



## Utility of coronal contrast-enhanced fat-suppressed FLAIR in the evaluation of optic neuropathy and atrophy

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### ABSTRACT

**Background and purpose:** Evaluating chronic sequelae of optic neuritis, such as optic neuropathy with or without optic nerve atrophy, can be challenging on whole brain MRI. This study evaluated the utility of dedicated coronal contrast-enhanced fat-suppressed FLAIR (CE-FS-FLAIR) MR imaging to detect optic neuropathy and optic nerve atrophy.

**Materials and methods:** Over 4.5 years, a 3 mm coronal CE-FS-FLAIR sequence at 1.5T was added to the routine brain MRIs of 124 consecutive patients, 102 of whom had suspected or known demyelinating disease. Retrospective record reviews confirmed that 28 of these 102 had documented onset of optic neuritis >4 weeks prior to the brain MRI. These 28 were compared to the other 22 (“controls”) of the 124 patients who lacked a history of demyelinating disease or visual symptoms. Using coronal CE-FS-FLAIR, two neuroradiologists separately graded each optic nerve (n = 50 patients, 100 total nerves) as either negative, equivocal, or positive for optic neuropathy or atrophy. The scoring was later repeated.

**Results:** The mean time from acute optic neuritis onset to MRI was  $4.1 \pm 4.6$  years (range 34 days–17.4 years). Per individual nerve grading, the range of sensitivity, specificity, and accuracy of coronal CE-FS-FLAIR in detecting optic neuropathy was 71.4–77.1%, 93.8–95.4%, and 85.5–89.0%, respectively, with strong interobserver ( $k = 0.667 - 0.678$ ,  $p < 0.0001$ ), and intraobserver ( $k = 0.706 - 0.763$ ,  $p < 0.0001$ ) agreement. For optic atrophy, interobserver agreement was moderate ( $k = 0.437 - 0.484$ ,  $p < 0.0001$ ), while intraobserver agreement was moderate-strong ( $k = 0.491 - 0.596$ ,  $p < 0.0001$ ).

**Conclusion:** Coronal CE-FS-FLAIR is quite specific in detecting optic neuropathy years after the onset of acute optic neuritis, but is less useful in detecting optic nerve atrophy.

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### 1. Introduction

Optic neuritis is an inflammatory condition commonly affecting patients with multiple sclerosis, in which inflammation and demyelination of the optic nerve causes clinical symptoms of acute vision loss, ophthalmalgia, and/or dyschromatopsia [1–3]. While the symptoms of optic neuritis can resolve quickly, the sequelae of subacute/chronic optic nerve changes – i.e. optic neuropathy either with or without nerve atrophy – may be detected clinically via dedicated testing once the acute symptoms have resolved [4].

MRI evaluation of the optic nerves can be difficult given the inherent difficulties of orbital imaging, such as motion artifact, small optic nerve size, surrounding osseous structures, and adjacent CSF or fat [5]. Various sequences with CSF or fat suppression and faster acquisition times have improved the detection of acute optic neuritis, such as contrast-enhanced (CE) fat-suppressed (FS)-T1WI, FS-FLAIR, FS-FSE T2WI, DIR, STIR, SPIR-FLAIR, and HASTE [6–10]. However, the diagnosis of its chronic sequelae can be more diagnostically challenging. As opposed to an enlarged, enhancing nerve in acute optic neuritis, the MRI findings in the subacute/chronic stages may be less apparent [11–16].

