Original Article

Neuro-ophthalmic features of patients with spontaneous cerebrospinal fluid leaks

Timothy Do [1], Jui-Kai Wang [2,3], Toby Steele [4], E. Bradley Strong [4], Kiarash Shahlaie [5] and Yin Allison Liu [5,6,7]

[1] *School of Medicine, University of California, Davis, USA*
[2] *Department of Ophthalmology and Visual Sciences, University of Iowa, Iowa, USA*
[3] *Center for the Prevention and Treatment of Visual Loss, Iowa City VA Health System, Iowa, USA*
[4] *Department of Otorhinolaryngology, University of California, Davis, USA*
[5] *Department of Neurological Surgery, University of California, Davis, USA*
[6] *Department of Ophthalmology, University of California, Davis, USA*
[7] *Department of Neurology, University of California, Davis, USA*

ABSTRACT

Background: Increased intracranial pressure is a potential cause of spontaneous cerebrospinal fluid (sCSF) leak. Associated neuro-ophthalmic features have not been well studied, particularly relationships with idiopathic intracranial hypertension (IIH). We hypothesized that neuro-ophthalmic features routinely used in evaluations for IIH can be useful in the investigation of a causal relationship between IIH and sCSF leak. We reviewed the neuro-ophthalmic examination and office-based ophthalmic imaging data of all consecutive patients with sCSF leaks and at least one repair to investigate the clinical and neuro-ophthalmic features of increased intracranial pressure.

Methods: We conducted a retrospective longitudinal study at a single institution by querying the electronic medical record system for CSF leak Current Procedural Terminology (CPT) codes (G96.00 and G96.01) from June 1, 2019, to July 31, 2022. For patients with a confirmed diagnosis of sCSF leak, demographic information, eye examination results, and ophthalmic imaging details for both eyes were collected.

Results: A total of 189 patients with CSF leaks were identified through CPT coding; 159 had iatrogenic or traumatic CSF leaks, and 30 individuals (3 male, 27 female) had confirmed sCSF leaks. The mean age of patients with sCSF leaks was 46 years (range: 29 – 81), with a mean body mass index of 35.2 kg/m^2 (range: 18.2 – 54.1). Only 11 of 30 underwent eye examinations (8 before surgical repair and 10 after). The mean pre-repair and post-repair best-corrected visual acuity were 20/30 (range: 20/20 – 20/55) and 20/25 (range: 20/20 – 20/40), respectively (P=0.188). The mean retinal nerve fiber layer thickness was 99 µm (range: 96 – 104) pre-repair and 97 µm (range: 84 – 103) post-repair (P=0.195). The mean ganglion cell complex thickness was 84 µm (range: 72 – 94) pre-repair and 82 µm (range: 71 – 94) post-repair (P=0.500). Humphrey visual field average mean deviation was -5.1 (range: -12.4 – -1.8) pre-repair and -1.0 (range: -10.1 – 2.1) post-repair (P=0.063).

Conclusions: Serial neuro-ophthalmic examinations are recommended for patients with sCSF leaks to screen for signs of current or prior increased intracranial pressure. Larger studies are required to clarify the longitudinal changes in neuro-ophthalmic features, to investigate the incidence of IIH in cases of sCSF leak development or recurrence after surgical repair, and to explore potential causal relationships to guide post-repair management and prevent recurrent leaks. A multicenter consortium is also suggested to develop a standard clinical protocol for comprehensive management of sCSF leaks.

KEYWORDS

spinal cerebrospinal fluid leak, spontaneous, idiopathic intracranial hypertension, benign intracranial hypertension, associations, optical coherence tomography, visual field

Correspondence: Yin Allison Liu, Department of Ophthalmology, University of California, Davis, USA. Email: aycliu@ucdavis.edu. ORCID iD: https://orcid.org/0000-0003-4483-9951

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INTRODUCTION

Spontaneous cerebrospinal fluid (sCSF) leaks occur when cerebrospinal fluid (CSF) exits the subarachnoid space in the anterior or middle cranial fossa and flows into the adjacent sinonasal cavities through a dehiscence in the lamina dura [1]. They are not associated with trauma, surgery, iatrogenic causes, or any other leading events. sCSF leaks account for 4% of all CSF leaks [2]. Patients typically present with clear, watery drainage into the nasal cavities or middle ear, resulting in rhinorrhea and/or otorrhea. The diagnosis may be overlooked because of a low level of suspicion or the absence of active leakage during the clinical examination [1, 3].

