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Defining the Phenotype and Prognosis of People With Idiopathic Intracranial Hypertension After Cerebrospinal Fluid Diversion Surgery

YOUSEF F. HYDER, VICTORIA HOMER, MARK THALLER, MARIAN BYRNE, GEORGIOS TSERMOULAS, RACHEL PICCUS, SUSAN P. MOLLAN, AND ALEXANDRA J. SINCLAIR

• PURPOSE: To characterize the phenotype of patients with idiopathic intracranial hypertension (IIH) who received cerebrospinal (CSF) diversion surgery and to detail the trajectory of recovery.
• DESIGN: Prospective cohort registry study.
• METHODS: Patients with IIH with sight-threatening papilledema presenting to a single United Kingdom neuroscience center between 2019 and 2021 were included. Outcomes consisted of perimetric mean deviation (PMD) and optical coherence tomography measures of papilledema (retinal nerve fiber layer [RNFL]) and macular ganglion cell layer (GCL) in both eyes. Headache outcomes included monthly headache days (MHD). Logistic regression methods were used to model long-term outcomes.
• RESULTS: Fifty-one patients without previous surgical interventions were included (92% female, mean age 28.1 years [SD 8.4], body mass index 37.4 kg/m^2 [SD 9.7], mean days of follow-up 330 [SD 209]). Measurements before surgery showed mean PMD −11.4 dB (SD 9.7), RNFL 364 μm (SD 128), Frisén grade papilledema 4.3 (SD 0.9). and MHD 23 (SD 10.6). At 1 month postoperatively, RNFL and PMD had improved by 38% and 4%, respectively. At 4 months postoperatively, papilledema had resolved. GCL declined by 13% over 12 months. MHD reduced by 75% 3 months postoperatively before returning to baseline levels by 12 months. Five patients (9.8%) required revision surgeries.
• CONCLUSIONS: Detailed characteristics of patients with sight-threatening IIH who received CSF diversion surgery and their typical postoperative recovery are presented. These parameters should guide physicians as to when patients with IIH may require surgery and enable the early identification of outliers who fail to respond. Papilledema and PMD recovered but GCL atrophy continued for 12 months. The implication of this delayed atrophy is unknown. (Am J Ophthalmol 2023;250: 70–81. © 2023 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/))

IDIOPATHIC INTRACRANIAL HYPERTENSION (IIH) IS A neurologic disorder characterized by raised intracranial pressure (ICP) in the absence of mass lesions or hydrocephalus. Common symptoms include headache, pulsatile tinnitus, and transient visual obscurations.[1] Cognitive changes and obstructive sleep apnea are also increasingly recognized.[2,3] The pathogenesis is incompletely understood but mounting evidence indicates a metabolic disease with insulin resistance, dysregulated lipogenesis, fertility and birth complications, and increased cardiovascular disease.[4–8] Furthermore, weight modification was shown to achieve disease remission.[9,10] There are no licensed drugs for IIH, yet drugs to reduce cerebrospinal fluid (CSF) secretion such as acetazolamide and topiramate are frequently used.[11]

Emergency intervention is required in patients with rapidly deteriorating vision.[12] This may include aggressive medical therapy or temporizing measures such as a lumbar drain. CSF diversion surgery, through ventriculoperitoneal or lumboperitoneal shunt insertion,[13] is the most common definitive surgical procedure used in the United Kingdom and the United States for this purpose.[12,14] Other procedures commonly used include optic nerve sheath fenestration and cerebral venous sinus stenting,[12] and randomized clinical trials such as the HYDROPTIC and IIH Intervention trials are currently underway to compare surgical op-

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From the Translational Brain Science (Y.F.H., M.T., S.P.M., A.J.S.), Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, United Kingdom; Department of Neurology (Y.F.H., M.T., A.J.S.), University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK; Centre for Endocrinology, Diabetes and Metabolism (Y.F.H., M.T., A.J.S.), Birmingham Health Partners, Birmingham, UK; Cancer Research (UK) Clinical Trials Unit (V.H.), University of Birmingham, Birmingham, Birmingham, UK; Department of Neurosurgery (M.B., G.T.), Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK; and Birmingham Neuro-Ophthalmology (R.P., S.P.M.), Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

Inquiries to Alexandra J. Sinclair, Institute of Metabolism and Systems Research (IMSR), University of Birmingham, Birmingham, B15 2TT, UK; e-mail: a.b.sinclair@bham.ac.uk

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tions for patients with IIH. Because of the risks of complications and frequent need for revision surgeries, guidelines recommend that surgery should only be performed when there is a risk of permanent sight loss despite using medical therapy.[12] Yet this threshold has not been precisely defined and is subject to interpretation within the clinical context. Patient-led research prioritization has highlighted the importance of identifying the optimal approach to preserve vision in IIH.[15] Systematic reviews of surgical interventions for IIH have shown improvements in visual symptoms after surgery.[16,17] However, these results do not detail how much improvement in visual outcomes can be expected and over what period of time. Furthermore, it is unknown whether earlier intervention would have ensured better long-term outcomes.

There are limited published optical coherence tomography (OCT) data in patients with IIH requiring surgery. One case series used OCT[18] but only reported the peripapillary retinal nerve fibre layer thickness (RNFL). Importantly, in severe papilledema the segmentation of retinal layers is known to be less accurate, leading to errors in RNFL measurement[19]; the boundaries for measuring total retinal thickness (TRT) can be more easily identified. In addition, multiple other OCT measures of the optic nerve head (ONH) and macula are used clinically by neuro-ophthalmologists which reflect changes in ICP and visual function.[20] In this study, we sought to define the clinical characteristics of patients with IIH who received CSF diversion surgery at a UK tertiary neuroscience center using clinically relevant measures of visual function, OCT imaging measures, headache, and ICP. Second, we aimed to evaluate their short- and long-term outcomes after surgery.