Hence, as both unenhanced and CE-FS-FLAIR have demonstrated utility in diagnosing acute optic neuritis and various CNS disorders, CE-FS-FLAIR may also be useful in detecting optic neuropathy or atrophy, particularly if the patient is a poor historian or the ophthalmologic findings are indeterminate [6,15–20]. Thus, the purpose of this study was to evaluate the utility of coronal CE-FS-FLAIR MR

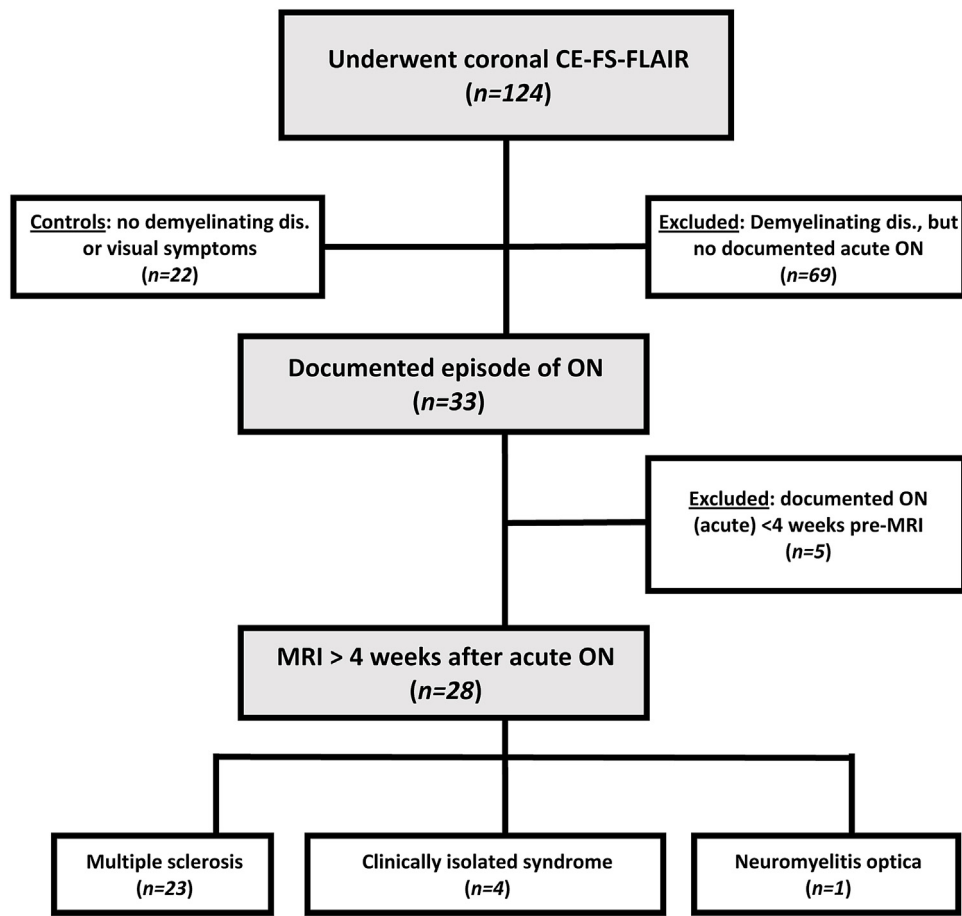
**Abbreviations:** CE, Contrast-Enhanced; CE-T1WI, Contrast-Enhanced T1WI; FS, Fat-Suppressed; CE-FS-FLAIR, Contrast-Enhanced Fat-Suppressed FLAIR.

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**Fig. 1.** Cohort and control selection criteria. CE-FS-FLAIR = contrast-enhanced fat-suppressed-FLAIR; dis. = disease; ON = optic neuritis.

images in detecting both optic neuropathy and optic nerve atrophy as chronic sequelae of acute optic neuritis.

