Open-Angle Glaucoma in Idiopathic Normal Pressure Hydrocephalus Before and After Ventriculo-Peritoneal Shunt Surgery: An Interventional Prospective Study

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■ OBJECTIVE: **To assess the frequency of open-angle glaucoma in Caucasian patients affected by idiopathic normal pressure hydrocephalus (iNPH) prior to ventriculo-peritoneal shunt surgery, and to evaluate the progression of optic nerve damage 1-year postsurgery.**

■ METHODS: **Thirty-five consecutive patients diagnosed with iNPH were prospectively recruited between November 2021 and June 2023. Assessments included visual acuity, intraocular pressure, macular ganglion cell complex thickness, retinal nerve fiber layer thickness, visual field test, central corneal thickness, axial length, and corneal hysteresis. Patients with newly diagnosed open-angle glaucoma were initiated on intraocular pressure-lowering medications. Eighteen patients were re-evaluated after a mean of 1 year postshunt surgery to assess the progression of optic nerve damage.**

■ RESULTS: **A total of 35 eyes of 35 iNPH patients were included. The mean age of participants was 75.75 ± 6.67 years, with 34.3% being females. Primary open-angle glaucoma was identified in 22.8% of nonshunted iNPH patients, including 11.4% who received a new diagnosis. After a mean follow-up of 14.9 ± 4.8 months postsurgery, there were no significant changes in retinal nerve fiber layer and ganglion cell complex thickness, nor were there any observed progressions in visual field defects or significant alterations in corneal biomechanics ($P > 0.05$).**

■ CONCLUSIONS: **Approximately 1 in 5 nonshunted iNPH patients exhibited primary open-angle glaucoma, with 50% being undiagnosed. These findings indicate the importance of conducting ophthalmological evaluations at the time of iNPH diagnosis, as early intervention may mitigate optic nerve damage progression following shunt surgery.**

INTRODUCTION

Idiopathic normal pressure hydrocephalus (iNPH) is a chronic neurological syndrome distinguished by the gradual development of gait disturbances, cognitive decline, and urinary incontinence.[1] iNPH primarily affects the elderly population, and it is characterized by expansion of intracerebral ventricles despite normal intracranial pressure (ICP) and no evident blockage to cerebrospinal fluid (CSF) flow.[2] The precise pathophysiological process in iNPH remains debated, with proposed factors including diminished CSF drainage, neuroinflammation, vascular insufficiency, and compromised

Key words
- Glaucoma
- iNPH
- Ventriculo-peritoneal shunt surgery

Abbreviations and Acronyms
AL: Axial length
CH: Corneal hysteresis
CSF: Cerebrospinal fluid
GCC: Ganglion cell complex
ICP: Intracranial pressure
iNPH: Idiopathic normal pressure hydrocephalus
IOP: Intraocular pressure
NTG: Normal tension glaucoma
OAG: Open-angle glaucoma
ORA: Ocular response analyzer
POAG: Primary open-angle glaucoma
RNFL: Retinal nerve fiber layer
TCPG: Translaminar cribrosa pressure gradient
VF: Visual field
VP: Ventriculo-peritoneal

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glymphatic circulation potentially contributing to its onset and progression.[3,4] Notably, iNPH is one of the few causes of dementia that may potentially be reversed through ventriculo-peritoneal (VP) shunt surgery, which is associated with an average reduction of 3 mmHg in ICP and a success rate of up to 85% within 12 months.[5]

In recent years, several studies reported a higher prevalence of open-angle glaucoma (OAG) in iNPH patients compared to the general population.[6,7,8,9] The most commonly associated condition with iNPH was normal tension glaucoma (NTG), a subtype of OAG where optic nerve damage occurs despite normal intraocular pressure (IOP).[8-10] The pathophysiological mechanisms and epidemiology of OAG in iNPH patients appear to differ based on whether patients have undergone shunt surgery. In nonshunted patients, glaucomatous damage is thought to be caused by impaired CSF flow and fluctuations in ICP wave amplitude.[9,11] Conversely, in shunted iNPH patients, increased glaucomatous damage risk is attributed to reduced ICP postshunt surgery, resulting in elevated translaminar cribrosa pressure gradient (TCPG) and compression of retinal ganglion cell axons.[7]