A hypothesized mechanism of the association between sCSF leaks at the skull base and elevated intracranial pressure (ICP) is the gradual erosion of the skull base and/or dura by persistently high and pulsatile CSF pressure [4]. The potential causal relationship between idiopathic intracranial hypertension (IIH) and sCSF leaks has been investigated [4, 5]. According to a review [5], there is substantial demographic overlap between patients with IIH and those with sCSF leaks. Surgical repair of CSF leaks is the standard of care to prevent complications such as meningitis and pneumocephalus [6]. However, neuro-ophthalmic features have not been researched in patients with sCSF leaks, particularly their associations with IIH prior to leakage and after surgical repair. Recommendations for pre-operative evaluation and post-operative management are inconsistent and anecdotal [7].

Optical coherence tomography (OCT) is a non-invasive ophthalmic imaging technology that enables three-dimensional (3D) cross-sectional imaging of the retina and optic nerve. Peripapillary retinal nerve fiber layer (RNFL) thickness, total retinal thickness, and optic nerve head (ONH) volume are standard objective measurements to assess papilledema severity [8, 9]. The global and regional thicknesses of the ganglion cell plus inner plexiform layer (GCIPL) in an annulus grid centered at the fovea are also commonly used to evaluate retinal nerve structure [8, 10].

We hypothesized that neuro-ophthalmic features routinely used in evaluations for IIH can be useful in the investigation of a causal relationship between IIH and sCSF leak. In this study, we retrospectively reviewed the neuro-ophthalmic examination and office-based ophthalmic imaging data of all consecutive patients with sCSF leaks and at least one repair to investigate the clinical and neuro-ophthalmic features of increased ICP.

METHODS

This single-institution, retrospective, longitudinal study was conducted at the University of California Davis Medical Center in Sacramento, California, USA. De-identified patient data were utilized. The institutional review board at the University of California, Davis, reviewed and approved this research protocol.

A query was performed in the electronic medical record system spanning the period between June 1, 2019, and July 31, 2022. The Current Procedural Terminology (CPT) codes G96.00 and G96.01 were used to identify consecutive patients with CSF leaks. Chart review and positive beta2-transferrin test results confirmed the diagnosis of sCSF leak [11]. Patients without a confirmed sCSF leak diagnosis, at least one surgical repair, or at least one eye examination were excluded from the analysis.

Demographic data, which included age, biological sex, race/ethnicity, and department of presentation, were recorded. Metrics documented at each neuro-ophthalmic examination included symptoms at presentation, body mass index (BMI), best-corrected visual acuity (BCVA) using a Snellen chart (Nikon Chart Projector NP-3S; Nikon Inc., Melville, NY, USA), and intraocular pressure (IOP) measurement using either the Goldmann applanation tonometer (AT900, Haag-Streit, Koeniz, Switzerland), iCare tonometer (IC100, Revenio Group, Vanta, Finland), or Tono-Pen (Tono-Pen AVIA®, Reichert Inc., Depew, NY, USA) in both eyes. The Snellen-equivalent BCVAs were converted to logarithm of the minimum angle of resolution (logMAR) values. Ophthalmic imaging data included OCT measurements of the RNFL and the ganglion cell complex (GCC) at each clinic visit, visual field index (a staging index for the total amount of visual field loss), and mean deviation on Humphrey visual field 24-2 SITA Standard test (HVF) (Humphrey Field Analyzer 750 II-I; Carl Zeiss Meditec).

We analyzed a total of 84 OCT ONH scans and 76 OCT macular scans (Cirrus HD-OCT Model 5000; Carl Zeiss Meditec) from the 11 patients in our study sample. Regarding OCT image dimensions, each available ONH scan had $200 \times 200 \times 1024$ voxels covering $6 \times 6 \times 2$ mm^3, and each available macular scan had $512 \times 128 \times 1024$ voxels also covering $6 \times 6 \times 2$ mm^3. To quantify the retinal structure, multiple retinal layers in the ONH and macular scans were automatically segmented using the 3D Iowa graph-based algorithm [12, 13]. For the ONH scans, the ONH volume was calculated by estimating the 3D space between the internal limiting membrane and the lower boundary of the retinal pigment epithelium complex. For the global peripapillary RNFL and total retinal thicknesses, the mean thicknesses of the RNFL and total retinal layer were individually estimated along

the peripapillary circle, which was aligned at the optic disc center and had a radius of 1.73 mm (as in the Cirrus protocol). For the macular scans based on layer segmentation of the inner retina, the fovea was automatically detected first. Then, the GCIPL thicknesses of six sectors were measured in the fovea-centered annulus grid. Details of the segmentation and grids were described in the Idiopathic Intracranial Hypertension Treatment Trial studies [8-10].

