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Scleritis and episcleritis in patients with idiopathic small fiber neuropathy☆

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ABSTRACT

Purpose: To report the prevalence of scleritis and episcleritis in patients with idiopathic small fiber neuropathy (SFN).

Methods: The Mass General Brigham (MGB) hospital database was queried for patients with SFN, scleritis and episcleritis using diagnostic codes and natural language processing. Electronic medical chart review of patients diagnosed with SFN and episcleritis/scleritis who had at least one ophthalmology visit was conducted. The prevalence of scleritis and episcleritis in patients diagnosed with SFN was compared to those without SFN using logistic regression to adjust for covariates. All statistical analyses were performed in RStudio 4.2.1.

Results: From the 2100 SFN patients with an eye exam in the MGB database, 23 patients had episcleritis or scleritis (1.1 %) confirmed by chart review. Ten patients had episcleritis (0.48 %) and thirteen patients had scleritis (0.62 %). Of the episcleritis and scleritis patients, 16 (69.6 %) were women and 7 (30.4 %) were men. Ten (43.5 %) had bilateral ocular disease. The mean age of ocular diagnosis was 51.0 years (range, 22–77 years). Out of the 507,128 controls without SFN in the MGB database, 1481 (0.29 %) had scleritis and 1430 (0.28 %) had episcleritis. Episcleritis and scleritis were more prevalent in patients with SFN than in those without SFN: 0.48 % vs. 0.28 % for episcleritis and 0.62 % vs 0.29 % for scleritis (P values = 0.32 and 0.02, respectively).

Conclusions and Importance: There were higher rates of scleritis in SFN patients compared to non-SFN patients. This potential systemic disease association had not been previously reported.

1. Introduction

Small fiber neuropathy (SFN) is caused by widespread selective damage to small-diameter somatic and autonomic unmyelinated C-fibers and/or thinned myelinated A-delta fibers.[1] Although there are some known etiologies, one-third to half of cases are considered idiopathic and these idiopathic cases are felt to be immune-mediated[2] and have an inflammatory pathophysiology.[3,4]

Ocular anatomic changes in patients with SFN have been reported. A study using confocal microscopy showed a reduction in corneal nerve fiber density, branch density, and fiber length, as well as an increase in nerve fiber tortuosity in patients with SFN.[5] The corneal sub-basal nerve fiber density and length have also found to be significantly reduced in SFN patients.[5,6] After conducting a literature review on 4/1/24 utilizing PubMed and Google Scholar using the key words “scleritis”, “episcleritis”, “small fiber neuropathy” and “SFN”, we did not find any prior reports of the prevalence of ocular inflammation in patients with SFN. In our practice, we have encountered several patients with idiopathic SFN who develop scleritis and/or episcleritis in the absence of other immune-mediated disorders. The purpose of this report is to describe the prevalence of episcleritis and scleritis in patients with idiopathic SFN in a large hospital database and present two patients with SFN and scleritis who responded well to intravenous immunoglobulin (IVIg).

2. Methods

This retrospective review was approved by the Mass General Brigham Institutional Review Board. The electronic medical record of the Mass General Brigham Health System, which includes the Massachusetts Eye and Ear Infirmary, was queried to identify patients with SFN.

To identify patients with idiopathic SFN, natural language processing search of the notes was performed with the following terms: small

☆ **Claims of Priority:** After conducting a literature review on 4/1/24 utilizing PubMed and Google Scholar using the key words “scleritis”, “episcleritis”, “small fiber neuropathy” and “SFN”, we did not find any prior reports of scleritis or episcleritis in small fiber neuropathy patients.

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fiber neuropathy and SFN. We also searched using the International Classifications of Diseases (ICD) code G62.9 (polyneuropathy, unspecified). To confirm the SFN diagnosis, detailed medical chart review was performed. Patients with a secondary cause for their SFN including diabetes, Sjogren's syndrome, relapsing polychondritis, undifferentiated connective tissue disease, granulomatosis with polyangiitis (GPA), multiple sclerosis, and psoriatic arthritis, were excluded.

Among the patients with idiopathic SFN, we searched for those with a documented examination by an eye care professional. Among those with a documented eye examination, we queried notes with ICD-10 codes and natural language processing for scleritis and episcleritis. Detailed medical chart review to confirm the noninfectious scleritis and episcleritis was performed. Patients were excluded if they had other underlying autoimmune or autoinflammatory diseases, such as GPA, rheumatoid arthritis and inflammatory bowel disease, that could be an underlying cause for their ocular inflammation.

