

# Optic Nerve Head Drusen and Visual Field Loss in Normotensive and Hypertensive Eyes

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**Objective:** To compare visual field loss (VFL) in eyes with optic nerve head drusen (ONHD) with or without ocular hypertension (OHT).

**Methods:** The records of all patients aged 45 years or older with a diagnosis of ONHD at 2 centers were reviewed. OHT was defined as intraocular pressure  $\geq 22$  mm Hg. We categorized ONHD into 3 grades based on visibility on disc photographs.

**Results:** We identified 22 eyes (13 patients) with both ONHD and OHT and 81 normotensive eyes (47 patients) with ONHD. VFL was present in 20/22 (90.9%) of hypertensive eyes compared with 54/81 (66.7%) of normotensive eyes ( $P = 0.03$ , Fisher exact test). Drusen grade III and OHT were both independently and significantly associated with greater incidence of VFL (logistic regression analysis).

**Conclusions:** VFL occurs more frequently in eyes with ONHD that also have OHT. Eyes with grade III ONHD are at increased risk for VFL compared to eyes with grade I drusen with the same intraocular pressure status. Patients with OHT and ONHD should undergo close surveillance for disease progression and be treated appropriately to prevent additional VFL.

**Key Words:** optic nerve head drusen, ocular hypertension, visual field loss

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Optic nerve head drusen (ONHD) are calcified, laminated hyaline deposits anterior to the lamina cribosa and are thought to be products of degenerating axons of retinal ganglion cells.<sup>1</sup> They are usually

bilateral<sup>2–6</sup> and no clear sex predilection has been established.<sup>4,5</sup>

In clinical studies, the prevalence has been reported to be as high as 3.4 per 1000 in adults<sup>4</sup> and 4 per 1000 in children,<sup>2</sup> whereas a histologic study of adult autopsy eyes revealed an incidence of 20.4 per 1000.<sup>7</sup> Patients with ONHD and concomitant ocular hypertension (OHT) are seen much less frequently than patients with ONHD and normal intraocular pressure (IOP).

Clinically, ONHD appear as globular bodies embedded in the optic nerve head or protruding from the disc. They are often buried within the substance of the optic nerve head in children, but become exposed on the disc surface with aging,<sup>6,8,9</sup> owing to enlargement by continuous calcium apposition.<sup>10</sup>

ONHD are often associated with visual field defects.<sup>10</sup> The frequency of visual field defects in adults with ONHD has been reported to range from 24% to 87%,<sup>4,11–14</sup> with the highest rate of occurrence in eyes with superficial drusen.<sup>14</sup> Visual field loss (VFL) is more frequent in the lower nasal quadrant.<sup>11</sup> Reported visual field defects include arcuate defects, enlargement of the blind spot, and/or generalized constriction.<sup>10</sup> In most cases, visual acuity is well preserved. Eyes with ONHD and coexisting OHT often represent challenging diagnostic and therapeutic dilemmas. The role of IOP in the etiology of VFL in the presence of ONHD remains unknown. The purpose of this study is to compare VFL in eyes with ONHD with and without OHT.

## SUBJECTS AND METHODS

This study was approved by the institutional review boards of The New York Eye and Ear Infirmary, New York, NY and the University of Würzburg, Würzburg, Germany. The records of all patients aged 45 years or older with a diagnosis of ONHD at the 2 centers were reviewed. All patients had undergone a complete eye examination, dilated ophthalmoscopy, and achromatic perimetry. OHT was defined as IOP  $\geq 22$  mm Hg, based on maximum recorded IOP. ONHD were visible during clinical and/or imaging evaluation. Patients with a history of vascular events, such as vascular occlusion, subretinal neovascularization, or ischemic optic neuropathy, were excluded from the study.

ONHD were graded independently by 4 examiners (E.G., M.S., T.G., and W.S.) based on their clinical

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features at the time of review of disc photographs. In grade I (Fig. 1), ONHD were not clinically visible and diagnosis required the aid of B-scan ultrasonography (Fig. 2), grade II (Fig. 3) had < 7 visible drusen, and grade III (Fig. 4) had ≥ 7 visible drusen.