METHODS

Data were collected prospectively as part of the longitudinal cohort registry study IIH:Life.[21] This is a database of people with IIH, established at the University of Birmingham, that allows long-term prospective evaluation of clinical outcomes. We included all sequential patients with IIH and all data were collected as part of routine clinical care. Patients were enrolled onto the database at their initial visit to the University Hospitals Birmingham IIH clinic and written informed consent was obtained from all patients.

• **ETHICS APPROVAL:** The study was approved by NHS National Research Ethics Committee (14/LO/1208), IIH:LIFE study and was conducted in accordance with the Declaration of Helsinki

• **STUDY POPULATION:** The study population consisted of subjects attending a specialist IIH clinic at a single neuroscience center (University Hospitals Birmingham National Health Service Foundation Trust [UHB], United Kingdom) undergoing their primary CSF diversion surgery for sight-threatening IIH between January 1, 2019 and June 31, 2021.

All patients were reviewed by a member of the multidisciplinary team (MDT) at UHB that included neurology and neuro-ophthalmology before inclusion in the study. Eligibility criteria necessitate a confirmed diagnosis of adult IIH by the MDT, as per the revised Dandy criteria.[22] This included papilledema, neuroimaging excluding a venous sinus thrombosis or structural lesion and lumbar puncture opening pressure (LPOP) >25 cm H_2O.[12,22] Those included in the study were determined to have sight-threatening IIH as per recommendations made by neuro-ophthalmology experts at UHB NHS Foundation Trust (Table 1). Patients could be at any time in their disease course after a diagnosis of IIH.

Patients were excluded if they had a secondary cause of intracranial hypertension, IIH without papilledema, or pseudopapilledema. Patients with previous surgeries for IIH were also excluded. Patients with clinically determined optic atrophy (temporal pallor on examination with reduced RNFL on OCT) before surgery were excluded from the OCT analysis.

• **CSF DIVERSION SURGERY:** CSF diversion surgery for these patients was performed based on the Birmingham IIH Shunt protocol, which was developed and implemented at UHB NHS Foundation Trust in July 2019.[12,23,24] Typically, a frontal ventriculoperitoneal shunt was inserted by neurosurgeons with specialist expertise in CSF disorders. A frameless stereotactic system (AxiEM Electromagnetic StealthStation Navigation System, Medtronic) was used for ventricular cannulation in all cases and the peritoneal end was inserted laparoscopically in a significant proportion of cases. The vast majority of shunts had an adjustable gravitational valve (proGAV 2.0 with Gravitational Unit; Aesculap-Miethke) and a telemetric ICP sensor (M.scio; Aesculap-Miethke) to optimize CSF drainage and troubleshoot the shunt in cases of suspected malfunction. A lumboperitoneal shunt was offered in the small number of patients who did not wish their driver's license restricted for 6 months as per UK driving restrictions surrounding ventriculoperitoneal shunts, or they did not accept the small risks of ventricular cannulation. If surgery could not be arranged within 24 hours, a temporizing lumbar drain was performed under local anaesthetic and CSF diversion surgery arranged shortly thereafter. The schedule of visits after intervention was pragmatic according to the treating physician.

• **OUTCOME MEASURES:** Baseline data were preoperative data collected immediately before CSF diversion surgery (<15 days) as part of clinical care. Data from the patient's first IIH clinic attendance, visits immediately before surgery, and all visits after surgery as part of clinical care

TABLE 1. Sight-Threatening Idiopathic Intracranial Hypertension is Defined as A OR B, AND C, as Determined by Experts' Clinical Judgement at the Treating Center

A	If first visit: presence of severe papilledema[a] (confirmed on fundoscopy and optical coherence tomography imaging) and the loss of visual field noted on a reliably performed visual field
OR	
B	On follow-up: increasing papilledema (confirmed on fundoscopy and optical coherence to tomography imaging) and the increasing loss of visual field noted on a reliably performed visual field
AND	
C	Imminent irreversible visual loss considered definite or probable without intervention from urgent cerebrospinal fluid diversion surgery. Alternative therapeutic approaches would be unlikely to alter the trajectory of irreversibly imminent visual loss (medical therapy with or without weight loss, if appropriate)

[a]There is no international consensus on the definition of severe papilledema. Features of severe papilledema include a Frisén grade ≥3, with intraretinal fluid or subretinal fluid tracking toward the macula.

were used to model longitudinal outcomes before and after surgery.

Ophthalmologic outcomes included Frisén grading of papilledema,[25,26] logarithm of the minimum angle of resolution (logMAR) visual acuity (VA), and perimetric mean deviation (PMD) (Humphrey 24–2 [Swedish Interactive Testing Algorithm] standard test pattern using a size III white stimulus). OCT imaging was performed with the Spectralis OCT (Heidelberg Engineering). OCT parameters included RNFL, TRT, ONH central thickness (ONHCT), ONH volume (ONHV), and macular ganglion cell layer volume (GCL). Manual resegmentation of RNFL and TRT in peripapillary scans, and of the RNFL, basement membrane, and inner limiting layer for all cross-sections of optic disc scans was performed when required to ensure accuracy.[19] The Early Treatment Diabetic Retinopathy Study grid was used to determine ONHV (1-, 2.22-, and 3.45-mm volume scan), and GCL (1-, 3-, and 6-mm), by macular volume or posterior pole methods. The patient's worst eye was defined by most severe PMD at baseline or first available measure. If PMD was unavailable, most severe RNFL was used.

Headache outcomes included monthly headache days (MHDs), presence of daily headache, and analgesic use. Before surgery, CSF pressure was taken from LPOP. After surgery, ICP measurements were available in patients with telemetric ICP monitors using a standardized recording over 5 minutes in the supine position. Additional data included body mass index (BMI), personal history of migraine, disease duration (defined as time from the first IIH clinic visit to the time of surgery), and details of the surgery and CSF shunt type.

Adverse events were graded in accordance with the Clavien-Dindo criteria, a widely used classification of surgical complications.[27] In addition, CSF underdrainage was defined as either inadequate resolution of papilledema, persistent headache consistent with a raised-pressure phenotype, or measured raised ICP that required adjustment of the CSF shunt valve to increase CSF drainage. CSF overdrainage was defined as low-pressure headache with ICP monitoring demonstrating a clinically relevant postural drop in ICP that required adjustment of the shunt valve to reduce CSF drainage.