GraphPad Prism software version 9.5.1 (GraphPad Software Inc., San Diego, CA, USA) was used for statistical analyses. Descriptive statistics were used to analyze the baseline characteristic of our sample. Mean values were calculated for ophthalmic parameters, combining right and left eye measurements. The Wilcoxon matched-pairs signed rank test was used as a non-parametric test to compare dependent samples, and a *P*-value < 0.05 was considered statistically significant.

RESULTS

From our query, a total of 189 patients were identified using the CPT codes G96.00 and G96.01 (Figure 1); 159 had iatrogenic or traumatic CSF leaks, and 30 individuals (3 male, 27 female) had confirmed sCSF leaks. The mean age of patients with sCSF leaks was 46 years (range: 29 – 81), with a mean body mass index of 35.2 kg/m^2 (range: 18.2 – 54.1). Only 11 of 30 underwent eye examinations. Of the 11 patients who fulfilled our inclusion criteria, 8 underwent at least one examination prior to CSF leak repair and 10 underwent at least one eye examination after the repair. A total of 8 patients completed both the pre-repair and post-repair eye examinations. All 11 patients included in our study were female, with a mean (standard deviation [SD]) age of 46 (12) years at the time of sCSF leak diagnosis. The races/ethnicities of the patients are displayed in Figure 2A. The mean (SD) BMI was 37.9 (7.4) kg/m^2. No comorbid ophthalmic diseases such as glaucoma and macular disease were documented, and no patients were taking IOP-lowering eye drops.

The median time from symptom onset to diagnosis of sCSF leak was 2 years 3 months (range: 1 month – 20 years). Nine patients presented with CSF rhinorrhea, 1 with CSF otorrhea, and 1 with both CSF rhinorrhea and otorrhea. The patients presented with a sCSF leak diagnosis at several different departments in our medical center: 7 (64%) in otorhinolaryngology, 2 (18%) in neurosurgery, 1 (9%) in family medicine, and 1 (9%) in the emergency department. The median (Q1 – Q3) period between sCSF leak diagnosis and the first neuro-ophthalmic eye examination was 41 (14 – 120) days, and the mean (SD) was 126 (200) days. Of the 8 patients who underwent at least one ophthalmic examination prior to the initial CSF leak repair, 6 patients had examinations within 1 month prior to repair, 1 had examinations 1 – 2 months prior to repair, and 1 had examinations 8 – 10 months prior to repair. Of the 10 patients who underwent ophthalmic examinations in the year following their initial CSF leak repair, 5 had examinations at 3-month intervals for at least 1 year. Of the remaining patients, 2 had one examination at 3 months after the repair; 1 had one eye examination at 1 year after the repair; 1 had examinations at 6 months and 2 years; and 1 had examinations at 3-month intervals for only 9 months.

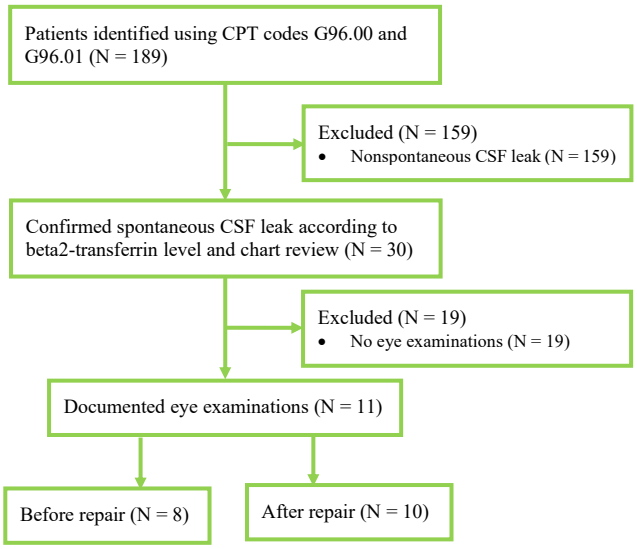

Figure 1. Flow diagram of recruitment, inclusion, and follow-up of study participants. Abbreviations: CPT, Current Procedural Terminology; N, number of patients; CSF, cerebrospinal fluid.