Glaucoma is the leading cause of irreversible blindness worldwide, and it has been estimated that the number of patients with glaucoma will globally increase by 74% by 2040.[12] The global prevalence is 3.54% for individuals aged between 40 and 80 years but rises to nearly 10% for patients aged more than 80 years.[13] Numerous studies have documented the significant impact of glaucoma on patient's quality of life, as visually impaired patients face a greater risk of accidents, social withdrawal, and depression compared to their sighted peers.[14] Additionally, nearly half of individuals with glaucoma experience falls over a year.[15,16]

Previous studies suggested that a deeper comprehension of the prevalence and progression of glaucomatous damage in iNPH patients may underscore the necessity for a comprehensive ophthalmological screening within this patient population.[7] However, ophthalmological screening is not routinely carried out in iNPH patients at the time of diagnosis or after shunt surgery, partly due to the limited research investigating the association between iNPH and glaucoma. Furthermore, no previous studies have prospectively examined the optic nerve damage progression before and after VP shunt surgery in iNPH patients. Therefore, the main objective of the present study was to assess the prevalence of OAG in Caucasian patients affected by iNPH before VP shunt surgery, and to identify the number of previously undiagnosed patients. Additionally, we aimed to assess the progression of the glaucomatous damage 1 year after shunt surgery.

MATERIALS AND METHODS

Study Population

Patients were recruited between November 2021 and June 2023 from an ongoing interventional prospective study at the University of Bologna, in collaboration with the Bologna PRO-HYDRO study group. The study adhered to the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of Bologna, Italy (Cod CE: 809/2021). Written informed consent was obtained from all patients.

The primary objective was to assess the prevalence of OAG in patients with iNPH prior to shunt surgery and to identify the number of undiagnosed patients at the time of screening. The secondary objective was to evaluate the progression of glaucomatous damage 1 year after shunt surgery and to examine changes in the biomechanical properties of the globe following the surgical intervention.

Inclusion and Exclusion Criteria

The multidisciplinary Bologna PRO-HYDRO study group reviewed the medical charts and the available brain images of patients with a suspected diagnosis of iNPH.[17] Eligible patients underwent 3-T brain magnetic resonance imaging. Those exhibiting clinical characteristics and neuroimaging findings consistent with iNPH were enrolled in the inpatient iNPH program, where they underwent a CSF tap test. Following a comprehensive review of clinical and imaging data, and considering the response to CSF tap test, the multidisciplinary team established the diagnosis of "probable" iNPH and identified patients suitable for VP shunt surgery, as previously described.[2,17] Patients were excluded from shunt surgery if they had significant comorbidities that could independently impact neurological function or contraindicate surgery. Those diagnosed with "probable" iNPH and indicated for VP surgery were referred for ophthalmological assessment before and after shunt surgery. We excluded iNPH patients with severe cognitive decline or those who were bedridden and unable to undergo the ophthalmological assessment. Additionally, patients with a history of ocular trauma, retinal detachment, corneal opacities, advanced cataracts, age-related macular degeneration, diabetic retinopathy, high myopia (> -6 diopters), axial length (AL) > 26 mm or < 21 mm, or history of uveitis were also excluded. Furthermore, patients with angle-closure glaucoma, angle-closure suspect conditions, or secondary glaucoma were not included in the study.