Unless specified otherwise, all analyses were predetermined by the authors before any data exploration or formal analyses. Statistical evaluation was performed with R software (v 4.1.0; www.R-project.org) and outcomes were summarized by means and standard deviation (SD).

• **MODELING PROGNOSTIC OUTCOMES AFTER CSF DIVERSION SURGERY:** Where available, for each patient both eyes were included in the hierarchical modeling with non-independence accounted for through including group-level effects and the nesting of eyes within patients. The progression of all outcomes was ascertained using logistic regression models. For OCT parameters of papilledema, restricted cubic splines were necessary to capture the rapidly decreasing trend following surgery before stabilization. Where restricted cubic splines models were used, knots were placed pragmatically at timepoints 3 months before surgery, at surgery, and at 1 and 5 months postoperatively. Sensitivity to knot placement was performed, with minimal changes to outcomes. The maximal reduction was defined as the lowest value reached after CSF diversion surgery.

A post hoc sensitivity analysis was performed to assess outcomes in patients with PMD better or worse than –7 dB in their best eye at baseline. This value was consistent with thresholds set within the literature for medically treated IIH of –7 dB and proposed recruitment for a surgical IIH trial.[11] Patients without PMD measured 15 days before surgery could not be categorized and were excluded from this sensitivity analysis.

Further analyses explored which factors impacted prognosis. This included LPOP, BMI, and age at surgery, change in BMI after surgery, disease duration, and RNFL. For headache outcomes, additional factors included personal history of migraine or daily headache immediately before surgery. Models for each outcome were developed independently using forward stepwise regression and fitted using lme4,[28] assuming a continuous form of the dependent

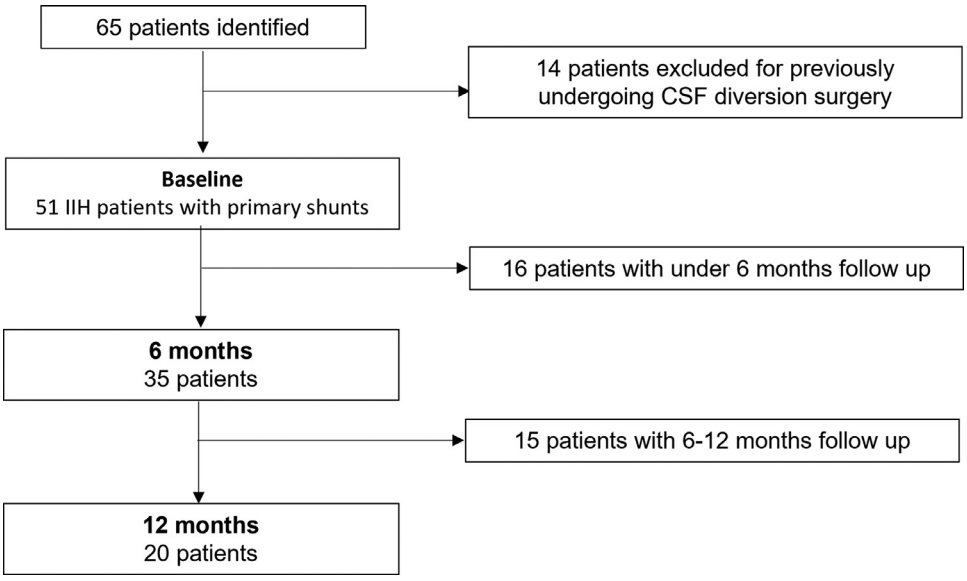

FIGURE 1. CONSORT (Consolidated Standards Of Reporting Trials) diagram showing the number of patients at each time point. CSF = cerebrospinal fluid; IIH = idiopathic intracranial hypertension.

variables. Population-level terms were used to estimate the average response value, an adjustment for time, and an interaction between variables of interest and time point. Patient-level intercepts were included to address serial correlation in responses, and the nesting of measurements from eyes within patients (as modeling included data from both eyes). There were no diagnostic problems in model fitting. Where covariates were added to models, they were transformed or centered around the median as appropriate.

Further post hoc analyses explored which factors impacted final VA and RNFL outcomes. These were chosen because of the observed ceiling effect of the outcomes. Analogous methods to those described above were used with the exception that as longitudinal time courses were not analyzed, inclusion of time covariates was not necessary. The factors explored were the same as in the longitudinal analyses of these variables as well as baseline outcome values.

RESULTS

• **PARTICIPANTS:** Sixty-five patients were screened. Fourteen patients with previous CSF diversion surgeries were excluded. In total, 51 patients had primary CSF diversion surgery for sight-threatening papilledema (Figure 1). Preoperatively, 2 patients had optic atrophy and were excluded from the OCT analysis.

The cohort was 92% female with a mean age 28.1 years (SD 8.4) and BMI 37.4 kg/m^2 (SD 9.7). Thirty-seven percent were prescribed acetazolamide (variable doses) at the time of surgery. An additional 18% were previously prescribed acetazolamide but had stopped the medication, and 1 patient was prescribed topiramate. The mean disease duration was 229 days (SD 521) and the mean duration of follow-up after surgery was 330 days (SD 209) (Table 2). At the time of analysis, 20 patients had 1 year of follow-up (Figure 1).

The majority of shunts were ventriculoperitoneal (98%) (Supplemental Table 1). 96% had a Progav valve (Christoph Miethke) with 86% having an initial valve setting of 15 cm H_2O. Two patients underwent lumbar drains before surgery. No patients had undergone bariatric surgery to modify weight or other surgeries such as optic nerve sheath fenestration.

