90)	1.727 (1.427–2.089)	<0.0001
Coronary artery disease	106 (3.63)	405 (2.31)	1.649 (1.314–2.069)	<0.0001

Discussion

On the basis of a thorough review of the relevant research, this study appears to be the only nationwide, population-based, case-controlled study to evaluate the association between recent topical ophthalmic corticosteroid use and CSCR. We analyzed 2921 CSCR patients and 17,526 control participants. Our results revealed that CSCR patients who used ophthalmically administered corticosteroids were at a much higher risk of CSCR than the general population, after the data were controlled for comorbidities.

Corticosteroids have been implicated in the development and pathogenesis of CSCR. Although the pathophysiology of CSCR is poorly understood, changes in choroidal circulation and dysregulation of RPE function have been hypothesized to play important roles. Enhanced depth imaging spectral-domain optical coherence tomography and indocyanine green angiography have demonstrated that hyperpermeability in choriocapillaries may be related to increased hydrostatic pressure within the choroidal circulation.[27] Fundus autofluorescence imaging has indicated reduced amounts of autofluorescent components within the cells, which may suggest reduced metabolic activity of the RPE in chronic CSCR.[28] The exact role of corticosteroids in the pathogenesis of CSCR is unclear. The hypothesis is that corticosteroids may alter choroidal microcirculation and increase choriocapillary hyperpermeability, by promoting blood coagulation and affecting the production of prostaglandins. In addition, corticosteroids may result in choriocapillary ion pumping dysfunction by inhibiting collagen formation and altering ion and water transport in epithelia.[12] Furthermore, El Zaoui et al.[14] and Torriglia et al.[17] demonstrated that corticosteroids triggered a reduction in mitochondrial activity, and an activation of a caspase-independent cell death mechanism in RPE cells. Corticosteroids have a propensity to delay reparative processes in disrupted RPE cells by suppressing fibroblastic activity and inhibiting the synthesis of extracellular matrix components. Following damage to RPE tight junctions, which constitute the outer blood–retinal barrier, corticosteroids change the permeability of ocular barriers leading to an accumulation of subretinal fluid.

Table 3. Covariate-Adjusted ORs for Corticosteroid Use Among the Sampled Patients ($n = 20{,}447$)

	Adjusted OR* (95% CI)	*P*
Corticosteroid use		
Ophthalmic agent	6.036 (5.512–6.610)	<0.0001
Oral	1.222 (1.097–1.361)	0.0003
Nasal spray	1.374 (1.038–1.817)	0.0228
Injection	1.177 (1.000–1.386)	0.0496
Inhaler	0.786 (0.463–1.337)	0.3427
Comorbidity		
Hypertension	1.068 (0.907–1.257)	0.4300
Diabetes mellitus	1.113 (0.907–1.364)	0.3048
Hyperlipidemia	1.107 (0.892–1.373)	0.3572
Chronic renal disease	1.416 (0.945–2.122)	0.0923
Peptic ulcer	1.366 (1.116–1.673)	0.0025
Psychiatric disease	1.138 (0.941–1.376)	0.1818
Allergic respiratory disease	1.192 (0.950–1.495)	0.1290
Coronary artery disease	1.320 (1.016–1.716)	0.0378

* Adjusted OR was calculated by conditional logistic regression that was conditioned on age group, sex, geographic region, and the year of index date.

Recently, several studies investigated the role of corticosteroids in the pathogenesis of CSCR. These studies highlight the importance of the MR, which interacts with corticosteroids and contributes to choriocapillary hyperpermeability.[15,16] Corticosteroids can be subdivided into glucocorticoid (cortisol) and mineralocorticoid (aldosterone) hormones, and bind not only to the glucocorticoid receptor but also the MR, with similarly high affinity.[29] Mineralocorticoid receptor is expressed by endothelial cells of choroid vessels, choriocapillaries, and the neuroretina.[15,30] An excess of corticosteroids activates the MR pathway in the endothelial cells of choroid vessels, thereby inducing choroidal vessel and choriocapillary vasodilation and focal leakage, both of which cause choroidal thickening.[15,16] If the hypothesis that activation of the MR pathway by corticosteroids leads to choroid hyperpermeability is correct, then this constitutes additional evidence of the role of corticosteroids in the pathogenesis of CSCR.