Clinical Assessment

Patients received an ophthalmological evaluation both before and 1 year after VP shunt surgery. Information regarding medical therapies and comorbidities was collected. Each patient underwent a comprehensive ophthalmological assessment, which included an evaluation of best-corrected visual acuity, spherical equivalent, anterior segment examination via slit lamp, Goldmann applanation tonometry, gonioscopy, the 24–2 Humphrey visual field (VF) test using the Humphrey Field Analyzer 3 (Carl Zeiss Humphrey Systems, Dublin, USA), and indirect ophthalmoscopy for optic nerve assessment. Additionally, patients with iNPH underwent measurements of AL and central corneal thickness using the IOLMaster 700 (Carl Zeiss Meditec AG, Jena, Germany). The retinal nerve fiber layer (RNFL) thickness was assessed using a 360°, 3.4 mm diameter peripapillary circle scan as per standard optical coherence tomography protocol (Heidelberg Spectralis SD-optical coherence tomography, Heidelberg Engineering, Germany), and the macular ganglion cell complex (GCC) thickness was evaluated using the standard protocol on the Optovue device (Optovue Inc., Fremont, CA). Corneal biomechanics were assessed in vivo using the ocular response analyzer (Reichert

Instruments, Depew, New York), obtaining values for corneal hysteresis (CH), corneal resistance factor, Goldmann-correlated IOP, and corneal-compensated IOP, as previously described.[18] Ocular response analyzer examinations were conducted by 2 operators (N. V. and S. F.), blinded to the subjects' characteristics. All measurements were performed on the same day between 11 AM and 2 PM to minimize the potential confounding effects of diurnal variations in IOP. The right eye of each participant was included in the statistical analysis.

Diagnosis of OAG

A diagnosis of OAG was based on the following criteria: assessment of IOP, slit lamp examination including gonioscopy, clinical evaluation of the optic nerve (notable findings such as increased excavation, bayonet vessels, lamina cribrosa exposure, presence of splinter hemorrhages, thinning of the neural rim, or pallor of the optic nerve head), evaluation of RNFL thickness, assessment of GCC thickness, and identification of VF defects using the 24–2 Humphrey VF test.[19,20] Patients diagnosed with new-onset OAG were started on IOP-lowering medications.

Statistical Analysis

Normality was assessed using the Shapiro-Wilk test. Since the variables were normally distributed, they were reported as mean and standard deviation, and parametric tests were employed for statistical analysis. The χ^2 test was used to evaluate the association between 2 categorical variables. The paired t-test was used to assess the differences in demographic characteristics, RNFL thickness, GCC thickness, CH, corneal resistance factor, corneal-compensated IOP, Goldmann-correlated IOP, central corneal thickness, SE, AL, mean deviation, and pattern standard deviation before and after shunt surgery. A P value of less than 0.05 was considered statistically significant. Statistical analysis was conducted using IBM Statistical Package for Social Sciences version 26.

Table 1. Demographic Data of Idiopathic Normal Pressure Hydrocephalus Patients and the Control Group are Shown

Baseline Characteristics	iNPH Patients (n = 35)
Age (years), mean ± SD	75.8 ± 6.6
Sex (female), n (%)	12 (34.3%)
Cataract surgery, n (%)	10 (28.5%)
BCVA LogMar, mean (range)	0.1 (0.4–0)
IOP Goldmann (mmHg), mean ± SD	17.5 ± 5.2
Open-angle glaucoma, n (%)	8 (22.8%)
Primary open-angle glaucoma	8 (100%)
Diagnosis of open-angle glaucoma	
Previous diagnosis, n (%)	4 (50%)
New diagnosis, n (%)	4 (50%)
Mean deviation, mean ± SD	−9.6 ± 8.2
Pattern standard deviation, mean ± SD	5.5 ± 2.4
Axial length (mm), mean ± SD	23.2 ± 1.1
Spherical equivalent (D), mean ±SD	+1 ± 1.2
Central corneal thickness (μm), mean ± SD	535 ± 41.4
Corneal hysteresis (mmHg), mean ± SD	9.4 ± 1.9

iNPH, idiopathic normal pressure hydrocephalus; SD, standard deviation; BCVA, best-corrected visual acuity; IOP, intraocular pressure.

RESULTS

Demographic Characteristics

A total of 35 eyes of 35 iNPH patients were considered for the analysis. The mean age of patients was 75.75 ± 6.67 years, and 34.3% were females. The mean time between the onset of the neurological symptoms and the ophthalmological assessment was 2.8 ± 1.3 years. Demographic data are shown in Table 1.

