Optical Coherence Tomography Revealing Ganglion Cell Loss in Idiopathic Normal Pressure Hydrocephalus

Andreas Eleftheriou1,2, Yumin Huang-Link1,2, Fredrik Lundin1,2

BACKGROUND: Although there may theoretically be a disturbance in the eye or the visual pathways due to abnormal cerebrospinal fluid (CSF) dynamics in idiopathic normal pressure hydrocephalus (iNPH), it has not been studied systemically. Optical coherence tomography (OCT) is a noninvasive, reproducible procedure for quantitative and qualitative analysis of retinal morphology.

METHODS: OCT was used to study the eye fundus before and after a CSF tap test in patients with iNPH compared with healthy individuals (HIs). Twelve patients with iNPH (6 females and 6 males) with a median age of 76 years (64–84 years) and 21 HIs (11 females and 10 males) with a median age of 73 years (64–79 years) were included. The patients underwent neurological, cognitive, and physiotherapeutic evaluation. Brain magnetic resonance imaging, CSF tap test via lumbar puncture, and subsequently CSF analysis were performed. OCT was performed before and after CSF removal. HIs underwent OCT once.

RESULTS: The patients had significantly reduced retinal ganglion cell layer thickness 71 μm (56–81 μm) compared with the HIs, 79.5 μm (72–90 μm) (P = 0.001), but no significant changes were observed before or after the CSF tap test. All patients improved in motor function in a 10-m walk test after the CSF tap test. The median CSF pressure was 15 and 1 cm H₂O, respectively, before and after lumbar puncture with removal of median 43.5 mL CSF.

CONCLUSIONS: This pilot study shows OCT findings that differ from HIs and implies a rational for becoming a valuable tool in the diagnosis of iNPH. Further studies are warranted to elucidate the pathology of the retina in iNPH.

INTRODUCTION

Idiopathic normal pressure hydrocephalus (iNPH) is a disease affecting the elderly population.1 In order to be diagnosed as having probable iNPH, a patient must have clinical symptoms such as impaired gait combined with either or both cognitive dysfunction and urinary urgency.2 The diagnosis of probable iNPH is based on clinical history, physical findings, brain imaging, and physiological criteria according to the International iNPH guidelines from 2005.3,4 Because of the disturbed cerebrospinal fluid (CSF) dynamics in iNPH, it is possible that the retina could be affected in several ways, but evidence is lacking. Igarashi et al5 reported that iNPH patients with normal-tension glaucoma had higher intracranial cerebral pressure and shallow optic disc cupping compared with patients with normal-tension glaucoma without iNPH. Another study by Afonso et al6 reported retinal thickness changes after a shunt operation.

Brain magnetic resonance imaging is essential for diagnosing iNPH and enables the study of the gross anatomy of the optic pathways, but it does not give information about microscopic...
features. Furthermore, its utility is limited for evaluating disease progress. The biomarkers of CSF, tau, fosfo-tau, β-amyloid, and neurofilament (NFL) offer a complementary analysis of disease progress as well as tools for differentiating iNPH from other neurodegenerative disorders.7,8

Optical coherence tomography (OCT) scans have high sensitivity and reliability in defining papilledema and have been used to investigate the structural changes in the retina.5 OCT is a noninvasive, reproducible procedure for quantitative and qualitative analysis of retinal morphology.

The primary aim of this prospective pilot study was to explore retinal changes (retinal nerve fiber layer [RNFL] thickness, ganglion cell layer [GCL] thickness, optic disc area, rim area, and optic volume) in patients with iNPH compared with healthy individuals (HIs). The secondary aim was to study any changes in the clinical symptoms before and after a CSF tap test corresponding to the OCT findings.