To compare the prevalence of ocular inflammatory diseases in the SFN population to that in the general population in our health care system, we searched for all patients who did not have an ICD code for SFN or the terms SFN or small fiber neuropathy in their notes with natural language processing and who had an eye exam by an eye care provider. Among these patients, we searched for patients with scleritis and episcleritis within their notes using ICD codes and natural language processing.

Patient demographic data was expressed as mean with standard deviation for age, and percentages for each gender, race, and ethnicity. The demographic distributions were compared between the SFN population and non-SFN population using a two-sample *t*-test for age and a chi-square test for gender, race, and ethnicity. The prevalences of scleritis and episcleritis in idiopathic SFN patients were measured and compared with the prevalences in patients without SFN using a logistic regression model adjusting for age, gender, race, and ethnicity. A P-value of less than 0.05 was considered statistically significant. All statistical analyses were performed in RStudio 4.2.1.

3. Results

We identified 2100 patients with idiopathic SFN and an eye examination. Of these 2100 patients, 23 had a diagnosis of episcleritis and/or scleritis without another immune-mediated systemic disease. Among the 23 cases, the mean age was 51.0 years with a range of 22–77 years. Sixteen patients (69.6 %) were female, and race was self-reported as White in 17 patients (73.9 %), Black in four patients (17.4 %), Asian in one patient (4.3 %), and Not Available in one patient (9.1 %). Ethnicity was Non-Hispanic in 21 (91.3 %) patients and Unknown in one patient (4.3 %).

Given that 23 patients had episcleritis and/or scleritis, this yielded a prevalence of 1.1 % for episcleritis and/or scleritis among patients with idiopathic SFN. Ten (0.48 %) patients had episcleritis and thirteen (0.62 %) patients had either anterior or posterior scleritis. Ten of the 23 patients had bilateral disease.

The demographic data of SFN patients and controls are shown in Table 1. We identified 507,128 controls – patients without SFN and with documentation of at least one eye examination. 1481 (0.29 %) had scleritis and 1430 (0.28 %) had episcleritis. Compared with patients without SFN, patients with SFN included in the study were more likely to be women (70.8% vs .55.1%), more likely to be White (80.7% vs 68.9%), and less likely to be Hispanic (1.4% vs.2.8%).

In logistic regression models, the prevalence of scleritis in patients with SFN was significantly higher compared to the control group of patients without SFN (P value = 0.02) when adjusting for age, gender, race, and ethnicity. While the prevalence of episcleritis in patients with SFN was higher (0.48 %) than that of patients without SFN (0.28 %), this difference was not statistically significant in logistic regression models (P value = 0.32) (see Table 2).

Table 1
Demographic characteristics of study populations.

Demographic characteristics	SFN with scleritis and/or episcleritis (N = 23)	SFN with eye examination (N = 2100)	No-SFN with eye examination Controls (N = 507,128)	P-value[a]
Average Age (SD)	51.0 (12.6)	60.4 (17.8)	59.3 (20.8)	0.0047
Sex				4.33×10^{-47}
Female	16 (69.6 %)	1487 (70.8 %)	279,614 (55.1 %)	
Male	7 (30.4 %)	612 (29.1 %)	227,450 (44.9 %)	
Unknown	0 (0.0 %)	1 (0.05 %)	64 (0.01 %)	
Race				5.07×10^{-12}
White	17 (73.9 %)	1695 (80.7 %)	349,775 (68.9 %)	
Asian	1 (4.3 %)	71 (3.4 %)	28,214 (5.6 %)	
American Indian/Alaska Native	0 (0.0 %)	6 (0.3 %)	751 (0.1 %)	
Black or African American	4 (17.4 %)	127 (6.0 %)	38,388 (7.5 %)	
Native Hawaiian or Other Pacific Islander	0 (0.0 %)	1 (0.05 %)	351 (0.1 %)	
Other	0 (0.0 %)	115 (5.5 %)	35,834 (7.1 %)	
Not available	1 (4.3 %)	85 (4.0 %)	53,815 (10.6 %)	
Ethnicity				1.38×10^{-6}
Hispanic	1 (4.3 %)	29 (1.4 %)	14,238 (2.8 %)	
Non-Hispanic	21 (91.3 %)	1816 (86.5 %)	367,281 (72.4 %)	
Unknown	1 (4.3 %)	255 (12.1 %)	125,609 (24.8 %)	

[a] For comparison between SFN patients with an eye examination to No-SFN patients with an eye examination.