Of the 11 patients, 10 had a history of headaches and 2 had complications of meningitis prior to their CSF leak repairs. For post-operative management, 7 of the patients were prescribed acetazolamide for a median (Q1 – Q3) period of 13 (10 – 89) weeks. Only 1 patient underwent ventriculoperitoneal (VP) shunt placement for CSF diversion after a revision of the CSF leak repair. For weight loss management, 8 patients were referred to a weight-loss program; however, 1 of these never entered the program. Of the 7 patients active in the weight-loss program, only 2 achieved a loss of more than 10% of their initial body weight. Of 6 patients diagnosed with obstructive sleep apnea (OSA) by polysomnography, 5 began continuous positive airway pressure (CPAP) treatment.

Within our entire sample, 4 patients had recurrent leaks requiring at least one revision surgery. For those who required revision, the intervals between the initial and subsequent repairs were 34 days, 107 days, 200 days, and 509 days. All recurrent CSF leaks occurred at the same site of the initial leak. Of the 4 patients with recurrent leaks, only 3 were prescribed acetazolamide after the initial CSF leak repair, and 1 patient discontinued acetazolamide therapy after 1 week because of paresthesia. None of the 4 patients underwent VP shunt placement after the initial repair; however, 1 underwent shunt placement after revision. Of the 4 patients, 2 had notable weight loss between the times of initial repair and revision; 1 patient lost 13.58 kg and the other lost 15.82 kg. Two of those requiring revision were diagnosed with OSA and received CPAP treatment.

A total of 5 (45%) patients underwent lumbar puncture (LP) (Figure 2B); however, in 1 patient, opening pressure was noted only as extremely low with no numerical value given. Patient #2 underwent LP 15 months after surgical repair and received neither acetazolamide treatment nor VP shunting. Patient #6 underwent LP 2 months after surgical repair and received neither acetazolamide treatment nor VP shunting. Patient #8 underwent LP 7 months after the initial surgical repair and 1 week prior to revision surgery. She was prescribed acetazolamide 500 mg daily 2 days prior to LP and 500 mg twice daily the day prior to LP. She had no VP shunt at the time of LP. Patient #9 underwent LP 14 months prior to surgical repair and received neither acetazolamide therapy nor VP shunting. Patient #10 underwent LP 2 months after surgical repair and received neither acetazolamide therapy nor VP shunting.

A total of 7 patients had more than one eye examination after the initial surgical repair, and 3 patients had at least one eye examination after revision surgery. A non-parametric test for BCVA of the right eye (OD) and left eye (OS) demonstrated no significant difference between the two eyes when tested prior to sCSF leak repair ($P=0.625$) and after repair ($P=0.438$); therefore, OD and OS were not reported separately for eye examinations. Of the 8 patients who underwent at least one eye examination, the pre-repair data demonstrated a mean (range) Snellen BCVA of 20/30 (20/20 – 20/55) and a mean (SD) logMAR score of 0.17 (0.16). When

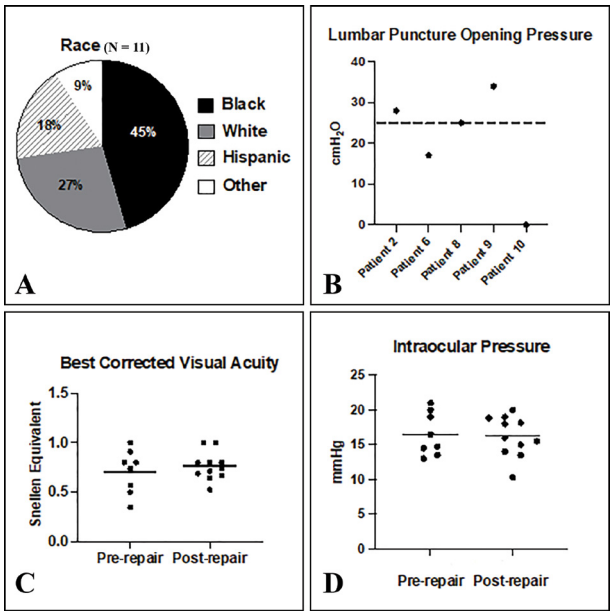

Figure 2. Patient demographic data, lumbar puncture results, and eye examination findings. (A) Distribution of races/ethnicities in our sample. (B) Lumbar puncture opening pressures in 5 patients. (C) Best-corrected visual acuity by Snellen chart (Nikon Chart Projector NP-3S; Nikon Inc., Melville, NY, USA) before and after surgical repair of spontaneous cerebrospinal fluid leak. (D) Intraocular pressure comparison before and after surgical repair. Abbreviations: n, number of patients; cmH_2O, centimeters of water; pre-repair, pre-operative; mmHg, millimeters of mercury.