• **CLINICAL CHARACTERISTICS BEFORE CSF DIVERSION SURGERY:** Clinical measures were recorded a mean 3 days (SD 6) before CSF diversion surgery. In the patients' worst eye, mean VA was 0.17 logMAR (SD 0.49) and mean PMD was −11.4 dB (SD 9.7) (Table 3). Performance indices were noted (Supplemental Table 2). The mean papilledema Frisén grade was 4.3 (SD 0.9). OCT measures of the worst eye showed a mean RNFL of 364 µm (SD 128), TRT of 758 µm (SD 224), ONHCT of 993 µm (SD 194), and ONHV of 9.5 mm^3 (SD 1.8). GCL in the worst eye was 1.09 mm^3 (SD 0.13). Patients reported a mean of 22.5 MHD (SD 10.6), although 75% had daily headaches. Mean LPOP before surgery was 44.6 cm H_2O (SD 15.2).

• **FACTORS ASSOCIATED WITH A MORE SEVERE IIH PHENOTYPE PREINTERVENTION:** We evaluated factors associated with increased severity of IIH before intervention. Worse VA was associated with greater papilledema as measured by RNFL and a higher BMI. For every 100-µm increase in RNFL, VA was compromised by 0.0432 logMAR (95% confidence interval [CI] 0.0112-0.0753). For every

TABLE 2. Patient Demographics and Characteristics

Characteristic	N = 51
Females, n (%)	47 (92.1)
Age (y), mean (SD), range	28.1 (8.4), 16-55
BMI (kg/m^2), mean (SD), range (n)	37.4 (9.7), 23.7-65.8 (48)
Diagnostic lumbar puncture opening pressure (cm H_2O), mean (SD), range (n)	41.2 (11.2), 27.5-80 (40)
Prescribed acetazolamide, n (%)	19 (37.3)
Prescribed headache preventatives, n (%)	7 (13.7)
Additional headache diagnoses, n (%)	
Migraine	12 (23.5)
Medication overuse	3 (5.9)
Duration of disease (days), mean (SD), range (n)	228.6 (521), 0-2200 (51)
Days from baseline measurements to CSF diversion surgery, mean (SD), range (n)	2.7 (6.2), 0-38 (51)
Days of follow-up post–CSF diversion surgery, mean (SD), range (n)	330.4 (209.1), 0-821 (51)

BMI = body mass index; CSF = cerebrospinal fluid; SD = standard deviation.

TABLE 3. Clinical Measures at Baseline

Clinical Measure	Mean (SD), n
Frisén grade (papilledema)	4.3 (0.9), 36
Retinal nerve fiber layer thickness (μm)	364 (128), 44
Total retinal thickness (μm)	758 (224), 42
Optic nerve head central thickness (μm)	993 (194), 44
Optic nerve head volume (mm^3)	9.5 (1.8), 44
Macular ganglion cell layer (mm^3)	1.09 (0.13), 42
Visual acuity (logMAR)	0.17 (0.49), 44
Visual field perimetric mean deviation (dB)	−11.4 (9.7), 26
Monthly headache days per 28-day cycle	22.5 (10.6), 32
Lumbar puncture opening pressure (cmH_2O)	44.6 (15.2), 22

Mean ophthalmologic measures in the patient's worst eye, headache frequency, and lumbar puncture opening pressure at the baseline visit within the 15-day period before shunt insertion.
logMAR = logarithm of the angle of resolution; SD = standard deviation.

1-kg/m^2 increase in BMI, VA was compromised by 0.008 logMAR (95% CI 0.003-0.013).

Papilledema, as quantified by RNFL, was less severe in patients with a longer disease duration. For every month increase in the disease duration, RNFL was −2.99 μm (95% CI −1.45 to −4.53). As expected, all OCT measures of papilledema were associated with greater RNFL. For every 100-μm increase in RNFL, TRT increased by 95 μm (95% CI 60-130), ONHCT by 85 μm (95% CI 48-122), and ONHV by 1.05 mm^3 (95% CI 0.7-1.4).

No factors predicted severity of PMD, GCL, or MHD.

• **OPHTHALMOLOGIC OUTCOMES AFTER CSF DIVERSION SURGERY:** Within 2 weeks postoperatively, a rapid improvement in papilledema was quantified by OCT (Figure 2, Table 4), with reduction in RNFL of 23%, ONHCT of 15%, and ONHV of 17%. By 1 month postoperatively, there had been reductions of 38%, 27%, and 31%, respectively. Maximal reduction was reached at 4 months for RNFL with 73% reduction to 85 μm (95% CI 68-102), and for TRT with 56% reduction to 307.7 μm (95% CI 284-332). ONHCT and ONHV demonstrated a maximal reduction by 3 months (Figure 2, Table 5). GCL steadily declined after surgery and after the markers of papilledema had settled. By 12 months, GCL had reduced by 13% to 0.95 mm^3 (95% CI 0.92-0.99) (Figure 3).

Visual function, as measured by PMD, demonstrated maximum recovery by 3 months to −5.3 dB (95% CI −3.6 to −7.0), a 20% improvement after shunting (Figure 2, Tables 4 and 5). VA was minimally impaired preshunt and showed no meaningful change postsurgery, fluctuating between 0.1 logMAR (95% CI 0.06-0.14) to 0.01 logMAR (95%CI −0.06 to 0.08) over 12 months (Supplemental Figure 1).

Sensitivity analysis was performed for patients with PMD better than or worse than −7 dB before surgery (Figure 2). Nine patients had PMD worse than −7 dB at baseline in their best eye, with mean PMD −14.7 dB (SD 7.6). A recovery of 72.3% was seen by 3 months to −3 dB (SD 16.6). This corresponded to a 10% loss of GCL at 12 months (from 1.01 mm^3 [SD 0.15] to 0.91 mm^3 [SD 0.19]). Seventeen patients had PMD better than −7 dB at baseline in their best eye, with mean PMD −2.89 dB (SD 2.04). In these, a recovery of 76.4% was seen by 3 months to −0.68 dB (SD 4.18). This corresponded to an 8.7% loss of GCL (from 1.15 mm^3 [SD 0.14] to 1.05 mm^3 [SD 0.18]).