Table 2
Prevalence of ocular inflammatory diseases in SFN patients and controls.

Ocular inflammatory disease	SFN patients (N = 2100)	Controls Without SFN (N = 507,128)	P-value
Scleritis	13 (0.62 %)	1481 (0.29 %)	0.02
Episcleritis	10 (0.48 %)	1430 (0.28 %)	0.32

4. Cases

Below we present two illustrative patients with SFN and scleritis who responded well to IVIg, a therapy commonly used for SFN. The patients also had simultaneous presentation of their ocular inflammation and neurologic symptoms.

5. Patient 1

A 61-year-old woman presented with right eye pain and right-sided temple pain. At presentation, her best-corrected visual acuity (BCVA) was 20/30 in the right eye and 20/30-1 in the left eye. Her anterior segment and fundus examinations were unremarkable. Her B scan showed T sign with thickened choroid in the right eye, and she was diagnosed with posterior scleritis. Her review of symptoms was positive for burning, pain and numbness over her whole body. Workup for infectious and noninfectious causes of scleritis was unremarkable including blood urea nitrogen/creatinine (BUN/Cr), urinalysis (UA),

angiotensin-converting enzyme (ACE), lysozyme, Lyme antibody, complete blood count (CBC), antineutrophilic cytoplasmic antibody (ANCA), double-stranded deoxyribonucleic acid (dsDNA) antibodies, rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP), rapid plasma reagin (RPR), QuantiFERON-TB Gold, and fluorescent treponemal antibody absorption test (FTA-ABS). She was started on Celebrex 200 mg daily without improvement, so she was given one infusion of intravenous methylprednisolone 1 g and started on Prednisone 40 mg daily with a 10 mg taper every 2 weeks. The right eye improved on Prednisone. She was evaluated for her neurologic symptoms. She had an extensive work up that was remarkable for a positive skin biopsy for length-dependent SFN affecting predominantly sensory fibers. She started on intravenous IVIg for both her scleritis and SFN. Her neuropathy and eye symptoms were controlled on IVIg for three years until she had to stop IVIg during the COVID pandemic, after which she was switched back to Celebrex and 40 mg Prednisone daily. She was tapered off Prednisone and then maintained on Celebrex monotherapy.

6. Patient 2

A 23-year-old woman presented with eye pain in both eyes. BCVA was 20/25 in the right eye and 20/20 in the left eye. Her anterior segment and fundus examinations were unremarkable. B-scan showed bilateral sclerochoroidal thickening temporally. The workup for infectious and immune causes of scleritis were all normal or negative: CBC, ACE, Lyme IgG/IgM, FTA-ABS, RPR, QuantiFERON-TB Gold, lysozyme, ANCA, RF, CCP, chest radiography (CXR), antinuclear antibody (ANA). She received 3 daily infusions of IV methylprednisolone 1g followed by a prednisone taper. Concurrently with her eye symptoms, the patient had paresthesias involving all four limbs. A skin biopsy was performed which was consistent with SFN and she was started on IVIg. The IVIg improved her paresthesias and ocular symptoms and allowed for her to taper the Prednisone down to 10 mg daily. The patient was subsequently transitioned to subcutaneous immunoglobulin (SCIg) due to ease of at home self-administration and has remained stable on SCIg 17g weekly and prednisone 5 mg daily for the past four years with no side effects.

7. Discussion

We report a higher prevalence of scleritis and episcleritis in SFN patients compared with patients without SFN, and this difference was statistically significant for scleritis in a large hospital database. It has been reported that up to half of scleritis patients have an underlying immune-mediated systemic inflammatory condition.[7] Episcleritis is most often idiopathic but sometimes associated with systemic collagen vascular disorders, autoimmune diseases, or infections.[8] After conducting a literature review on 4/1/24 utilizing PubMed and Google Scholar using the key words “scleritis”, “episcleritis”, “small fiber neuropathy” and “SFN”, we confirmed that scleritis and episcleritis have never been reported to occur in association with SFN. The two cases we present particularly support a potential association between SFNand scleritis as eye and SFN symptoms were temporally associated and jointly responded to therapy.