compared to the pre-repair data, the post-repair data demonstrated a mean (range) Snellen BCVA of 20/25 (20/20 – 20/40) and a mean (SD) logMAR score of 0.13 (0.11) (P = 0.188, Figure 2C). Prior to leak repair, the mean (SD) IOP was normal at 16 (3) mmHg and the mean (SD) IOP was normal at 16 (3) mmHg after repair (P = 0.669, Figure 2D). None of the patients in this sample had optic disc edema by examination or OCT. All patients had normal RNFL measurements; however, 5 patients had thinning of the GCC.

The ophthalmic imaging results of an index patient are displayed in Figure 3. Within our sample, the ophthalmic parameters observed on routine OCT prior to sCSF leak repair were found statistically similar to those taken after repair. The mean (SD) RNFL and GCC thicknesses were observed to be 99 (3) μm and 84 (7) μm, respectively, prior to CSF leak repair. After repair, the mean (SD) RNFL thickness was normal at 97 (5) μm (P = 0.195, Figure 4A) and the GCC was also normal at 82 (7) μm (P = 0.500, Figure 4B). For the HVF examination, the pre-repair data illustrated a mean (SD) value of mean deviation measurements of -5.1 (4.0), and the post-repair data revealed an improvement to -1.0 (3.0) (P = 0.063, Figure 4C), which falls within the reference range of - 2.00 to + 2.00. The mean (SD) visual field index was 89% (15%) prior to sCSF leak repair and improved to 97% (0.05%) after sCSF leak repair (P = 0.313). The trends of ophthalmic imaging and HVF changes in patients who had at least three eye examinations are displayed in Figure 4D-F. In the 4 patients with recurrent leaks, RNFL measurements were normal; however, there was GCC thinning in the superotemporal quadrants.