• **RECOVERY OF HEADACHE AFTER CSF DIVERSION SURGERY:** Mean MHD had reduced by 23% by 2 weeks postoperatively and 75% by 3 months (Figure 3, Table 5, Supplemental Table 3). However, by 12 months postoperatively, mean MHD was comparable to that observed presurgery. Daily headaches before shunting were common (75%) and these reduced to 9% by 3 months after surgery, before increasing to 33% at 6 months.

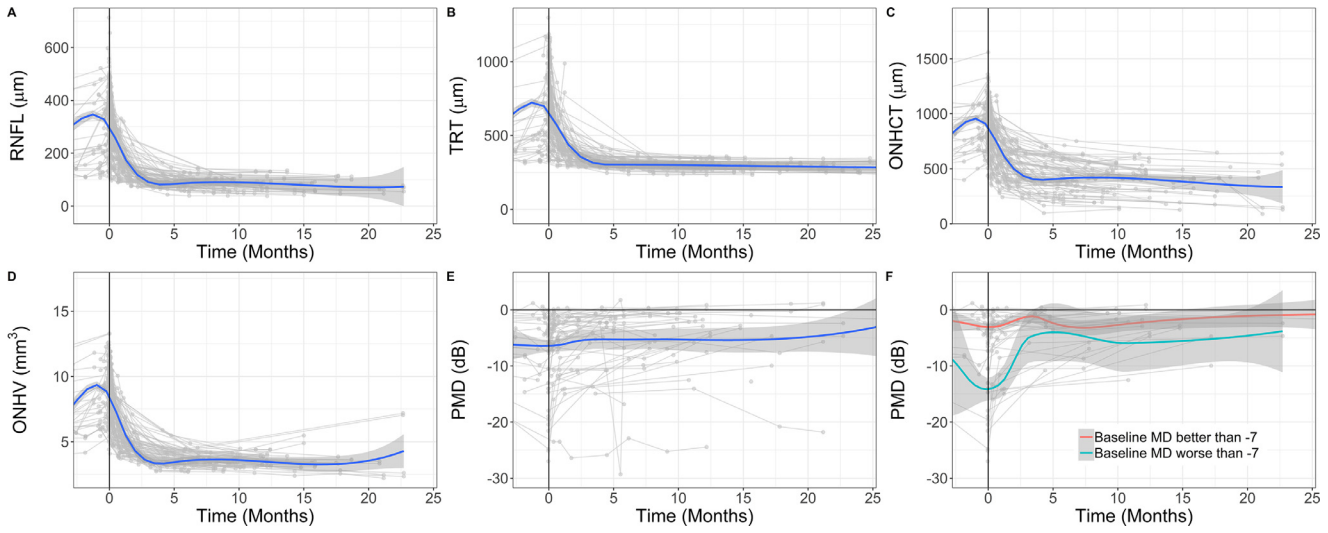

FIGURE 2. Longitudinal data for all study eyes with added locally estimated scatterplot smoothing smoothers and 95% confidence intervals to show trends. A. Retinal nerve fiber layer (RNFL) thickness. B. Total retinal thickness (TRT). (C) Optic nerve head central thickness (ONHCT). (D) Optic nerve head volume (ONHV). (E) Visual field perimetric mean deviation (PMD) for all study eyes. (F) Visual field PMD for patients categorized by whether PMD in the best eye was better (red) or worse (green) than −7 dB preoperatively. F. For the stratified analysis, only patients with Humphrey visual fields assessment within the 15-day baseline window before surgery are shown. Time 0 is taken as day of cerebrospinal fluid diversion surgery.