## 2. Materials and methods

### 2.1. Patient cohort and controls

After internal review board approval for this retrospective study, an electronic health record review was performed on 124 consecutive patients who underwent coronal CE-FS-FLAIR imaging on two 1.5T MRI scanners over a 4.5-year period at a single institution (Fig. 1). Of these 124 patients, 102 were obtained for known or suspected demyelinating disease. Inclusion criteria for the patient cohort was solely confirmation of a prior episode of optic neuritis >4 weeks prior to the MRI, as confirmed by a neurologist or ophthalmologist on dedicated neuro-ophthalmic evaluation. Of the 102 patients, 33 patients met the inclusion criteria. Exclusion criteria from this 33 patient cohort were: 1) an additional episode of optic neuritis that occurred within four weeks of the MRI ( $n=5$ ), or 2) the CE-FS-FLAIR MR images were too compromised by motion or artifact for review ( $n=0$ ). Ultimately, 28 patients were included as the “cohort”. Another 22 patients with various vague symptoms (e.g. headache, paresthesias, etc.) had a whole brain MRI series to exclude demyelinating disease. These patients had no history of optic neuritis or demyelinating disease, and their routine brain MRI had no findings to suggest optic nerve or orbital pathology, demyelinating disease, or other cerebral pathology. Thus, this group was included as “controls”.

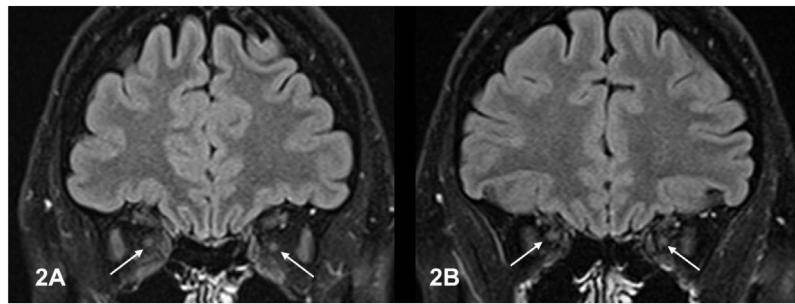
### 2.2. Image Acquisition/Technique

Over a 4.5-year period, 3 mm thickness postcontrast coronal CE-FS-FLAIR (spectral fat saturation) images of the entire brain were added to a routine brain MRI protocol used to evaluate for demyelinating disease. Notably, CE-T1WI of the entire brain was part of the protocol in both the patient cohort and controls, but neither coronal thin-section (3 mm) T1WI or CE-FS-T1WI was obtained of the orbits, as the clinical concern expressed was not specifically for optic evaluation.

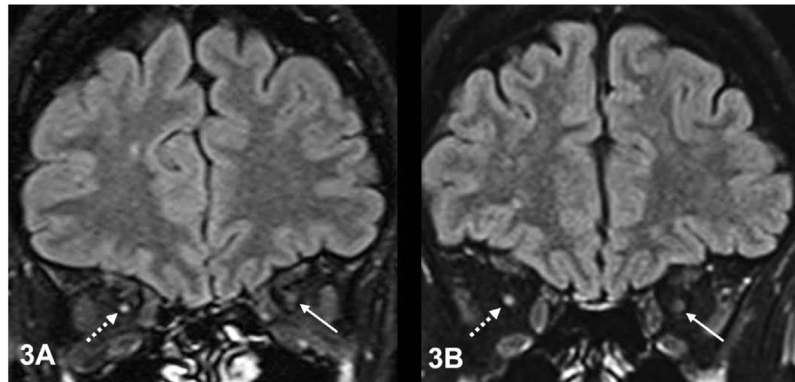
All examinations were performed on two 1.5T field strength MRI scanners (*Siemens 1.5T Symphony and Siemens 1.5T Avanto, Siemens Medical Solutions USA, Inc., Malvern, PA, USA*). The sequence parameters were: 6500–9000/105–110/2000–2100/1–2/15–23 (TR/TE/TI/NEX/echo train length). A weight-based dose of gadolinium-based contrast (gadobutrol) was administered (*Gadovist, Bayer Healthcare, Whippany, NJ, USA*) at 0.1 mmol/kg concentration, with a maximum dose of 10 ml. The CE-FS-FLAIR sequence was acquired between 5 and 7 min following the contrast bolus, and the acquisition time was 4–5 min.