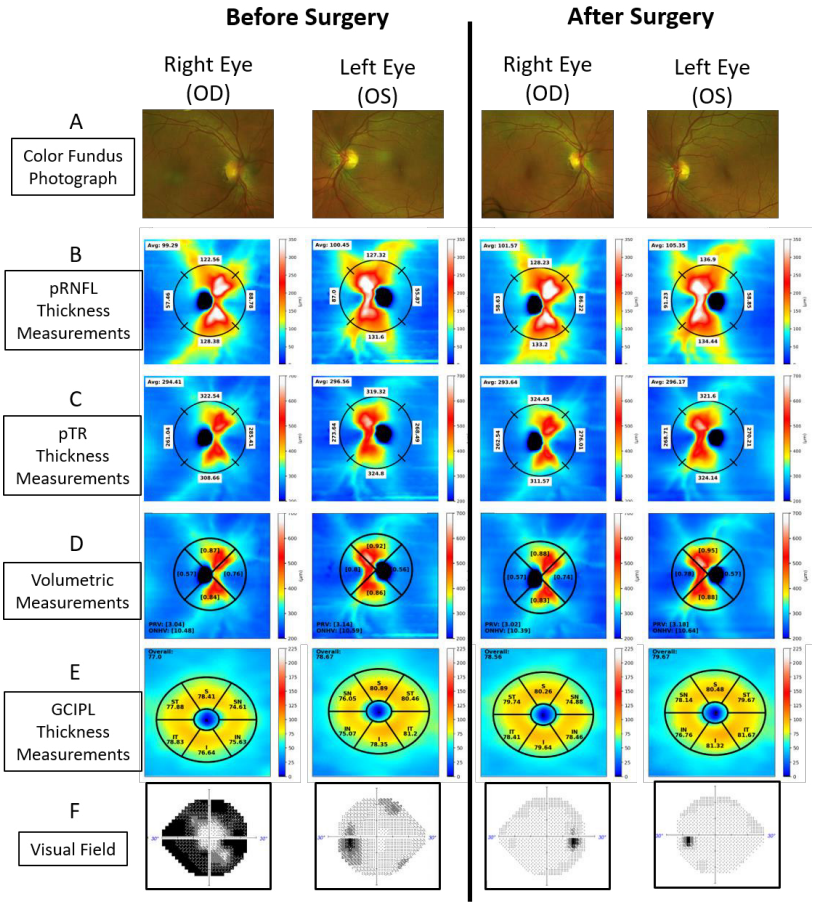

Figure 3. Ophthalmic testing of an index patient with spontaneous cerebrospinal fluid (sCSF) leak due to idiopathic intracranial hypertension before and after surgical repair. (A) Color fundus photographs show a blurred nasal margin of the right optic disc before surgery, which nearly resolved after surgery. Using the University of Iowa three-dimensional (3D) graph-based automated segmentation algorithm [12, 13], we demonstrated (B, C) the global and four (i.e., nasal, superior, temporal, and inferior)-quadrant mean thickness measurements of the retinal nerve fiber layer (pRNFL) and the total retina (pTR) along the peripapillary circle, centered at the optic disc with a 1.73-mm radius (as in the Cirrus protocol). (D) Volumetric measurements, including the optic nerve head volume (ONHV), the peripapillary region volume (PRV), and the volumes in each peripapillary quadrant. (E) Global and regional ganglion cell plus inner plexiform layer (GCIPL) thickness measurements in the standard annulus grid. All optical coherence tomography (Cirrus HD-OCT Model 5000; Carl Zeiss Meditec) measurements suggested no apparent optic nerve edema or atrophy before and after surgery. (F) Humphrey visual field 24-2 SITA Standard test (Humphrey Field Analyzer 750 II-I; Carl Zeiss Meditec) demonstrating severe visual defect of the right eye and an enlarged blind spot of the right eye before sCSF leak repair, which resolved after surgery.

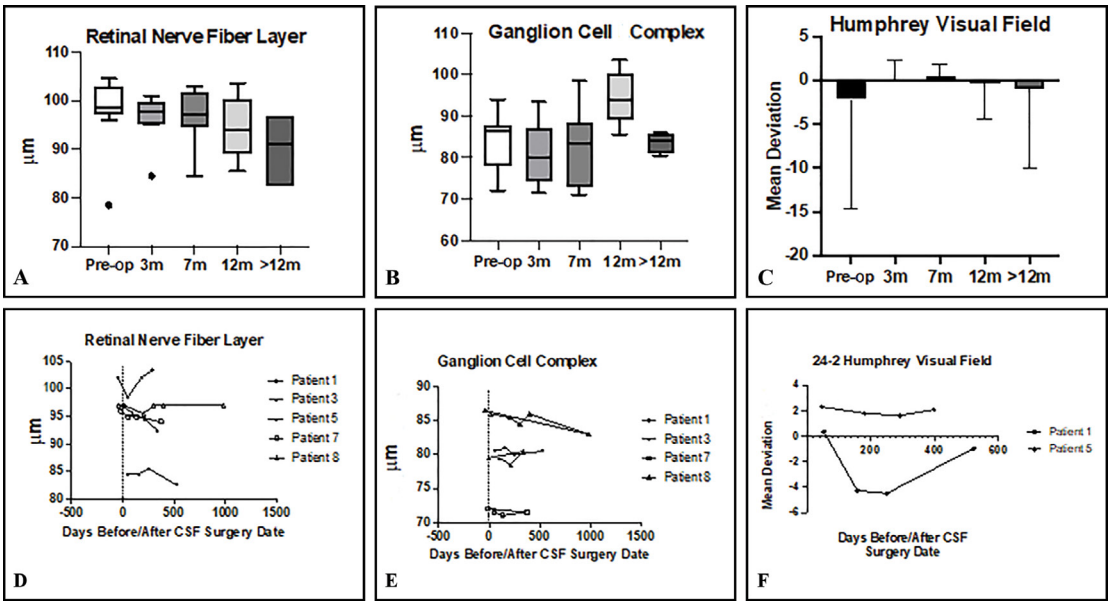

Figure 4. Ophthalmic imaging of patients with spontaneous cerebrospinal fluid (sCSF) leaks before and after surgical repair at 3 months, 7 months, 12 months, and after 12 months. (A) The optical coherence tomography (Cirrus HD-OCT Model 5000; Carl Zeiss Meditec Inc., Dublin, CA, USA) retinal nerve fiber layer thickness, (B) OCT ganglion cell complex thickness, (C) Humphrey visual fields (Humphrey Field Analyzer 750 II-I; Carl Zeiss Meditec). Trend plots for patients with more than 3 eye examinations: (D) retinal nerve fiber layer thickness, (E) ganglion cell complex thickness, and (F) Humphrey visual field mean deviations. Abbreviations: µm, micrometers; pre-op, pre-operative; CSF, cerebrospinal fluid; m, months.