MATERIALS AND METHODS

Patients

Twelve consecutive patients with probable iNPH diagnosed according to the International iNPH guidelines from 2005, namely 6 females and 6 males, with a median age of 76 (64–84) years were prospectively recruited from the outpatient clinic at the Department of Neurology, University Hospital, Linköping, Sweden, from November 2015 to November 2016.9 The median symptom duration was 26 months (12–72 months). The clinical characteristics of the patients are displayed in Table 1. None of the patients was diagnosed with glaucoma or other neurodegenerative diseases on the date of inclusion. Patients with known diabetic retinopathy, macular degeneration, and any type of retinal artery occlusion were not included. This study was approved by the Ethics Committee Review Board of Linköping University, Sweden, for OCT (reference numbers 2013/141-31 and for extraction of clinical data from the medical records an approval of the National Ethics Committee of Sweden 2019-02260). Written consent was obtained from all participants.

Healthy Individuals

By convenience sampling, 21 HIs with a median age of 73 years (64–79 years), 11 females and 10 males, were included. None of the HIs had glaucoma, diabetes mellitus, or any neurodegenerative disease. They considered themselves healthy and had normal balance, gait, and vision. All HIs underwent OCT once. No clinical evaluation of motor or cognitive evaluation was performed in the HIs.

Optical Coherence Tomography

Spectral-domain OCT employs low-coherence interferometry to detect the echo spectrum of the backscattered light by the sample tissues, and in comparison with reflections from a fixed reference mirror. OCT images (Cirrus 4000 high-definition SD; Carl Zeiss Meditec, Dublin, California, USA) were obtained of all subjects immediately before lumbar puncture (LP) and within 2 hours after LP with CSF removal. The OCT images were collected according to the recommended study-specific protocol for the optic disc and macular area.10 The examination was performed without mydriasis. None of the patients examined had a history of diabetes mellitus, optic neuritis, glaucoma, or macular disorders.

As mentioned in our previous study,11 the RNFL (µm) was obtained using the protocol of the Optic Disc Cube 200 × 200 centered on the optic nerve head. Data on GCL (µm) were collected using the protocol of the Macular Cube 512 × 128 centered on the fovea. GCL thickness is the sum of GCL and inner plexiform layer. The disc and macula margin were bounded automatically by software without manual modification. Only good-quality scans with a signal strength of 7 or more and no missing parts within the measurement circle were accepted. A neuro-ophthalmologic control was done clinically with visual acuity, contrast sensitivity, eye movement, and OCT before and after a CSF tap test. With OCT investigation, we controlled the RNFL, rim area, papillary area, optic nerve volume, automated visual field, and GCL.

As circadian rhythm has been shown to be associated with choroid thickness, OCT was performed in all patients at 9:00 AM before the tap test and again between 10:00 and 11:00 AM.11 The CSF tap test was performed between 9:00 and 10:00 AM. All HIs underwent OCT at 11:00 AM. All the investigations were performed in our outpatient clinic.

LP with a CSF Tap Test

A CSF tap test was performed in all patients in recumbent position. Once CSF was obtained, a spinal fluid manometer (Optidyneamic, Mediplast, Italy) was connected to measure the CSF pressure in cm H2O. The pressure was measured during a period of 1 minute to avoid artificially elevated levels. All the patients were relaxed and had their neck to a neutral position and their legs extended. Lumbar pressure was measured before and after the CSF tap test. According to our department’s routine, CSF was analyzed for cells, lactate, albumin, isoelectric focusing, antibodies against Borrelia burgdorferi, NFL, tau, f-tau, and β-amyloid.

Table 1. Clinical Characteristics of the Patients with iNPH

<table>
<thead>
<tr>
<th>Demography and Comorbidities</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (range)</td>
<td>76 (64-84)</td>
</tr>
<tr>
<td>Smoking</td>
<td>2/12</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3/12</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3/12</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>3/12</td>
</tr>
<tr>
<td>Stroke</td>
<td>1/12</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2/12</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1/12</td>
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</tbody>
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iNPH, idiopathic normal pressure hydrocephalus.
Clinical Evaluation

All patients underwent a neurological examination by a neurologist. The motor function was assessed by a physiotherapist (JR) using the following tests: time needed for a 10-m walk time and steps at a self-selected speed and at their usual walking aid;13; timed up and go test in seconds and steps, which is a timed test for standing up from a chair; walking 3 m; turning and walking back to the chair; and sitting down.14 An occupational therapist (KO) performed cognitive testing with the Mini-Mental State Examination.15 All pre-CSF tap test evaluations were performed 1 hour before the OCT or the day before the CSF tap test. All post-CSF tap test investigations were performed at approximately 1:00 PM.