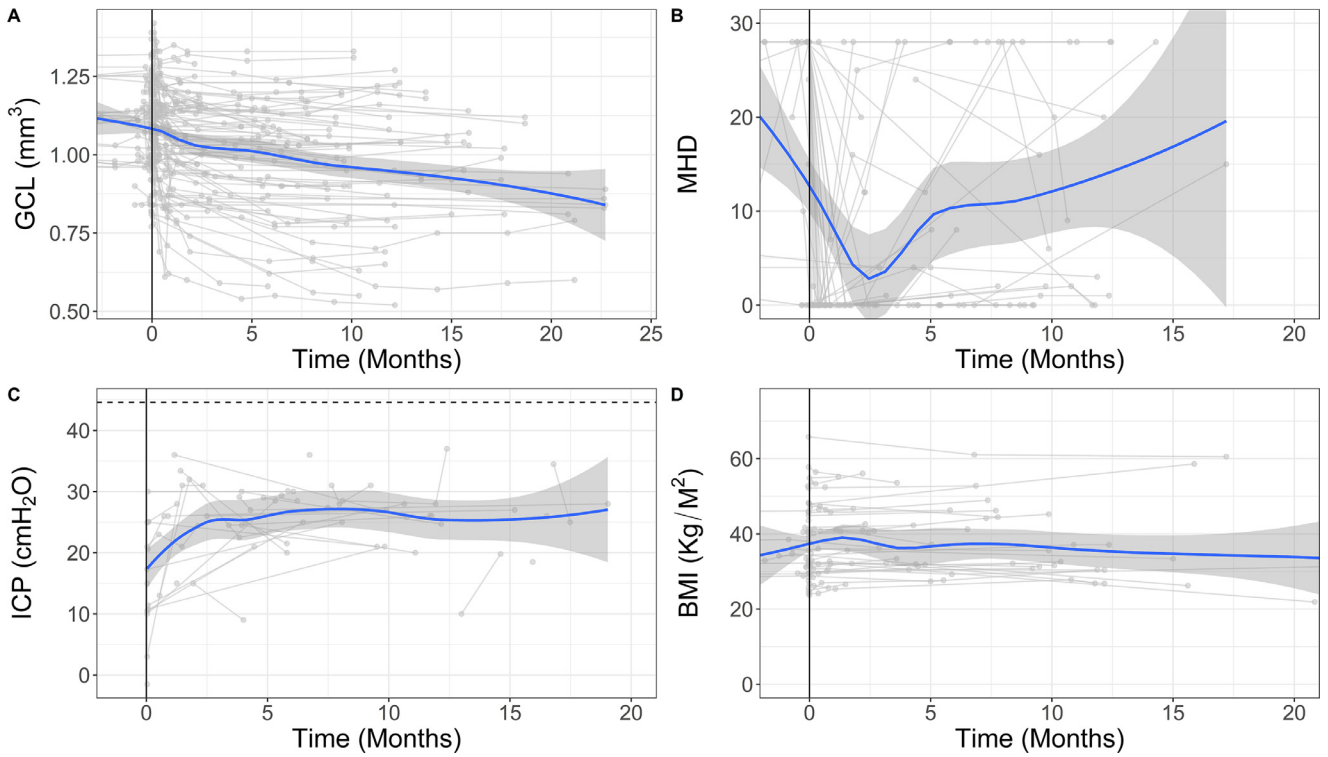

FIGURE 3. Longitudinal data for all study eyes with added locally estimated scatterplot smoothing smoothers and 95% confidence intervals to show trends. A. Macular ganglion cell layer volume (GCL). B. Monthly headache days (MHDs) per 28-day cycle. C. Intracranial pressure (ICP). Pre-shunt baseline lumbar puncture opening pressure (see Table 3) is plotted as a horizontal dashed line. D. Body mass index (BMI). Time 0 is taken as day of cerebrospinal fluid diversion surgery.

TABLE 4. Means and 95% Confidence Intervals Taken From the Logistic Regression Models for Ophthalmologic Outcomes After Shunt Insertion

	Time After Shunt Insertion				
	2 Weeks, n = 46	1 Month, n = 46	3 Months, n = 41	6 Months, n = 35	12 Months, n = 20
RNFL (μm)					
Mean	253.9	202.6	90.9	87.23	86.73
95% CI	243-365	190-215	72.8-109	69.9-105	65.6-108
Percent change	−22.6%	−38.2%	−72.3%	−73.4%	−73.6%
TRT (μm)					
Mean	585.0	512.7	332.0	302.2	297.9
95% CI	565-605	490-536	299-365	277-328	269-327
Percent change	−16.2%	−26.6%	−52.5%	−56.7%	−57.3%
ONHCT (μm)					
Mean	772.2	662.7	422.9	412.9	406.4
95% CI	750-794	637-688	386-460	377-449	362-451
Percent change	−15.1%	−27.2%	−53.5%	−54.6%	−55.3%
ONHV (mm^3)					
Mean	7.33	6.11	3.52	3.55	3.47
95% CI	7.14-7.52	5.89-6.33	3.21-3.83	3.24-3.86	3.09-3.85
Percent change	−17.3%	−31.0%	−60.3%	−59.9%	−60.8%
GCL (mm^3)					
Mean	1.08	1.06	1.02	1.00	0.95
95% CI	1.06-1.10	1.04-1.08	0.99-1.05	0.96-1.04	0.92-0.99
Percent change	−1.3%	−2.8%	−6.3%	−8.2%	−13.1%
VA (logMAR)					
Mean	0.10	0.09	0.01	0.02	0.10
95% CI	0.06-0.14	0.04-0.14	-0.06-0.08	-0.05-0.09	0.02-0.18
Percent change	−12.4%	−21.7%	−93.3%	−84.5%	−9.3%
PMD (dB)					
Mean	−6.55	−6.34	−5.35	−5.28	−5.35
95% CI	−7.68 to −5.42	−7.46 to −5.22	−7.01 to −3.62	−7.07 to −3.49	−7.45 to −3.25
Percent change	−1.0%	−4.2%	−19.2%	−20.2%	−19.1%

The model includes data for both eyes of each participant, accounting for correlation between eyes of a single individual. The percentage change from peak value around the time of shunt is reported.

CI = confidence interval; GCL = macular ganglion cell layer volume; ONHCT = optic nerve head central thickness; ONHV = optic nerve head volume; PMD = perimetric mean deviation; RNFL = retinal nerve fiber layer thickness; TRT = total retinal thickness; VA = visual acuity.

Before surgery, 7 patients were prescribed medications for headache prophylaxis (including topiramate, erenumab, amitriptyline, and pizotifen). In addition, 3 patients were prescribed opiates. At 6 months postsurgery, 6 patients continued with prophylactic medications for headache; however, an additional 4 patients were prescribed triptans for acute treatment of episodic migraine and headache.

• **ICP AFTER CSF DIVERSION SURGERY:** Before shunt insertion, the mean LPOP was 44.6 cm H_2O (SD 15.2) (Table 3). Supine ICP immediately after surgery (measured by telemetric ICP monitor) was 12.8 mm Hg (equivalent to 17.4 cm H_2O [95% CI 14.2-20.6]). By 3 months, this increased to 18.4 mm Hg (equivalent to 25 cm H_2O [95% CI 22.3-28.5]) (Figure 3, Table 5, Supplemental Table 3).

Acetazolamide was discontinued in 95% of patients after surgery. One patient was prescribed topiramate before surgery and continued this postoperatively.

• **PROGNOSTIC FACTORS:** The factors influencing prognosis were then evaluated. Those with the most papilledema, as quantified by RNFL, demonstrated the greatest recovery in VA after surgery (with additional reduction of −0.00374 logMAR/month for every 100-μm RNFL at baseline [95% CI −0.0073 to −0.0001]). In addition, those with the longest disease duration demonstrated the least improvement in RNFL (with 0.47 μm less reduction in RNFL/month for every month of disease duration [95% CI 0.21-0.72]).

No factors significantly influenced the change in PMD, GCL, MHD, or ICP after CSF diversion surgery. Neither LPOP, age at the time of surgery, personal history of migraine, or occurrence of daily headache before surgery had an impact on prognosis after surgery. Mean BMI did not change during the study (Figure 3).