### 2.3. Image review

Prior to image review, two staff neuroradiologists (AMM, JBR) agreed that optic neuropathy would be diagnosed as optic nerve hyperintensity relative to the intraorbital musculature. The cerebral hemispheres were covered in order to avoid bias from visualizing any cerebral abnormalities. Optic nerve atrophy would be subjectively assessed as a decreased caliber of the optic nerve.



**Fig. 2.** Control patient. A 41 year old male with no history of demyelinating disease, visual symptoms, or WM findings. Coronal CE-FS-FLAIR images (A and B) demonstrate normal signal within both optic nerves (arrows), with adequate CSF and fat suppression. Both nerves were scored “negative” by both neuroradiologists on both reviews.



**Fig. 3.** Optic neuropathy. A 42 year old female with a history of acute right optic neuritis 6.5 years earlier. On coronal CE-FS-FLAIR (A and B), both neuroradiologists were blinded to the clinical history, and graded the right optic nerve (dotted arrows) as “definitely positive”, and the left optic nerve (arrows) as negative for optic neuropathy on both reviews. Regarding atrophy, the right was variably graded as “definitely positive”, “equivocal”, and “negative”, based on the reviewer.

Utilizing solely the coronal CE-FS-FLAIR sequence and being blinded to the clinical history, the two staff neuroradiologists (AMM, JBR) separately graded each optic nerve in the 28 patient cohort and 22 controls as “negative”, “equivocal”, or “definitely positive”, regarding the presence of optic neuropathy and optic nerve atrophy (Figs. 2–5). Fifty total patients were reviewed, for a total of 100 optic nerves. MRI scoring was repeated 3–5 weeks later to avoid recall bias (each nerve was evaluated twice by two observers, for a total of 400 scores). The scorers identified any MRI artifacts or anatomic limitations precluding optic nerve evaluation.

#### 2.4. Statistical analysis

The sensitivity, specificity, and accuracy of the reviews of the coronal CE-FS-FLAIR sequence were compared to the prior clinical examinations at the time of the acute optic neuritis episode, which were used as the standard. Any prior episode with a positive clinical examination on a particular side was considered a true positive. The sensitivity, specificity, and accuracy were performed on both a “per nerve” basis, as well as a “per patient” basis (i.e. if either side was positive on MRI, then the patient was overall recorded as positive). Statistical analyses were performed via *Statsdirect* software (*Statsdirect Ltd., Altrincham, Cheshire, UK*). Both *interobserver* and *intraobserver* Cohen’s kappas were calculated regarding the optic nerve findings on CE-FS-FLAIR, with the significance threshold set to  $p < 0.05$ .

### 3. Results

#### 3.1. Patient demographics

The 28 patient cohort with a prior clinically confirmed episode of optic neuritis consisted of patients with: multiple sclerosis

( $n=23$ ), clinically isolated syndrome ( $n=4$ ), and neuromyelitis optica ( $n=1$ ). This cohort was composed of 15 females and 13 males (age range 15–58 years, mean  $41.0 \pm 11.2$ ). The control group consisted of 13 females and 9 males (age range 24–68 years, mean  $39.6 \pm 10.1$ ). In the patient cohort, the brain MRI including coronal CE-FS-FLAIR was performed a mean of  $4.1 \pm 4.6$  years (range 34 days–17.4 years) after the most recent episode of acute optic neuritis.