Statistical Analysis

Statistical analysis was performed using Statistica (data analysis software system), version (StatSoft, Inc., 2011). There was no significant difference between the right and the left eyes; therefore they were analyzed together. Descriptive statistics were expressed in median ± range. The Wilcoxon signed-rank test was used to investigate whether there was any significant difference in clinical and OCT data, before and after the CSF tap test, and between the iNPH and the HIs. Spearman’s rank correlation coefficient was used to analyze the correlation of OCT data with clinical data.

RESULTS

GCL was significantly lower in the patients before the CSF tap test compared with the HIs (71 μm, 56–81 μm vs. 79.5 μm, 72–90 μm; P = 0.001), and the difference after the CSF tap test was even more pronounced (P = 0.0001). RNFL in the patients was not significantly lower compared with the HIs (85 μm, 63–109 μm vs. 88.5 μm, 76–114 μm; P = 0.14), but became significant after the CSF tap test (84.5 μm, 65–109 μm vs. 88.5 μm, 76–114 μm; P = 0.02).

We also found a nearly statistical significant higher GCL thickness in patients with iNPH after the CSF tap test (72 μm, Table 2. Motor and Cognitive Data Before and After the Cerebrospinal Fluid Tap Test

<table>
<thead>
<tr>
<th>Motor and Cognitive Data</th>
<th>Patients with iNPH</th>
<th>HIs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before Tap Test, Median (Range)</td>
<td>After Tap Test, Median (Range)</td>
</tr>
<tr>
<td>10-m walk (steps)</td>
<td>24 (16-47)</td>
<td>22 (16-30)</td>
</tr>
<tr>
<td>10-m walk (seconds)</td>
<td>16 (8-44)</td>
<td>12 (8-18)</td>
</tr>
<tr>
<td>TUGt (seconds)</td>
<td>15.5 (9-38)</td>
<td>15.5 (8-25)</td>
</tr>
<tr>
<td>TUGs (steps)</td>
<td>23.5 (14-55)</td>
<td>22 (14-34)</td>
</tr>
<tr>
<td>Romberg (seconds)</td>
<td>17.5 (0-60)</td>
<td>48.5 (0-60)</td>
</tr>
<tr>
<td>MMSE</td>
<td>23.5 (16-27)</td>
<td>26 (15-29)</td>
</tr>
</tbody>
</table>

Table 3. OCT Parameters in Patients with iNPH Before and After the CSF Tap Test, and in HIs

<table>
<thead>
<tr>
<th>OCT Measurements</th>
<th>iNPH</th>
<th>HIs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before Tap Test, Median (Range)</td>
<td>After Tap Test, Median (Range)</td>
</tr>
<tr>
<td>RNFL (μm)</td>
<td>85 (63-109)</td>
<td>84.5 (65-109)</td>
</tr>
<tr>
<td>Rim area (mm²)</td>
<td>1.26 (0.78-1.53)</td>
<td>1.22 (0.8-1.5)</td>
</tr>
<tr>
<td>Optic disc area (mm²)</td>
<td>1.82 (1.11-2.19)</td>
<td>1.81 (1.13-2.21)</td>
</tr>
<tr>
<td>Optic volume (mm³)</td>
<td>0.135 (0.001-0.441)</td>
<td>0.122 (0.002-0.393)</td>
</tr>
<tr>
<td>GCL (μm)</td>
<td>71 (56-81)</td>
<td>72 (56-82)</td>
</tr>
</tbody>
</table>

OCT, optical coherence tomography; iNPH, idiopathic normal pressure hydrocephalus; CSF, cerebrospinal fluid; HIs, healthy individuals; RNFL, retinal nerve fiber layer; GCL, ganglion cell layer.
56–82 μm; \( P = 0.09 \)). There was no significant change in thickness of the RNFL area \( (84.5 \, \mu \text{m}, 65–109 \, \mu \text{m}; \, P = 0.17 \) ) after the CSF tap test. Regarding the rim and optic disc areas, there were no significant differences. The optic volume was unchanged (Table 2).