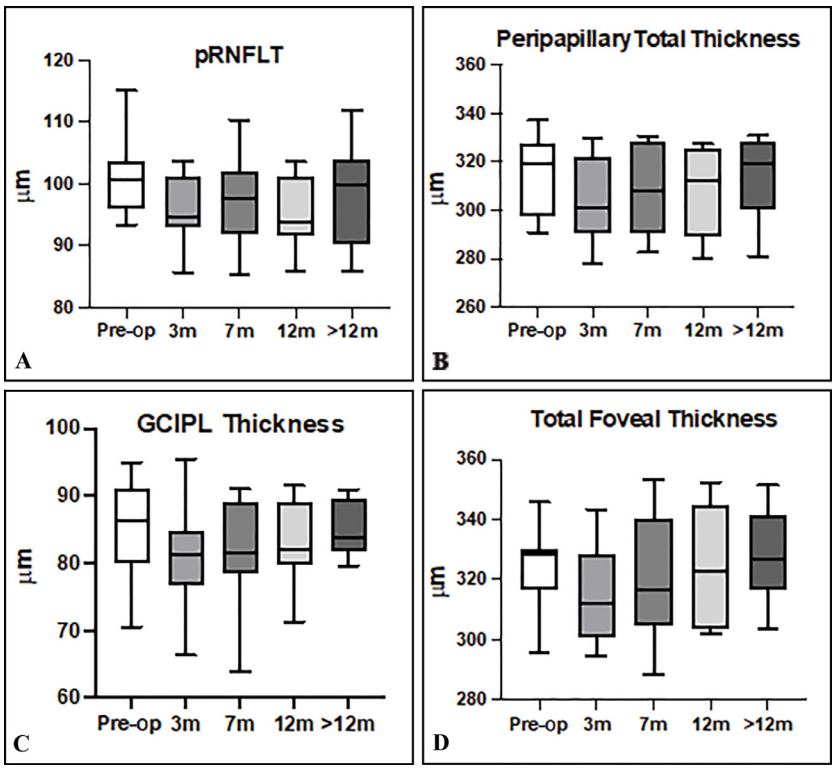

Figure 5. Validation of optical coherence tomography (Cirrus HD-OCT Model 5000; Carl Zeiss Meditec Inc., Dublin, CA, USA) results using the University of Iowa three-dimensional (3D) graph-based automated segmentation algorithm [12, 13]. Box plots of thickness measurements over time (before surgical repair and 3 months, 7 months, 12 months, and 1 year post-repair). (A) Peripapillary retinal nerve fiber layer thickness (pRNFLT), (B) peripapillary total retinal thickness, (C) ganglion cell plus inner plexiform layer (GCIPL) thickness, and (D) total retinal thickness at the fovea. Note: This is a descriptive comparison; no statistical method was used, as the results are almost identical by visualization. Abbreviations: µm, micrometers; pre-op, pre-operative; m, months.

Using the University of Iowa 3D graph-based automated segmentation algorithm, we regrouped patient data according to 5 time points: before repair and at 3 months, 7 months, 12 months, and more than 1 year after surgical repair. There were no detectable changes in the average peripapillary RNFLT thickness (Figure 5A), the peripapillary total retinal thickness (Figure 5B), GCIPL (Figure 5C), or total retinal thickness at the fovea (Figure 5D).

DISCUSSION

In this retrospective longitudinal study, we examined the clinical characteristics and neuro-ophthalmic features of patients with sCSF leaks. Our findings revealed similar demographic features in patients with IIH and those with CSF leaks. There was an improvement in patients' visual field defects after surgical repair despite the absence of papilledema and optic nerve abnormalities on ophthalmic imaging.