Some clinicians consider dry eyes as a common diagnostic symptom in patients with SFN although there are no definitive epidemiological studies connecting SFN and dry eye. In a study of 55 patients in China with neuropathic pain, they evaluated the diagnostic value of an SFN symptom inventory questionnaire of 13-items rated on a 4-point Likert scale including dry eyes, diarrhea, constipation, urinary tract problem, dry mouth, dizziness when standing up, palpitations, hot flashes, sensitive leg skin, burning feet, sheet intolerance and restless legs at night.[9] They diagnosed 20 patients with SFN using nerve conduction studies, skin biopsies, and the questionnaire. The most common etiology amongst those diagnosed with SFN was idiopathic. The results showed that this questionnaire had a moderate diagnostic value for SFN with 80 % sensitivity and 81.8 % specificity. This clinical study illustrates that dry eye symptoms are felt to be associated strongly enough to SFN by clinicians so as to include them in diagnostic questionnaires.

If SFN involves the cornea, it can cause symptoms of neuropathic corneal pain (NCP) including pain, aching, burning, irritation, dryness, and grittiness.[10] A recent case series described three patients with NCP and SFN confirmed by skin biopsy, suggesting an association between SFN and the pathogenesis of NCP.

It is important to know how to distinguish other SFN-related eye manifestations from scleritis and episcleritis because they can all present with eye pain but should have different treatment approaches. The vague symptoms in posterior scleritis and NCP could present a challenge for diagnosis. Scleritis can be differentiated from SFN-associated dry eyes and NCP through the redness and swelling of the sclera and lack of blanching of redness with topical vasoconstrictors in anterior scleritis or presence of a T sign on B scan in cases of posterior scleritis.[11] Performing a B scan in patients with SFN is crucial in order not to miss posterior scleritis. Episcleritis may be more difficult to distinguish so it is important to rule out dry eye and NCP. Dry eye may be confirmed with Schirmer testing and NCP may be confirmed by corneal confocal microscopy to reveal nerve fiber abnormalities. There are also varying phenotypes of episcleritis such as diffuse and nodular episcleritis. Simple or diffuse episcleritis is typically distinguished by sectoral and diffuse redness that resolves in one to two weeks, while nodular episcleritis is focal, raised, and can take longer to resolve. Since episcleritis is more difficult to distinguish, it is often a diagnosis of exclusion and other etiologies should first be ruled out.[12]

In recent years, IVIg has increasingly been used to treat idiopathic SFN because of its success in treating certain chronic immune-mediated polyneuropathies[13,14] and SFN secondary to other systemic conditions.[15–17] It may be important to identify SFN as an underlying disease in patients with scleritis since IVIg might be considered earlier in the disease course than it would otherwise, as IVIg is not usually first-, second- or even third-line steroid-sparing agent for scleritis. In the two patients in this report, IVIg led to good control of the scleritis activity as well as of their SFN-related symptoms.

Although scleritis and episcleritis were more prevalent among SFN patients than among patients without SFN, the difference was only statistically significant for scleritis cases. This could have been due to insufficient power. SFN, scleritis, and episcleritis are rare diseases, and even though this study was performed within a large health care system with over 6.5 million participants, there were only 2100 patients that met our inclusion criteria of having SFN and a documented eye examination. Of these 2100, only 23 had scleritis or episcleritis.

Our study has other limitations as well. Patients with SFN diagnosed within our system might have had eye examinations outside our system and we may have under ascertained the prevalence of scleritis and episcleritis. However, this misclassification bias would also have affected the controls (non-SFN patients) similarly, so it is unlikely to have altered the relative difference in scleritis/episcleritis rates between cases and controls. Another limitation is that not all of the patients with SFN had biopsy-proven disease and thus there may be misclassification of some of the cases. We did, however, exclude patients with other immune-mediated/autoimmune diseases that can cause neuropathies that mimic SFN, thus limiting the extent of misclassification of SFN.

8. Conclusions

In conclusion, scleritis was found to be statistically more prevalent among patients with SFN than non-SFN controls. Episcleritis was also more prevalent among patients with SFN, but not significantly. This potential association is important for therapeutic implications since IVIg is a treatment with proven benefits in SFN that might also be efficacious for scleritis.

CRediT authorship contribution statement

Atitaya Apivatthakakul: Writing – review & editing, Writing – original draft, Investigation, Data curation. **Renee Liu:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation. **Marez Megalla:** Writing – review & editing, Investigation, Data curation. **Daniel A. Brill:** Writing – review & editing, Investigation, Data curation. **Lucia Sobrin:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

9. Patient Consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors have no conflict of interest.

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