Twelve patients with iNPH underwent a CSF tap test, and all improved their motor function \( (10\text{-m walk time and steps}) \) significantly \( (P = 0.02, \, P = 0.03) \). However, their cognitive function, measured with the Mini-Mental State Examination, was not improved significantly \( (P = 0.60) \) (Table 2).

The median value of CSF pressure was \( 15 \) (13–23) and \( 1.0 \) (0–6) cm \( \text{H}_2\text{O} \), respectively, before and after LP with CSF removal of median \( 43.5 \) mL \( (35–50 \text{ mL}) \). From the pre–CSF tap test data, we found a strong, almost significant negative correlation between the rim area and the CSF pressure \( (r = -0.55, \, P = 0.059) \). There were no other correlations of interest. The mean values for albumin \( 194 \, \text{ng/L} \) \( (88–357 \, \text{ng/L}) \), NFL \( 900 \, \text{ng/L} \) \( (340–2000 \, \text{ng/L}) \), tau \( 168 \, \text{ng/L} \) \( (75–459 \, \text{ng/L}) \), and f-tau \( 21 \, \text{ng/L} \) \( (15–55 \, \text{ng/L}) \) were not elevated, and \( \beta \)-amyloid in CSF was lower at \( 505 \, \text{ng/L} \) \( (325–736 \, \text{ng/L}) \) in the patients with iNPH compared with a normal reference \( (>550 \, \text{ng/L}) \).

**DISCUSSION**

OCT is a rapid, safe, and noncontact systematic method producing in vivo cross-sectional histologic information on neural tissue with enough resolution to differentiate all retinal layers and subcellular photoreceptor elements. OCT can also give longitudinal information about neuro-ophthalmologic diseases. It is a reliable tool not only for the diagnosis and follow-up of neurodegenerative conditions such as multiple sclerosis, neuromyelitis optica, Alzheimer disease \( (\text{AD}) \), and Parkinson disease but also for other neurological conditions such as migraine and idiopathic intracranial hypertension.11,15,16,17 Especially, in patients with AD, OCT revealed RNFL thickness and increased optic disc cupping and differences compared with healthy controls.18

The pathophysiology of iNPH is poorly understood. Several possible mechanisms have been proposed, namely tissue distortion due to raised intracranial pressure, interstitial oedema with stagnation of fluid causing decreased clearance of toxic metabolites, and impaired cerebral blood flow in the subcortical areas resulting in defective regional autoregulation and ischemia.20 Radiological studies with the use of cerebral blood flow have revealed a reduced perfusion in the periventricular white matter compared with the perfusion of the subcortical white matter in patients with iNPH.21–24 In studies focusing on neuropathological findings, microinfarctions, lacunar infarction, microangiopathy, and axonal loss in the frontal area have been described.25 Leinonen et al16 found neuropathological similarities with higher \( \beta \)-amyloid brain deposition in iNPH and AD. Microvascular network alterations in the form of venular diameter changes have been shown in the retina of patients with AD andBinswanger disease.27–28 The existence of AD pathology in patients with iNPH is common, and diminished clearance of \( \beta \)-amyloid may also be involved in the pathogenesis of iNPH.29–31 Retinal thinning (RNFL and GCL reduction) has been observed in patients with neurodegenerative diseases such as Parkinson disease17,27–29 and AD.34–35 In contrast to AD, patients with iNPH have lowered \( \beta \)-amyloid but normal tau and f-tau. In 4 of the patients, we found isolated lower \( \beta \)-amyloid, and only 1 had isolated high tau. None of them had a combination of neurodegenerative markers, indicative of AD comorbidity. Regarding OCT findings, we could demonstrate a significantly lower GCL thickness in the patients compared with HIs, which suggests an ongoing neurodegenerative process.