IIH commonly presents in obese women aged 15 to 44 years [14]. The similarity in patient demographics between IIH and sCSF leaks has been previously recognized [5]. Our sample consisted of all-female biological sex with a mean BMI of 37.9 kg/m^2, features similar to those of prior studies [5, 15, 16]. The diagnosis of IIH typically requires a high opening pressure on LP [17]. Post-operative leaks occurred in 4 of 11 (36%) patients, a proportion analogous to that of prior reports [18, 19]. These patients shared similar demographic features with patients having IIH. However, none underwent LP for opening pressure measurements either immediately before or after repair. Of the 4 patients with recurrent leaks, 1 underwent LP after the final repair and another underwent LP prior to the first repair.

The optic nerve and retinal structural measurements on OCT were similar before and after surgical repair. All thickness measurements were within the normal ranges using both the Zeiss Cirrus automated segmentation and University of Iowa 3D graph-based automated segmentation algorithms. sCSF leaks may reduce ICP and prevent the manifestation of typical symptoms for patients with IIH [5], which can explain our findings. Another explanation could be the delay in ophthalmic architectural changes on OCT in the setting of increased ICP [20]. Severe and rapid elevation in ICP can cause papilledema within days, but a slow rise in ICP can cause papilledema not to present for weeks [21].

The clinical significance of this study lies in the improvement of patients' visual field defects, especially peripherally. The peripheral visual field features high sensitivity for motion detection and recognizing flicker stimuli, which are both integral in activities such as walking and driving on the road [22]. In our study, the mean deviation and visual field index were classified as abnormal prior to sCSF leak repair. Both values trended toward improvement after repair, although the difference was not statistically significant. We believe that post-operative management is the key in rescuing the mildly injured nerve fibers [23]. By adopting a structured post-operative management plan, we can prevent further optic nerve injury and fundamentally improve visual outcome.

Our data showed a prolonged interval between symptom onset and sCSF leak diagnosis, consistent with prior reports [24]. The time from sCSF leak diagnosis to the first eye examination also varied. Many patients were referred to the neuro-ophthalmology department for sCSF leaks after presenting in various other departments. Some were initially evaluated in the emergency department or at their primary care centers prior to obtaining a physician consultation with our North American Skull Base Society Multidisciplinary Team, prompting a neuro-ophthalmic consultation for IIH evaluation. Although eye examinations should not delay surgical repair, evidence of IIH found on eye examination can help guide post-operative care to prevent vision loss and recurrent leaks [25]. Therefore, we recommend regular neuro-ophthalmic examinations for patients with IIH and sCSF leaks.

The current management of sCSF leak is surgical repair [6]. However, there is no consensus on postoperative management of ICP, especially when IIH is suspected as an underlying pathology [4]. The current standard treatment for lowering ICP includes diuretics such as acetazolamide as first-line pharmacological agents [26]. However, additional studies are warranted to further evaluate their long-term role in preventing recurrent CSF leaks. OSA episodically increases the ICP and is a common comorbidity in patients with IIH [27]. One of the patients refused CPAP treatment, which reinforces the importance of education in OSA management. The role of screening and management of OSA should be incorporated into a multidisciplinary approach in caring for patients with recurrent CSF leaks [25]. Patients with IIH experience a wide array of symptoms; however, headaches seem to be the most prevalent and have a substantial impact on activities of daily living [28, 29]. In addition to exploring methods to reduce the risk of recurrent CSF leaks in patients with IIH, we must also emphasize symptom management for this chronic condition.

The strength of this study includes its emphasis on a multidisciplinary approach for patients with IIH and sCSF leaks. The limitations of this study include its small patient sample and retrospective design. Evaluation

for IIH was incomplete in most patients, and only a small portion met our diagnostic criteria. Additionally, our results may have limited generalizability because the study was conducted in a single academic institution. The causal relationship between IIH and sCSF leak remains elusive. Further research should include prospective clinical trials to investigate this association.

CONCLUSIONS

This study demonstrated the feasibility of using advanced office-based ophthalmic imaging to evaluate the effects of increased ICP in patients with sCSF leaks. The preliminary findings support the need for larger studies with serial eye examinations to investigate the potential causal relationship between IIH and sCSF leak. A multicenter consortium is also suggested to develop a standard clinical protocol for comprehensive management of sCSF leaks.

ETHICAL DECLARATIONS

Ethical approval: The institutional review board at the University of California, Davis, USA, reviewed and approved this research protocol. De-identified patient data were utilized.
Conflict of interest: None.

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