In the analysis of final VA, only the BMI at baseline, BMI at final visit, and baseline VA were influential factors

TABLE 5. Maximal Recovery After Intervention

	Value at Time 0 Mean (95% CI)	Maximal Recovery After Intervention Mean (95% CI)	Time to Maximal Recovery (Months)
RNFL (μm)	328.1 (316-341)	85 (67.7-102)	4
TRT (μm)	611 (591-631)	308 (284-332)	4
ONHCT (μm)	909.6 (886-934)	422.9 (386-460)	3
ONHV (mm^3)	8.86 (8.66-9.06)	3.52 (3.21-3.83)	3
Macular GCL (mm^3)	1.08 (1.06-1.10)	0.95 (0.92-0.99)	N/A
VA (logMAR)	0.10 (0.06-0.14)	0.10 (0.02-0.18)	N/A
PMD (dB)	−6.6 (−5.5 to −7.7)	−5.30 (−3.6 to −7.0)	3
MHD	12.7 (9.9-15.5)	3.4 (0.0-8.0)	3
ICP (cm H_2O)	17.4 (14.2-20.6)	25.4 (22.5-28.5)	3

Note: Values taken from the local regression models for ophthalmic and headache markers at time of shunt insertion and at maximal recovery after shunt insertion. The ophthalmic models include data for both eyes of each participant, accounting for correlation between eyes of a single individual.

CI = confidence interval; GCL = macular ganglion cell layer volume; ICP = intracranial pressure; logMAR = logarithm of the minimum angle of resolution; MHD = monthly headache days; N/A = not available; ONHCT = optic nerve head central thickness; ONHV = optic nerve head volume; PMD = perimetric mean deviation; RNFL = retinal nerve fiber layer thickness; TRT = total retinal thickness; VA = visual acuity.

in univariate analyses but not when combined, with baseline VA being the most influential, with final VA increasing with baseline VA. In the analysis of final RNFL, only baseline RNFL was influential, again with final RNFL increasing with baseline RNFL.

• **CSF SHUNT COMPLICATIONS:** During follow-up (mean 330.4 days [SD 209.1]), 12% of patients (n = 6) required further surgical procedures under general anesthesia (Clavien-Dindo grade 3b). Five patients (9.8%) required revision of their shunt (Supplemental Tables 4 and 5). Three occurred within 2 months and 2 at 12 and 15 months postoperatively.

In 25% (n = 13) of patients, adjustment of valve settings was required for underdrainage of CSF (Supplemental Table 4). Overdrainage of CSF that required adjustment of valve settings occurred in 1 patient.

DISCUSSION

We describe a cohort of patients with IIH who underwent CSF diversion surgery for sight-threatening IIH in a large UK tertiary specialist IIH service (Table 3). This work reports detailed phenotyping of visual function, OCT measures, headache severity, and ICP and provides useful parameters to guide physicians as to when patients with IIH typically receive surgery to prevent visual loss. This study expands on previous case series to include several measures not yet reported for this cohort but that are increasingly used in clinical practice. In addition, previous studies of surgical interventions for IIH have typically focused on a single time point to assess outcomes.[16–18] In contrast, our modeling shows the expected trajectory of recovery after surgery, enabling the earlier identification of outliers. The data demonstrate that papilledema and PMD reach maximal recovery over 3 to 4 months postsurgery. However, there is significant GCL atrophy in the 12 months after intervention (Figure 3, Table 4). Headache showed initial improvement but regressed to baseline levels by 12 months despite a normalization of ICP (Figure 3, Supplemental Table 3).

OCT imaging is increasingly used to monitor papilledema in IIH and reflects ICP.[20] Postintervention OCT imaging was used to monitor recovery and identify patients with possible intervention failure. For example, by 2 weeks postoperatively, RNFL typically reduced by 23% to 254 μm (95% CI 243-365) and TRT by 16% to 585 μm (95% CI 565-605). For patients without preexisting optic atrophy who are not achieving this degree of reduction in papilledema, we suggest evaluation for shunt underdrainage or blockage. Where underdrainage is a possibility, opening the shunt valve to increase drainage may result in improvement of papilledema on OCT. In future clinical trials seeking to compare treatment modalities for IIH, we recommend that similar modeling be undertaken to compare both the size and speed of the treatment effect. Given that OCT measures of the optic nerve correlate with ICP,[20] a slower resolution in papilledema may reflect a slower reduction in ICP with potential pathological effects ongoing.

Differentiating improvement of ONH edema from axonal loss has long been debated. For healthy individuals, the typical RNFL is measured at approximately 100 μm, whereas for individuals with complete atrophy the RNFL is approximately 40 μm. Therefore, up to 60 μm of the RNFL is vulnerable to atrophy, which can be recorded. We observed that RNFL reached maximal mean reduction from 328 to 85 μm (68-102). Consequently, the global RNFL after surgery was 15 μm (0-32) lower than expected in a healthy individual, indicating the degree of atrophy that

likely occurs in this situation of raised ICP. Thankfully, there was recovery of the visual field PMD despite this suspected atrophy of 15 μm in the RNFL. However, any delays in recognition or management of sight-threatening IIH would likely result in greater atrophy and potentially worse visual outcomes.