The only existing treatment is a shunt operation to ameliorate the CSF dynamics, resulting in improvement of the symptoms. Little is known about how the CSF flow is changed in the cerebrospinal system after the insertion of a shunt as caused by a complex interaction between a CSF hydrodynamic disturbance and cerebrovascular disease, mainly affecting the periventricular deep white matter. The major role of the venous system is to accumulate and detach metabolic waste, avoiding a concentration of neurotoxic materials in the nerve cells. Altered fluid dynamics could result in changes of intracranial pressure and CSF flow, differences in wall shear stresses, and modified clearance of metabolic waste. This could lead to a decreased clearance of \( \beta \)-amyloid and might result in neurodegeneration.36 A reduced intracranial pressure (ICP) after a CSF tap test probably leads to an increased net systolic pulse volume in the superior sagittal sinus and secondary to a better drainage in the periventricular and the retinal areas.

The optic disc form change is most likely due to the lowered CSF pressure, explaining the significant optic disc area difference between patients and HIs \( (P = 0.03) \). RNFL between patients and HIs was not significant but became significant after the CSF tap test \( (P = 0.02) \). However, we could not demonstrate any strong correlation between baseline ICP/ΔICP and any other OCT findings.

To the best of our knowledge, only 2 previous studies of patients with iNPH have been reported: a pilot study comparing nonshunted versus shunted patients with iNPH and controls, and another recent study with the aim of comparing optic disc characteristics between normal-tension glaucoma and iNPH.5,6 In the first study by Afonso et al, there was a significantly lowered or normal choroidal thickness in nonshunted versus shunted patients with iNPH, respectively, supporting the hypothesis of choroidal involvement in hemodynamic changes in iNPH. In the second study by Igarashi et al, there was a higher ICP in the iNPH group and normal-tension glaucoma group compared with the iNPH group without normal-tension glaucoma. They also found a significant difference in the cupping disc depth with a shallower depth in the glaucoma group with iNPH compared with the glaucoma group without iNPH.

It might be questioned what could be the role of OCT in a condition like iNPH. This rather new technique can bring new information about retinal changes in iNPH and has several possible advantages. The concept of less invasive testing for iNPH is valid for practical, safety, and discomfort, as well as financial reasons. No clear conclusion can be made about the utility of OCT in iNPH from the existing data, but the fact that there are differences between patients with iNPH and controls is interesting and warrants further studies in larger cohorts of patients.
compared with HIs and patients with other neurodegenerative diseases. It would also be of great value to explore any differences before and after a shunt operation. In addition, as the changes are very fast and fluid movement between compartments might not be so efficient, a lumbar infusion test with a recording of the CSF dynamics could also give new information of the effects on the venous pressure wave.

Limitation
First, the number of patients included in our study was small. Larger cohorts will be necessary to clarify the potential of OCT as a tool for following and diagnosing iNPH. Second, OCT was performed without clinical data. Third, the radiological investigation in the iNPH group included computed tomography and magnetic resonance imaging of the brain, without volumetric measures. Finally, OCT was performed in a prospective manner, but the clinical data were retrieved retrospectively.

CONCLUSION
The main finding of our study is a significant reduction of GCL in patients with iNPH probably caused by altered CSF dynamics ultimately resulting in neurodegeneration. The usefulness of OCT in iNPH has to be studied further.

REFERENCES

AVAILABLE OF DATA AND MATERIAL
We used the data from our Cambio COSMIC Healthcare System, which is a digital comprehensive healthcare system installed in all clinics in our region. Radiological material was obtained through Sectra Image Display System 7.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT
Andreas Eleftheriou: were the clinicians who performed the clinical and neurological evaluation, Writing - original draft. Yumin Huang-Link: Investigation, Writing - review & editing. Fredrik Lundin: were the clinicians who performed the clinical and neurological evaluation, Writing - review & editing.

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Conflict of interest statement: The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. We used the data from our Cambio COSMIC Healthcare system, which is a digital comprehensive health care system installed in all clinics in our region. Radiological material was obtained through Sectra Image Display System 7.

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