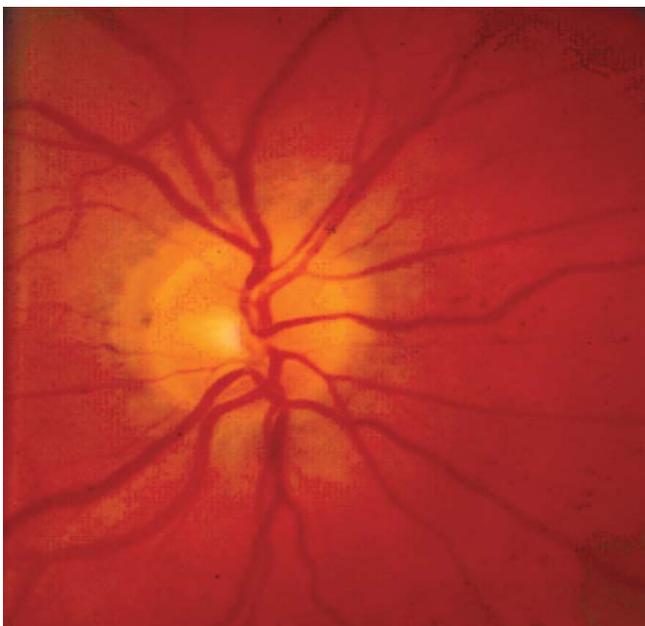
Subjects had undergone achromatic perimetry, either by Goldmann perimetry, Octopus 101 (Haag Streit GmbH, 22880 Wedel, Germany), Octopus 500 (Interzeag, Octopus 500 EZ), or Humphrey automated perimetry (Carl Zeiss Meditec, CA). For the Goldmann perimeter, the absence of a depression of the curve of stimulus I-4 was classified as within normal limits. Octopus 101 and 500 visual field examinations with program 31, 32, 33 or G1 were defined as within normal limits if no significant cluster/points were present. A significant cluster/point was defined as 3 or more adjacent test points with a deviation > 5 dB or one point with deviation > 10 dB within the difference table. Normal Humphrey visual field examinations were defined as a mean deviation of -2.0 dB or more, pattern standard deviation within the 95% confidence interval, and a glaucoma hemifield test within normal limits. To be considered abnormal, the Humphrey visual fields had to meet one of the following minimal criteria for visual field defects: glaucoma hemifield test results outside normal limits, corrected pattern standard deviation with a probability less than 5%, or a cluster of 3 or more points in the pattern deviation plot in a single hemifield (superior or inferior) with a probability less than 5%, one of which must have a probability level less than 1%.<sup>15,16</sup> Of the normotensive patients, 74% (60/81 eyes) had automated perimetry performed, whereas the remaining 26% (21/81 eyes) underwent Goldmann perimetry, primarily before automated perimetry became



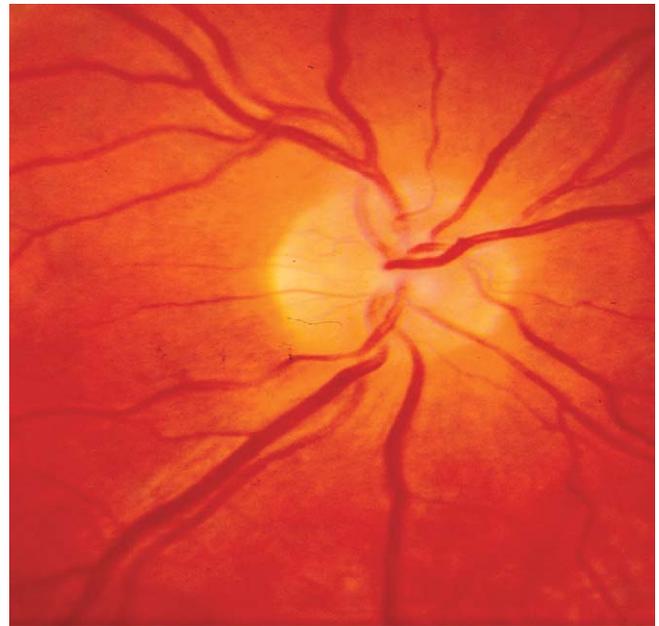
**FIGURE 2.** Ultrasonography image of a patient with ONHD. Hyper-echogenic image consistent with ONHD.

the standard of care. All of the ocular hypertensive patients underwent automated perimetry.

Visual fields were divided into those with VFL and those without it. The 2 groups were compared using *t* tests for continuous variables and  $\chi^2$  for categorical variables. We then conducted multiple logistic regression analysis using generalized estimating equations with a Logit Link



**FIGURE 1.** Disc photograph; example of ONHD grade I.



**FIGURE 3.** Disc photograph; example of ONHD grade II.



FIGURE 4. Disc photograph; example ONHD grade III.

(PROC GENMOD, SAS version 9.00) to calculate odds ratios and 95% confidence intervals for VFL compared with no VFL. Generalized estimating equations take into account the correlated nature, or lack of independence, of some of our observations because of the inclusion of data from both eyes of some of the study participants. Means are expressed with standard deviation ( $\pm$  SD).

**RESULTS**

We identified 103 eyes of 60 patients (24 men, 36 women) with ONHD. All patients were whites. Twenty-two eyes (13 patients) had OHT and 81 eyes (47 patients) were normotensive. Mean recorded IOP was  $27.1 \pm 5.0$  mm Hg in OHT eyes and  $15.7 \pm 2.4$  mm Hg in normotensive eyes. Mean patient age was  $63.7 \pm 10.9$  and  $60.1 \pm 9.3$  years in the OHT and normotensive groups, respectively ( $P = 0.24$ , Table 1).