Rate of OAG Before Shunt Surgery

Overall, 22.8% of iNPH patients presented primary open-angle glaucoma (POAG) at the baseline evaluation. Among them, 50% of patients received a new diagnosis of POAG. None of the patients with a previous documented diagnosis of POAG had undergone previous surgery or laser, and all patients were under treatment with IOP-lowering eyedrops, with well-controlled pressure values. Patients with a new diagnosis of POAG were started with IOP-lowering eye drops.

Post-VP Shunt Surgery Assessment

A total of 18 patients with iNPH underwent VP surgery, including 4 patients diagnosed with POAG. Patients were evaluated after a mean follow-up of 13.9 ± 4.8 months (range: 11.2 to 30.8 months) following surgery. No significant changes in RNFL thickness were observed before and after the shunt surgery. The mean values of GCC thickness showed a slight decrease in iNPH patients post-surgery, although these differences were not statistically significant ($P > 0.05$). As shown in Table 2, none of the patients exhibited optic disc changes indicative of a new diagnosis of OAG, and IOP values were well controlled in all patients following the procedure. Furthermore, there was no observed progression of VF defects. Additionally, the results of our study indicated no alterations in corneal biomechanics after surgery, as detailed in Table 3.

DISCUSSION

In this study, we found that 22.8% of nonshunted iNPH patients exhibited POAG, with 50% of those receiving a new diagnosis. We did not observe a significant reduction in RNFL and GCC after an average of 14 months following shunt surgery despite a slight decrease in GCC values. Additionally, there were no changes in VF parameters or corneal biomechanical properties postsurgery. Previous research has indicated a higher prevalence of OAG in iNPH patients compared to the general population. For instance, a retrospective study by Chang et al. reported a history of glaucoma in 18.1% of 72 shunted and nonshunted iNPH patients, compared to 5.6% in age-matched controls in the United States.[6] However,

Table 2. Assessment of Retinal Nerve Fiber Layer Thickness and Ganglion Cell Complex Thickness in Idiopathic Normal Pressure Hydrocephalus Patients Before and After Shunt Surgery

	iNPH Baseline (n = 18)	iNPH Postshunt (n = 18)	*P* Value
Retinal nerve fiber layer (RNFL) thickness (μm), mean ± SD			
RNFL average	95.3 ± 16.0	96.6 ± 13.1	0.639
RNFL superior	121.1 ± 24.2	116.6 ± 22	0.338
RNFL nasal-superior	104.8 ± 20.2	102.8 ± 26.4	0.615
RNFL temporal-superior	136.3 ± 33.9	130.2 ± 23.0	0.292
RNFL inferior	119.8 ± 18.8	121.4 ± 19.3	0.409
RNFL temporal inferior	136.4 ± 26.4	129.0 ± 27.4	0.128
RNFL nasal inferior	102.9 ± 22.7	112.3 ± 22.1	0.058
RNFL medial	71.6 ± 16.2	74.7 ± 20.6	0.251
RNFL lateral	67.3 ± 18.4	66.7 ± 12.5	0.812
Ganglion cell complex (GCC) thickness (μm), mean ± SD			
GCC average	93 ± 9.3	92 ± 8.8	0.373
GCC superior	92.9 ± 9.7	92.3 ± 8.8	0.465
GCC inferior	93.1 ± 9.6	92.9 ± 10.9	0.924

Values for RNFL and GCC are reported in μm. Means and standard deviations are reported.
iNPH, idiopathic normal pressure hydrocephalus; SD, standard deviation; RNFL, retinal nerve fiber layer; GCC, ganglion cell complex.

this study did not differentiate between types of glaucoma and included both presurgery and postsurgery patients. A recent prospective study by Igarashi et al. found a prevalence of NTG in 55% of 20 nonshunted iNPH individuals. Still, it did not assess optic nerve damage progression after shunt surgery.[9] Our findings suggest that nonshunted iNPH patients face a significant risk of developing both NTG and POAG. The variation in glaucoma types may be partly attributed to ethnic differences, particularly the high prevalence of NTG in the Japanese population, where it accounts for up to 90% of OAG cases, compared to only 30%–40% in European countries.[21] Thus, our results support the notion that POAG may be the predominant form of glaucoma in Caucasian nonshunted iNPH patients. Further research is needed to explore the underlying pathophysiological mechanisms contributing to the different forms of OAG in this population.