To date, no treatment has yet been shown to be thoroughly effective for the treatment of chronic CSCR, or shorten the duration of serous detachment in acute CSCR. To our knowledge, many novel treatments have been proposed to reduce steroid levels or effects in accordance with hypotheses on pathogenesis, such as mifepristone (a glucocorticoid receptor antagonist),[31] finasteride (an inhibitor of dihydrotestosterone synthesis),[32] ketoconazole (a partial inhibitor of

steroid synthesis),[33] and rifampicin (an enzymatic activator administered to speed corticosteroid metabolism).[34] Furthermore, the success of these treatments constitutes supportive evidence for a role of corticosteroids in the development of CSCR.

Our study is the first to investigate the association between topical ophthalmic steroids and CSCR. We detected an increased prevalence of topical ophthalmic corticosteroid use in CSCR patients (OR 6.328, 95% CI 5.786–6.921, $P < 0.0001$). The CSCR patients were more likely to have recently used topical ophthalmic corticosteroids than the controls (OR 6.036, 95% CI 5.512–6.610, $P < 0.0001$) after adjustment for other comorbidities. The ophthalmic route of administration of corticosteroids is the most direct route of delivery to ocular tissue, and it is frequently prescribed by ophthalmologists. Several approaches can be used to facilitate the diffusion of topically applied agents that are at least theoretically capable of reaching the posterior segment. Topical administration of corticosteroids may allow the agents to reach the posterior segment through either the transcorneal or transconjunctival pathways.[35,36] Additionally, topical ophthalmic corticosteroids may diffuse into the iris root or via the pars plana to penetrate and distribute to the posterior segment of the eye, without encountering the blood-retinal barrier.[37] Furthermore, ophthalmically administered topical corticosteroids can diffuse across the sclera and choroid, and subsequently penetrate the Bruch's membrane and RPE. Finally, topical ophthalmic corticosteroids can gain access to the retinal vessels, or be absorbed into the systemic circulation via conjunctival vessels or the nasolacrimal duct, to a lesser extent.[35–39] Extra caution should be exercised by ophthalmologists prescribing ophthalmic administration of topical corticosteroids, and patients should be advised of the associated risk of CSCR.

We found a statistically significant association between CSCR and oral corticosteroid use (crude OR 1.620, 95% CI 1.472–1.783, $P < 0.0001$; adjusted OR 1.222, 95% CI 1.097–1.361, $P = 0.0003$), consistent with many previous reports. Recently, Tsai et al.[18] demonstrated that current use of oral corticosteroids was associated with a risk of CSCR (OR 2.40; 95% CI 1.49–3.89, $P < 0.0001$) in a population-based study. Haimovici et al.[11] reported a retrospective, case-controlled study including 312 CSCR patients and 312 controls. They reported that systemic steroid use was a significant risk factor for CSCR (OR 37.1, 95% CI 6.2–221.8). With regard to the lower OR of oral corticosteroids than that of topical ophthalmic corticosteroids for CSCR, it is possible that orally administered corticosteroids reach parts of the posterior segment of the ocular, such as the choroid and retina, via systemic circulation. However, ocular components and the systemic circulation are separated by the blood-ocular barrier, which is maintained by tight junctions at the retinal vascular endothelium, the iris vascular epithelium, and the nonpigmented ciliary epithelium.[38–41]

A statistically significant association between CSCR and intranasal corticosteroid use was demonstrated in our study, consistent with many previous reports.[22,24] Intranasal steroids and second-generation antihistamines are recommended as first-line allergic rhinitis therapy drugs, which are aimed at reducing allergy-related inflammation.[42] Notably, only four cases of CSCR specifically linked to intranasal corticosteroids were detected in a search of the English literature. Our report is the largest population-based case-controlled study to investigate the association between intranasally administered corticosteroids and CSCR development.