#### 3.2. Optic neuropathy

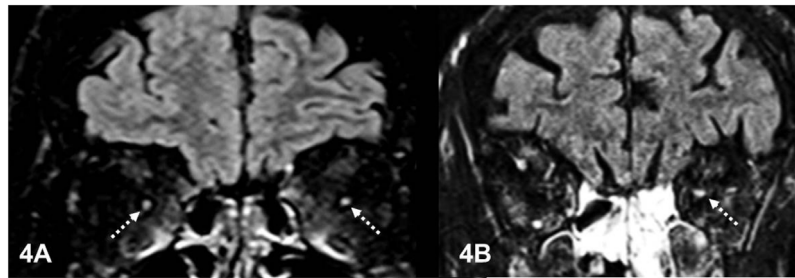
Based on the individual nerve evaluation of 100 optic nerves, when scoring the nerves as “definitely positive” for optic neuropathy, the ranges of sensitivity, specificity, and accuracy were: 71.4–77.1%, 93.8–95.4%, and 85.5–89.0%, respectively, per observer. Based on a per-patient evaluation of the 50 patients, the ranges were: 75.0–83.9%, 100–100%, and 86.0–91.0%, respectively.

Alternatively, if a score of either “definitely positive” or “equivocal” were both considered as “positive” for having optic neuropathy, the individual “per-nerve” evaluation ranges of sensitivity, specificity, and accuracy were: 88.6–90.0%, 76.2–86.9%, and 81.5–87.5%, respectively. Alternatively, on a “per-patient” evaluation, the ranges were: 91.1–94.6%, 75.0–84.1%, and 84.0–91.0%, respectively.

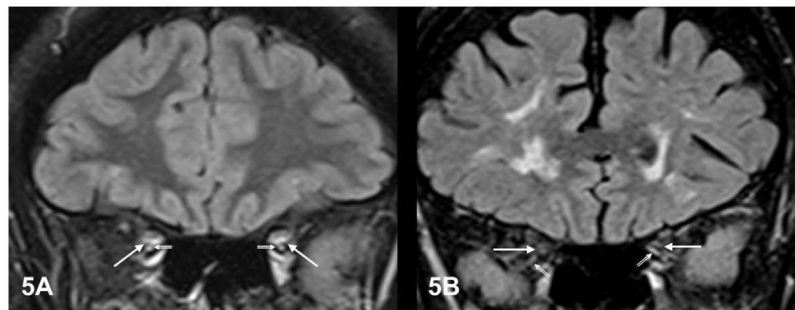
The calculated *interobserver* agreement for optic neuropathy was  $k=0.667 - 0.678$  ( $p < 0.0001$ ), while the *intraobserver* agreement was  $k=0.706 - 0.763$  ( $p < 0.0001$ ).

#### 3.3. Optic nerve atrophy

The *interobserver* and *intraobserver* agreement for the subjective assessment of optic nerve atrophy was  $k=0.437-0.484$  ( $p < 0.0001$ ) and  $k=0.491 - 0.596$  ( $p < 0.0001$ ), respectively. Documentation from a neurologist or ophthalmologist as to the presence



**Fig. 4.** Optic neuropathy, atrophy, and interobserver discrepancy. A: In a 29 year old male with bilateral optic neuritis 16–20 months prior, both nerves (*dotted arrows*) are bright on CE-FS-FLAIR, and were scored “definitely positive” for neuropathy and atrophy twice by both observers. B: In a 48 year old male with optic neuritis 17.4 years prior, the left nerve was graded “definitely positive” for neuropathy (*dotted arrows*) twice by one observer, whereas the other graded it “definitely positive”, then “equivocal”. Regarding atrophy, both reviewers variably scored the left nerve on both reviews.



**Fig. 5.** Examples of artifacts. A: In a 56 year old female with bilateral optic neuritis 9 months prior, bright signal surrounds both nerves (*arrows*), perhaps from venous plexi or CSF non-suppression. Both nerves were variably graded “equivocal” or “negative” by both observers for optic neuropathy. B: In another 39 year old female with left optic neuritis 15.5 years prior, bright signal was noted in adjacent ophthalmic vessels (*tiny arrows*). Both nerves were variably graded by both observers as “equivocal” and “negative” for optic neuropathy. Regarding atrophy, both nerves were variably scored on both reviews.

or absence of optic nerve atrophy at the time of MRI was uncommonly available. Thus, no reliable gold standard for optic nerve atrophy was available in this study.