Another finding of the present study was that 50% of patients with POAG received a new diagnosis , indicating that POAG may be underdiagnosed prior to shunt surgery. In a previous study, we found that only 4.8% of 63 iNPH patients were being treated with

Table 3. Assessment of Visual Acuity, Intraocular Pressure, Visual Field Parameters, and Corneal Biomechanical Properties Before and After Shunt Surgery

	iNPH Baseline (n = 18)	iNPH Postshunt (n = 18)	*P* Value
BCVA LogMar, mean (range)	0.1 (0.4–0)	0.1 (0.4–0)	0.732
IOP Goldmann (mmHg), mean ± SD	18.9 (± 5.6)	17.2 ±3.2	0.162
IOPcc, mean ± SD	18.2 ± 3.6	17.1 ± 2.8	0.178
Mean deviation, mean ± SD	−8.7 ± 6.2	−8.9 ± 6.7	0.834
Pattern standard deviation, mean ± SD	6.5 ± 2.7	6.8 ± 2.9	0.886
Corneal hysteresis, mean ± SD	9.93 ± 1.9	9.96 ± 1.6	0.949
Corneal resistance factor, mean ± SD	11.04 ± 1.9	10.5 ± 1.6	0.100

iNPH, idiopathic normal pressure hydrocephalus; BCVA, best-corrected visual acuity; IOP, intraocular pressure; SD, standard deviation; IOPcc, corneal compensated intraocular pressure.

antiglaucoma eye drops, significantly underestimating the prevalence of POAG identified in the present study.[22] Therefore, our findings suggest that regular ophthalmological screening should be recommended at the time of iNPH diagnosis to identify patients with OAG, as early and timely treatment could reduce the progression of optic nerve damage following shunt surgery.

After a mean of 14 months after surgery, we did not observe any new diagnosis of OAG. Moreover, RNFL, GCC, and VF parameters did not present any significant changes after surgery. In a previous study in shunted iNPH patients, Gallina et al. reported a prevalence of NTG of 40.9% among 22 patients after 76 months from VP shunt placement.[7] Moreover, they recently reported that 75% of iNPH patients had been diagnosed with NTG within 10 years after VP surgery, suggesting that a crucial risk for the development of NTG in shunted iNPH is the duration of optic nerve exposure to lower values of ICP.[8] On the other hand, Kemiläinen et al. did not observe an increased prevalence of OAG in shunted iNPH patients compared to age-matched individuals.[23] However, a main limitation of the aforementioned studies is that they did not systematically assess the prevalence of OAG at the time of iNPH diagnosis. As OAG might be underestimated prior to shunt surgery, additional research is needed to evaluate whether timely intervention for OAG could effectively reduce the incidence of glaucomatous damage after VP surgery. Also, since POAG may progress over an extended follow-up period, we plan to prolong our observation to assess its prevalence and potential progression several years after shunt placement. This longer follow-up will provide valuable insights into the long-term effects of shunting on glaucoma progression.