Injected corticosteroids were mildly significantly associated with CSCR after adjustment. The injection of corticosteroids may be used for intravenous, retrobulbar, subconjuctival, intravitreal, epidural, or intra-articular administration. There was a general trend of statistical significance with regard to the associations between CSCR and the various injection routes for corticosteroids. Further research is required to clarify the associations between the injection of corticosteroid formulations via various different routes, and CSCR.

In addition to associations between CSCR and the administration of corticosteroids via different routes, our results confirmed that several previously well-recognized comorbidities, such as hypertension, diabetes mellitus, hyperlipidemia, chronic renal disease, peptic ulcer, psychiatric disease, coronary artery disease, and allergic respiratory disease, are risk factors for CSCR (Table 2).[43] However, only peptic ulcer and coronary artery disease remained significant risk factors after conditional logistic regression was conducted (Table 3). This finding was consistent with the results of several previous studies reporting that patients with preexisting peptic ulcer or coronary heart disease had a higher incidence of CSCR.[43,44] Additionally, several reports have demonstrated that after antibiotic treatment for *H. pylori* infection, patients with both peptic ulcer and CSCR showed an improvement in CSCR.[26,45,46]

This study had several strengths. Because it was based on a nationwide and population-based dataset, selection bias with regard to referral centers was not a concern. The NHIRD contains electronically recorded claims data, which ensured accuracy and obviated recall bias. Furthermore, several previous studies using the same database have proven to be valid.[47,48] In addition, the study was case-controlled, and incorporated 10 years of longitudinal data on recently administered topical ophthalmic corticosteroids in CSCR patients and a comparison cohort. Our results are reliable, because hypertension, diabetes, hyperlipidemia, chronic renal disease, peptic ulcer, psychiatric disease, and allergic respiratory disease were recognized as potentially confounding factors when assessing the associations between administration of corticosteroids via various routes, and OR in patients with CSCR, and appropriate adjustments were made for these potentially confounding variables.

This study had several limitations. The medical history of the patients sampled could be traced only back to 1996. Therefore, there is no information to confirm that the controls had no CSCR history before January 1996, potentially compromising our findings. Second, although the ICD-9 code 362.41 is relatively specific and new-onset CSCR with typical serous neurosensory retinal detachment is relatively straightforward to diagnose, interpretation of the imaging studies was impossible using the insurance-claim data source; thus, the diagnoses could not be confirmed. To mitigate this problem, we excluded causes of RPE leaks other than CSCR to reduce the potential influence of misdiagnosis. Notably, similar analyses have been used to identify CSCR and have proven valid in previous ophthalmic studies using similar exclusion criteria.[44,49,50] Differences in the doses and frequencies of topical ophthalmic corticosteroid use were not adjusted for in comparisons between the CSCR patients and the control patients. However, Han et al.[51] characterized the influences of high-dose corticosteroids on choroidal thickness, and concluded that steroid-induced CSCR could be an idiosyncratic reaction in vulnerable individuals, rather than a dose-dependent response. In a related point, Tsai et al.[18] showed that the dosage and duration of treatment with oral corticosteroids were not associated with CSCR risk. This observation suggests that the fact that doses and frequencies of topical ophthalmic corticosteroid use were not adjusted for in the current study may not have had a substantial impact on the results of the analyses. Finally, personal characteristics that might contribute to CSCR, such as psychological stress, were not available in the administrative database, potentially compromising our results.

We evaluated psychiatric disease as a confounding factor, to mitigate this problem.

In summary, after controlling for hypertension, diabetes, hyperlipidemia, chronic renal disease, peptic ulcer, psychiatric disease, and allergic respiratory disease, patients who had used topical ophthalmic corticosteroids within 1 year before the index date of CSCR diagnosis were at a higher risk of developing CSCR than controls. This association should be clarified in future studies, to enhance understanding of the pathophysiology of CSCR. Finally, as frequent prescribers of topical ophthalmologic corticosteroids, ophthalmologists should warn patients in need of corticosteroids of the potential for associated CSCR development.

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