### 3.4. Artifacts/Limitations

Overall, 54/400 nerves (13.5%) were graded as “equivocal” for optic neuropathy (range 9–20 per reviewer per round of 100 optic nerves), and 54/400 nerves (13.5%) were graded as “equivocal” for optic nerve atrophy (range 8–22 per observer per round of 100 optic nerves). The most common artifacts included patient motion and incomplete fat or CSF suppression, each present in 13/50 patients (26%). Anatomic confounders such as an adjacent ophthalmic vessel occurred in 11/50 patients (22%) (Fig. 5). However, neither observer found that such artifacts precluded the CE-FS-FLAIR images from review in any of the cohort or controls.

## 4. Discussion

Optic neuritis and optic neuropathy are typically considered clinical diagnoses, with MRI ordered primarily to exclude other pathology or to evaluate for concomitant demyelinating disease [21]. Yet, optic nerve T2/FLAIR hyperintensity or enhancement could suggest a prior episode of optic neuritis in patients with no clinical history of optic neuritis [15,20].

This study aimed to determine the utility of coronal CE-FS-FLAIR in detecting optic neuropathy and atrophy as chronic sequelae of acute optic neuritis. Accordingly, coronal CE-FS-FLAIR has a high specificity (93.8–100%) and relatively high accuracy (85.5–91.0%) for detecting optic neuropathy. While the sensitivity (71.4–83.9%) is suboptimal, in clinical practice the pre-test probability for optic neuropathy increases with additional information such as a history

of demyelinating disease or concomitant WM abnormalities on MRI (e.g. multiple sclerosis plaques). Thus, the true sensitivity and accuracy of this sequence may actually be higher, as evidenced by the fact that when the equivocal nerves were included with the definite positives, sensitivity increased to 88.6–94.6%. Nevertheless, the strong inter- and intraobserver agreement in detecting optic neuropathy highlights the reproducibility of recognizing these findings.

In contrast, there was only moderate inter- and intraobserver agreement in detecting optic nerve atrophy, suggesting detecting optic nerve atrophy is less reproducible on coronal CE-FS-FLAIR. One possible way to increase atrophy detection would be to increase the field strength to 3T, which has been shown to improve lesion detection in acute optic neuritis; however, to our knowledge, no study has evaluated coronal CE-FS-FLAIR at 3T in detecting optic neuropathy or atrophy [8,22].

Several studies have evaluated the utility of FLAIR/T2WI in detecting acute optic neuritis, but few have evaluated FLAIR/T2WI in detecting optic neuropathy [6,9,10,20]. A small study of 6 patients with an episode of optic neuritis >4 weeks prior were imaged with noncontrast, whole brain extended echo-train acquisition FLAIR, which demonstrated a specificity of 100% for detecting optic neuropathy [20]. Conversely, none of these patients had optic nerve enhancement on coronal CE-FS-T1WI. Another study by Hickman et al. showed optic neuropathy on coronal-oblique FS-T2WI FSE images for all 17 patients with an episode of optic neuritis 3–81 months prior to imaging. Compared to the aforementioned sequences, coronal CE-FS-FLAIR has similar specificity for detecting optic neuropathy, and superior sensitivity compared to coronal CE-FS-T1WI. By adding CE-FS-FLAIR to routine brain MRI protocols that were ordered to evaluate for demyelinating disease, the radiologist may gain a more confident diagnosis of optic neuropathy, as well as detect concomitant intracranial pathology [17–19].

A key finding of this study was the length of time in which optic nerve hyperintensity was visible after the onset of optic neuritis, occurring up to 17.4 years later. To the authors' knowledge, no prior study has demonstrated persistent hyperintensity on CE-FLAIR from optic neuropathy so many years after the onset of optic neuritis. Rather, a study by Youl et al. suggested that optic nerve enhancement commonly ceases within four weeks of the episode of optic neuritis [29].