The reasons for the increased prevalence of OAG in iNPH patients compared to the general population have yet to be fully understood. In nonshunted iNPH patients, glaucomatous damage is thought to be caused by impaired CSF flow, leading to neurotoxin accumulation and decreased nutrition for retinal ganglion cell axons. Also, in the initial stages, iNPH is characterized by fluctuations in ICP wave amplitude, causing ventricular expansion without increased ICP.[24] These fluctuations are thought to increase the TCPG, the difference between the IOP and ICP across the lamina cribrosa (the mesh-like membrane present in the sclera where retinal ganglion cell axons exit from the eye) leading to compression of the retinal ganglion cell axons, with progressive optic nerve damage and cellular loss.[9,11] On the other hand, in shunted iNPH patients, increased glaucomatous damage risk is attributed to reduced ICP postshunt surgery, resulting in elevated TCPG and compression of retinal ganglion cell axons.[7] In a recent study, we observed a significantly lower CH in nonshunted iNPH patients compared to healthy age-matched individuals, which may potentially contribute to the risk of development of glaucomatous optic nerve damage, since a lower CH might reflect a decreased ability of the globe to absorb and dissipate IOP and ICP changes.[18] In the present study, we did not observe any significant changes in CH after shunt surgery, suggesting that the unchanged ocular biomechanical properties after surgery may potentially contribute to the risk of glaucomatous optic nerve damage in iNPH patients both before and after shunt surgery.

The higher occurrence of POAG among iNPH patients could play a significant role in their clinical assessment. Several studies reported mobility and balance problems in patients with OAG. Popescu et al. showed that patients with POAG performed significantly worse at the Time Up and Go test than controls.[25] Furthermore, previous studies reported an increased risk of falls in patients with glaucoma.[15] Also, glaucoma can significantly impact the ability to perform daily activities in affected patients.[26] These results suggest that glaucoma might affect the clinical evaluation of iNPH patients, impacting their quality of life and potentially influencing the outcomes of clinical tests. Therefore, given the increased prevalence of OAG in iNPH patients compared to the general population, regular ophthalmological assessments for individuals newly diagnosed with iNPH should be recommended. These assessments should aim to evaluate IOP values and treatment compliance in patients with prior diagnoses, and identify cases of undiagnosed OAG, as early initiation of appropriate treatment may potentially reduce the progression of the optic nerve damage. Additionally, considering that iNPH is frequently underdiagnosed, we recommend that patients with OAG who present with clinical signs and symptoms consistent with iNPH undergo an appropriate neurological evaluation to exclude or confirm its presence. This interdisciplinary approach may improve early diagnosis and optimize patient management.

The main limitation of the present study is the small cohort of patients included. A larger cohort would provide more robust data, allowing for a more comprehensive assessment of the relationship between iNPH and POAG. Additionally, the limited follow-up may underestimate the actual prevalence of OAG after shunt surgery. Therefore, further research with extended follow-up is required to accurately determine the prevalence of OAG after shunt surgery, assess the progression of optic nerve damage after shunting, identify risk factors associated with an increased likelihood of developing optic nerve damage, and establish the optimal timing for postoperative ophthalmological assessments.

CONCLUSION

In the present study, we found that 1 in 5 patients with iNPH had POAG, with 50% being undiagnosed. After a mean follow-up of 14 months postsurgery, we did not observe any progression of optic nerve damage or new diagnoses of OAG. Given the higher prevalence of POAG in iNPH patients compared to the general population, we recommend regular ophthalmological screenings for individuals newly diagnosed with iNPH, as early treatment may help reduce the progression of optic nerve damage and positively impact the quality of life for these patients.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Nicola Valsecchi: Writing — review & editing, Writing — original draft, Visualization, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Matilde Roda:** Writing — review & editing, Supervision, Methodology, Investigation, Conceptualization. **Simone Febbraro:** Writing — review & editing, Methodology, Investigation, Data curation. **Matteo Elifani:** Writing — review & editing, Methodology, Data curation. **Eleonora Trolli:** Writing — review & editing, Investigation, Data curation. **Matteo Nicolò Russo:** Writing — review & editing, Data curation. **Giorgio Palandri:** Writing — review &

editing, Validation, Supervision, Methodology, Investigation, Data curation, Conceptualization. **Giulia Giannini:** Writing — review & editing, Data curation. **David Milletti:** Writing — review & editing, Data curation. **Costantino Schiavi:** Writing — review & editing, Validation, Supervision, Conceptualization. **Luigi Fontana:** Writing — review & editing, Writing — original draft, Validation, Supervision, Conceptualization. **Antonio Moramarco:** Writing — review & editing, Validation, Supervision.

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