In the normotensive group, 30 eyes were classified as grade III, 32 as grade II, and 19 as grade I. In the OHT groups, 5 eyes were classified as grade III, 15 as grade II, and 2 as grade I (Table 2).

VFL was present in 20/22 (90.9%) of OHT eyes compared with 54/81 (66.7%) of normotensive eyes

TABLE 1. Age and IOP Values for the Eyes Included in the Ocular Hypertensive and the Normotensive Groups

Group	Eyes, n	Age, y (Mean $\pm$ SD)	IOP, mm Hg (Mean $\pm$ SD)
OHT	22	63 $\pm$ 10.9	27.1 $\pm$ 5
NT	81	60.1 $\pm$ 9.3	15.7 $\pm$ 2.4

NT indicates ocular normotensive.

TABLE 2. Number of Eyes With Drusen Visibility Grade 1, 2, and 3 for the Ocular Hypertensive and the Normotensive Group

Drusen Visibility, Grade	OHT Eyes, n	NT Eyes, n
1	2	19
2	15	32
3	5	30

NT indicates ocular normotensive.

( $P = 0.03$ , Fisher exact test; Table 3 and Fig. 5). Logistic regression analysis indicated that OHT and the ONHD grade III both were independently and significantly associated with VFL (Table 4). In this model, neither age nor sex were important confounders.

**DISCUSSION**

The simultaneous occurrence of ONHD with elevated IOP presents a diagnostic and management dilemma. Our results verify that concomitant OHT increases the likelihood of VFL in these eyes.

**Pathophysiology of ONHD**

The pathophysiology of ONHD and associated VFL is not completely understood. ONHD have been suggested to originate from axoplasmic derivatives of disintegrated nerve fibers,<sup>17</sup> secondary to altered axoplasmic transport in an anatomically small scleral canal,<sup>18</sup> or from abnormal axonal metabolism leading to deposition of calcium crystals in mitochondria, axonal disruption, and mitochondrial extrusion into the extracellular space with continuous calcium apposition.<sup>19</sup> Although past investigators supported the hypothesis of a small scleral canal in association with ONHD,<sup>18,20,21</sup> recent evidence suggests that this might not be an etiologic factor.<sup>22</sup> On the basis of family studies of the incidence of ONHD and related optic disc anomalies among relatives of those affected, Antcliff and Spalton<sup>23</sup> concluded that the primary pathology is likely to be an inherited dysplasia of the optic disc and its blood supply.

**VFL in ONHD**

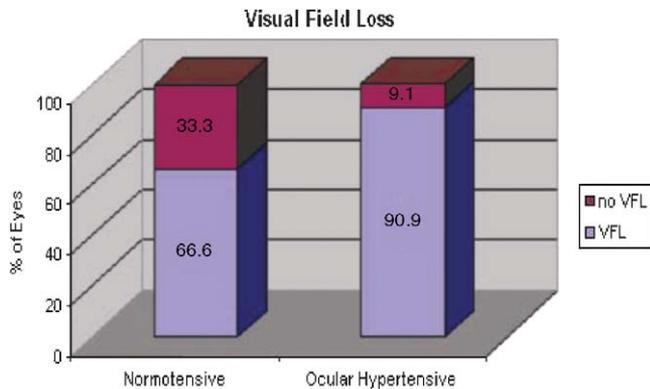
Lauber<sup>24</sup> was the first to correlate ONHD with VFL. Visual field defects may occur secondary to nerve fiber layer injury or to vascular events. A crowded small disc with an anomalous vascular pattern predisposes eyes to vascular complications. Acute VFL in ONHD is

TABLE 3. Presence of VFL in Ocular Hypertensive and Normotensive Groups

VFL	OHT Eyes, n (%)	NT Eyes, n (%)
No	2 (9.1)	27 (33.4)
Yes	20 (90.9)	54 (66.6)

$P = 0.03$ , Fisher exact test.

NT indicates ocular normotensive.