Persistent hyperintensity on CE-FS-FLAIR may be primarily a result of T2/FLAIR signal prolongation, as previously described [15,20]. Alternatively, the hyperintensity could represent low-grade residual inflammation, such as from ongoing demyelination, enhancing scar tissue, or another less understood mechanism that reflects neuronal and blood-brain barrier injury. In this regard, Hickman et al. showed that optic nerve atrophy occurs primarily in the first few years following the acute episode, but suggested that sequelae of optic neuritis may extend beyond the phase of optic nerve atrophy [14]. Future research could focus on serially measuring the degree of intensity in the affected optic nerves over time on coronal CE-FS-FLAIR to help determine whether there is active inflammation (fluctuating intensity), scar tissue (relatively stable intensity), or some other etiology.

Another possible utility of coronal CE-FS-FLAIR relates to the common finding of ubiquitous cerebral deep or periventricular WM abnormalities on T2WI and FLAIR imaging, which can invoke a long list of differential diagnoses, including chronic small vessel vasculopathy, infectious/inflammatory etiologies, migraines, or various systemic diseases [23–26]. In this scenario, optic nerve hyperintensity could increase the radiologist's confidence in suggesting multiple sclerosis, as the presence of WM disease in combination with sequelae of optic neuritis increases the likelihood of developing multiple sclerosis [27,28]. Conversely, if optic neuritis or its sequelae is the only MRI abnormality, the likelihood of developing multiple sclerosis is relatively low. Thus, coronal CE-FS-FLAIR has the potential ability to add prognostic value for these patients.

Limitations of the current study are that the interobserver agreement for the presence of optic nerve atrophy was only moderate, and that no clinical corroboration was obtained to confirm optic nerve atrophy. Although comprehensive neuro-ophthalmic exams were commonly documented in the acute optic neuritis phase, commentary on optic nerve atrophy at the time of MRI in this patient cohort was inconsistent. In this regard, other studies have evaluated the degree of optic atrophy via cross-sectional measurements and segmentation, based on DTI, FS-short echo FLAIR, and magnetization transfer imaging [12,14–16]. Also, alternative imaging modalities such as optical coherence tomography have directly measured optic nerve atrophy via quantification of the microscopic retinal nerve fiber layer [16,30]. Thus, some form of clinical or other imaging corroboration of optic atrophy would have been useful to confirm the finding of atrophy on coronal CE-FS-FLAIR.

Another limitation of coronal CE-FS-FLAIR was incomplete suppression of the orbital fat or perineural CSF, which was noted in 26% of patients. However, the artifacts did not preclude adequate evaluation of any of the optic nerves in this study. Alternative MRI sequences have been developed to reduce artifacts surrounding the optic nerve. For example, 3D DIR may achieve adequate CSF and WM suppression, with a reported sensitivity and specificity of 95% and 94%, respectively, for detecting optic neuritis [9]. SPIR-FLAIR is an alternative technique combining fat and CSF suppression to improve the sensitivity of detecting optic nerve abnormalities by increasing contrast-to-noise [10]. However, these techniques have not been utilized to detect chronic sequelae of optic neuritis. Thus, while fat and CSF suppression is not always uniform, the high specificity of coronal CE-FS-FLAIR highlights its utility in detecting optic neuropathy.

## 5. Conclusion

In conclusion, coronal CE-FS-FLAIR is, by itself, very specific in detecting optic neuropathy, with highly reproducible results. Importantly, optic neuropathy may be detectable over 17 years after the acute optic neuritis episode. With additional clinical information and standard accompanying brain MRI sequences, the sensitivity and accuracy of coronal CE-FS-FLAIR for detecting sequelae of optic neuritis could potentially be significantly heightened. However, coronal CE-FS-FLAIR, by itself, seems less effective in evaluating for optic nerve atrophy.

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## Conflicts of interest

None.

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