At 12 months postoperatively, GCL had atrophied by 12% despite normalization of ICP and papilledema and an improvement in visual field PMD over 4 months postoperatively. Our observations raise concern for GCL atrophy either caused by the initial injury with severe papilledema or ongoing injury despite surgery. Indeed, as can be seen in Figure 3, some patients experienced a rapid decline in GCL within 2 to 3 months postoperatively. The reasons for this are unclear because in this analysis no factor was identified to predict GCL outcome. One potential mechanism is a decompression injury caused by rapid relief of axoplasmic stasis by reversing the ICP quickly. It should be noted that those with the most significant GCL atrophy tended to have the longest duration of follow-up. Importantly, we excluded those with preexisting optic atrophy from this analysis. Errors in GCL measurement have been reported in cases of severe papilledema on Cirrus OCT platforms.[29,30] Because of eye tracking on the Heidelberg Spectralis, this platform is thought to be less prone to GCL analysis error. The mean GCL before surgery of 1.09 mm^3 in our cohort is comparable to the mean of 1.09 mm^3 for women and 1.13 mm^3 for men.[31] An age-related decline in GCL of 0.26% per year is expected beginning in an individual's late thirties,[32] although the mean age in our cohort was 28 years. GCL atrophy has been found to predict worse visual field function in patients with IIH,[33,34] and in this study those with worse visual field PMD at baseline tended toward a lower GCL at baseline and at 12 months. Therefore, these patients may be at increased risk of further visual loss throughout their lifetime, through age-related decline on the setting of this reduction caused by this episode of severe disease. Currently there is little evidence to guide clinicians on when to intervene in IIH. In our center, we reserve CSF diversion surgery for cases of sight-threatening papilledema where medical interventions have failed or are unlikely to prevent impending visual loss. The data from our cohort showing delayed postintervention GCL atrophy could indicate that we may be intervening too late to prevent GCL loss. However, our cohort had less severe VA impairment at baseline compared with historical studies.[35] Furthermore, given the relationship between GCL and the visual field, it is essential that clinical trials assessing the relative merits of different surgical interventions (eg, CSF diversion surgery vs optic nerve sheath fenestration) should assess the comparative sparing effects on the GCL as an indicator of long-term visual outcomes.

An initial dramatic (75%) improvement in MHD was observed after surgery, corresponding to marked improvement in the ICP. This response is akin to the effect of therapeutic LP on severe headache.[36] Furthermore, patients with IIH with greater reductions in ICP over 12 months typically experience larger reductions in headache symptoms.[37] Unfortunately, for many patients in our cohort, headache returned by 12 months despite normalization of ICP and papilledema. Although a systematic review of surgical interventions for IIH has shown general improvement in headache burden,[17] persistent symptoms have been reported in previous case studies.[38] The mechanisms driving headache in IIH are complicated.[39] While ICP is one component, the surgery, valve settings, and possible medication overuse may contribute to headache morbidity. The data suggest that surgery should not be considered for long-term headache treatment. Modern medical therapy such as Erenumab, a monoclonal antibody to calcitonin gene–related peptide, has already been shown to have benefit in patients with IIH headache,[40,41] and may have potential for treatment of postsurgical IIH headache where ICP is controlled.

We observed that before intervention those with greater RNFL and BMI had the most compromised VA. CSF diversion surgery improved visual outcomes but does not modify the underlying pathophysiology. Weight loss interventions such as bariatric surgery are highly effective at reducing ICP and achieving disease remission.[9,42] However, BMI did not change significantly for our cohort. Given that CSF shunts can fail, it is important that weight loss is emphasised to prevent relapses of IIH.

It is also noteworthy that the mean disease duration was >32 weeks in this cohort, while the definition for fulminant disease suggests an onset within 4 weeks.[43] This highlights that the nomenclature for severe sight-threatening disease may require revision to remove the duration of the disease diagnosis of fulminant IIH. Our analysis identified that patients with a longer duration of disease before undergoing surgery had less severe papilledema at baseline. This can potentially be explained by these patients having already experienced some degree of axonal loss and optic atrophy, thereby limiting the extent of papilledema. Alternatively, patients who present earlier in their disease course (for example, because of headache burden or after an incidental finding of optic edema on ocular examination) will be monitored closely and any deterioration in visual function identified earlier and intervention used sooner.

Only 37% of patients were prescribed acetazolamide at the time of surgery, although a further 18% had stopped taking the medication for reasons such as significant side effects. The remaining patients presented acutely with sight-threatening disease (Table 1), which prompted urgent referral to neurosurgery rather than medical management or weight loss trials, both of which would have resulted in considerable delays. The period of this study overlaps with societal lockdowns resulting from the COVID-19 pandemic. It is possible that lack of access to opticians and in-person appointments, in combination with lifestyle changes that promoted weight gain, may have contributed to delayed presentations with sight-threatening disease.[44]

• **LIMITATIONS:** A major limitation of this study is the lack of comparator group that did not receive CSF diversion surgery. However, because of the threat of permanent visual deterioration, it would have been unethical to withhold surgical intervention. As this is a real-world longitudinal cohort, missing data were observed. For example, some patients underwent Goldmann visual fields which could not be directly compared with the Humphrey visual field. The OCT images were manually resegmented when required; however, peripapillary hyperreflective ovoid mass structures were not documented or quantified. These could have altered some of the OCT measures of the ONH, but any effect would have been largely consistent within an individual over time. Our model may overestimate impairment in PMD. Ideally, we would have excluded data from unreliably performed Humphrey visual fields with 15% false-positive rates and 30% fixation losses and false-negative rates as according to previous criteria,[45] and also performed 3 visual fields per assessment. However, this is a real-world cohort, and our results reflect those experienced commonly in real clinical practice.

Our data are strongest in the acute postoperative period where patients have multiple follow-up appointments and good attendance. However, at the time of analysis, only 20 patients (39%) had undergone 12 months of follow-up and were contributing to the model, which is reflected in the widening confidence intervals seen in Figures 2 and 3. Importantly, patients with increasingly severe illness may be more likely to return for follow-up over a longer period. Therefore, our model may overestimate GCL atrophy and headache frequency after surgery. It should also be noted that as all patients had a different length of follow-up, the timing of final VA and RNFL was not consistent when modeling prognostic outcomes after surgery. Finally, this study represents the experience at a single UK tertiary neuroscience center, which may introduce selection bias. There is currently no recognized international consensus on the definitions of severe papilledema or visual field loss requiring surgery. Future work is required to define these systematically.

In summary, we have detailed the phenotype of patients with IIH who received CSF diversion surgery for sight-threatening papilledema at a large UK tertiary IIH service. These parameters can inform physicians when patients with IIH require surgery for impending visual loss. Papilledema and PMD reached a maximal recovery over 3 to 4 months, although GCL atrophy was delayed and continued up to 12 months after intervention. CSF diversion surgery did not provide long-term benefit for headache symptoms.

ALL AUTHORS HAVE COMPLETED AND SUBMITTED THE ICMJE FORM FOR DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST.

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