**FIGURE 5.** Graphic representation of VFL in both normotensive and ocular hypertensive groups.

usually due to vascular events such as ischemic optic neuropathy,<sup>25,26</sup> arterial or venous occlusions, or sub-retinal neovascularization. Some reports have shown dramatic VFL in eyes with ONHD without signs of prior vascular insufficiency, such as edema, hemorrhage, or documented hypoperfusion of the optic disc on fluorescein angiography.<sup>27,28</sup> If vascular events do not develop, VFL usually progresses slowly.<sup>9,12,29</sup> At the same time, elevated IOP is the most common known risk factor for axonal damage and VFL in glaucoma.<sup>30</sup>

**ONHD and OHT and/or Glaucoma in the Literature**

Only single case reports or small case series have described ONHD and glaucoma and/or OHT.<sup>31-34</sup> Samples et al<sup>31</sup> reported 5 cases of ONHD with coexistent risk factors for glaucoma and VFL. Others have reported single cases of primary open-angle glaucoma,<sup>33</sup> juvenile OHT,<sup>35</sup> and exfoliative glaucoma.<sup>32</sup> Roh et al<sup>36</sup> suggested that OCT may be a sensitive and early indicator of NFL thinning in patients with ONHD and patients with both ONHD and glaucoma.<sup>34,37</sup>

**Frequency of VFL in Patients With ONHD With and Without Elevated IOP in the Literature**

VFL secondary to ONHD can appear during childhood.<sup>6</sup> ONHD become more visible and superficial with time, secondary to enlargement due to continuous calcium apposition.<sup>10</sup> The incidence of VFL increases in patients with visible ONHD in comparison with patients

with buried ONHD.<sup>14</sup> We studied patients 45 years of age and older and found that patients with drusen grade III (visible drusen) had more VFL than patient with drusen grade I (buried drusen).

Although case series studying the characteristics of VFL in patients with ONHD exist, none specifically compared VFL in ONHD patients with and without OHT. Savino et al<sup>11</sup> performed Goldmann perimetry in 99 eyes with pseudopapilledema and subdivided his population into 2 groups based on visibility of ONHD on fundoscopic examination. Seventy-one percent of those with visible ONHD demonstrated visual field abnormalities compared with 21% without visible ONHD. IOP were not reported. In a study with 144 ONHD eyes with normal tension, Schargus et al<sup>38</sup> found that increasing VFL was correlated with increasing age and visibility of the ONHD. Stevens and Newman<sup>13</sup> found abnormal visual fields in 75% of their patients with visible ONHD, but did not differentiate between OHT and normotensive patients. Mustonen<sup>12</sup> found VFL in 73% of 263 eyes with ONHD. Of 119 patients in whom IOP was measured, only 11 eyes had elevated IOP. Four patients were diagnosed with glaucoma and 2 with OHT. The criteria for glaucoma diagnosis were not specified and glaucomatous patients were excluded from the study. None of these studies directly compared VFL in eyes with and without OHT.

Our study is the first to compare VFL in normotensive and hypertensive eyes in a large series of patients with ONHD. The deleterious influence of elevated IOP on already damaged but functional retinal ganglion cells may accelerate the apoptotic process leading to VFL. Coexisting OHT increases the likelihood of VFL in eyes with ONHD.

Some of the individuals included in this study who underwent Goldmann perimetry, primarily before automated perimetry became the standard of care may have had VFL that could have been detected by automated perimetry. Patients with normal-tension glaucoma or high-tension glaucoma could be present in our groups. At the present time, it is not possible to determine if the VFL is secondary to ONHD or concomitant glaucoma. We did not report the wide variety of disc appearance in the current set of patients as the appearance of the optic disc particularly when the drusen is buried may be misleading.

There is no current effective treatment for ONHD. Patients should be followed regularly for the onset of OHT. Patients with ONHD and elevated IOP should be monitored closely for disease progression and treated appropriately with antiglaucomatous therapy to prevent further VFL. We feel that, because of these difficulties and because of the increased susceptibility to VFL and the dual origin of VFL in patients with both ONHD and OHT, all such patients would potentially benefit from lowering IOP. This may also improve blood flow to the optic nerve head,<sup>39-43</sup> potentially reducing the chance of vascular events due to the presence of ONHD.

The simultaneous occurrence of 2 different disorders affecting the same structure presents diagnostic and

**TABLE 4.** Multiple Logistic Regression Analysis of Risk Factors for VFL Compared to no VFL

Risk Factor	Odds Ratio (95% CI)
Drusen grade 1	1 (reference category)
Drusen grade 2	1.3 (0.5-3.6)
Drusen grade 3	9.7 (2.2-42.7)
NT	1 (reference category)
OHT	6.6 (1.3-33.2)

CI indicates confidence interval; NT, ocular normotensive.

management challenges. Although VFL is common in normotensive eyes with ONHD, our results confirm that coexisting OHT increases the likelihood of VFL in these eyes. Further studies are necessary to better understand the role of elevated IOP in patients with ONHD and VFL and the possible long-term benefits of lowering IOP. Prospective studies to evaluate the effectiveness of lowering IOP and the role of neuroprotective agents and agents which increase ocular blood flow in patients with ONHD will be beneficial. At the present time, we recommend that all eyes with ONHD and OHT be treated to lower IOP. This is particularly true for eyes with greater numbers of ONHD.

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