Optic Nerve Hypoplasia With Isolated Tortuosity of the Retinal Veins

A Marker of Endocrinopathy

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Objective: To investigate whether children with optic nerve hypoplasia and pituitary hormone insufficiencies have specific ocular fundus characteristics that may facilitate early diagnosis and treatment.

Design: From May 15, 1995, through December 15, 1997, 17 children (8 girls and 9 boys, aged 0.3 to 13 years) with optic nerve hypoplasia were referred to the Department of Pediatric Ophthalmology, Children's Hospital, Göteborg, Sweden, and divided into 2 groups dependent on the presence (n = 8) or absence (n = 9) of pituitary deficiency. Morphological characteristics of the ocular fundus were evaluated by digital image analysis of fundus photographs, and the morphological characteristics of the brain structures were studied by magnetic resonance imaging.

Results: An isolated venous tortuosity noted among the children with optic nerve hypoplasia and endocrinopathy was the morphological ocular fundus variable that discriminated between the 2 groups of patients with optic nerve hypoplasia. Both groups of children demonstrated significantly reduced optic disc, cup, and neuroretinal rim area and few vascular branching points.

Conclusion: Optic nerve hypoplasia with isolated tortuosity of the retinal veins may potentially help the ophthalmologist in identifying children who should undergo a thorough diagnostic workup of endocrine function.

The association between ocular fundus abnormalities, midline brain lesions, and hormone deficiencies has been well described in the septo-optic dysplasia syndrome. The ophthalmologist plays an important role in identifying this syndrome, since early recognition of these children may prevent developmental delay, adrenal crisis, and even sudden death. A relationship between optic nerve hypoplasia (ONH) and isolated growth hormone deficiency, without agenesis of the septum pellucidum, has also been shown. Thus, an association between morphological characteristics of the ocular fundus and hormone deficiency has been demonstrated. It is not known, however, if the ONH associated with pituitary deficiency has any specific characteristics that could help the ophthalmologist in identifying these patients. As stated by Siatkowski et al., increased knowledge is needed to guide ophthalmologists and pediatricians to a more appropriate and cost-effective treatment of these children. The aim of the present study was to characterize ocular fundus morphological characteristics to facilitate early diagnosis and treatment in children with ONH and endocrine deficiencies.

The group with ONH and pituitary deficiency had a significantly higher median index of venous tortuosity (Figure 1, left) than the children with ONH without pituitary deficiency (P = .02) (Figure 2). Six of the 8 children with ONH and pituitary deficiency had a venous tortuosity index above the 95th percentile of the reference group, as compared with none of the 9 children with ONH without pituitary deficiency.

Both groups of children with ONH demonstrated a significantly smaller optic disc area, cup area, and neuroretinal rim area, increased tortuosity of the veins, and fewer vascular branching points than the reference group (Table 2, Figure 2, and Figure 3). The retinal arteries were narrow in all 8 children who had ONH and endocrinopathy and in 5 of 9 in the ONH group without endocrinopathy, as judged from ophthalmoscopy and fundus photographs.
PATIENTS AND METHODS

From May 15, 1995, through December 15, 1997, 17 children with ONH, 8 girls and 9 boys aged 0.3 to 13 years (median gestational age, 39 weeks; range, 26-43 weeks) were referred to the Department of Pediatric Ophthalmology, Children’s Hospital, Göteborg, Sweden. In addition, they underwent endocrinological and neuroimaging examination. Eight of the children had ONH with pituitary hormone deficiency, and 9 children had ONH without pituitary hormone deficiency. The age, sex, brain anomalies, and hormonal deficiencies of the 17 children are shown in Table 1.

The study was approved by the Committee for Ethics at the Medical Faculty, Göteborg University. Informed consent was obtained from the parents.

OPHTHALMOLOGIC EXAMINATION AND DIGITAL IMAGE ANALYSIS

All children underwent an eye examination, including assessment of visual acuity, cycloplegic refraction, motility, ophthalmoscopy, and fundus photography (Table 1). The diagnosis of ONH was based on impaired visual function and/or morphological signs indicating a subnormal number of optic nerve axons, such as pallor of the optic disc, small size of the optic disc, small neuroretinal rim area, and an abnormal retinal vascular pattern.

All ocular fundus photographs were taken with the patient under general anesthesia, before the magnetic resonance (MR) imaging examination, with a fundus camera (Nikon Retinopan 45II; Carl Zeiss, Inc, Thornwood, NY) and analyzed quantitatively by means of a specifically designed computer-assisted digital mapping system.6

The optic disc area was measured by marking the outlines with a cursor. The inner border surrounding the nerve tissue defined the optic disc; care was taken not to include the white peripapillary scleral ring. The cup was defined by contour and its definition was facilitated by the course of the vessels and its pallor. The neuroretinal rim area was obtained by subtraction of the cup area from the disc area. The indexes of tortuosity for arteries and veins were defined as the path length of the vessel divided by the linear distance from the vessel origin to a reference circle 3 mm from the center of the optic disc. Vessels were also marked from their branching point to the reference circle, and the total number of branching points (arteries and veins), ie, retinal vessels, within this area was calculated. To minimize magnification errors, the optic disc and cup areas were corrected for the refraction values.10

MR IMAGING

Brain morphological characteristics were studied by MR imaging in all children. All the MR imaging examinations were performed on a 1.0-T magnet (Signa, General Electric Co, Milwaukee, Wis). The examination was done with the patient sedated or under general anesthesia. Detailed data from this investigation will be presented elsewhere.

HORMONE ANALYSES AND MEASUREMENTS

The children without endocrinopathy (n = 9) had normal length and weight measurements at the time of the ophthalmologic examination, and there were no clinical or morphological (on MR imaging) signs of pituitary hormone deficiency. Six of the children (without periventricular leukomalacia) had normal results of a basic endocrinological workup.

The maximum growth hormone level was estimated in the children with pituitary hormone deficiency (n = 8) before the start of treatment with somatotropin, from values obtained during measurement of spontaneous 24-hour growth hormone secretion11,12 and/or during an arginine insulin tolerance test.11

Replacement therapy of the pituitary hormones is shown in Table 1.

PRENATAL DATA

The mothers of the children were interviewed according to a standardized protocol regarding adverse events during pregnancy, to identify general disease, gynecologic bleeding, infections, alcohol or drug abuse, and other complications of pregnancy. The maternity and delivery files were available in all 17 cases. One mother was a carrier of the gene for adrenocortical hyperplasia, and 1 mother admitted binge drinking of alcohol in week 6 of gestation (after menstruation).

STATISTICAL METHODS

The mean value of the 2 eye measurements was calculated for each fundus variable. The distribution of the measurements of the fundus variables were compared with the fifth and 95th percentiles of reference values.13 The binomial distribution was used to estimate the probability of the observed number of individuals outside the fifth or 95th percentile of the reference interval.14 The Mann-Whitney test was used to compare the median values between the 2 groups.

COMMENT

Among the children with ONH and endocrinopathy, a specific ocular fundus appearance with isolated tortuosity of the retinal veins was noted (Figure 1, left). Tortuosity of the major retinal vessels has been shown in association with ONH.15 However, among the children with ONH and pituitary deficiencies in the present study, isolated tortuosity of the retinal veins was demonstrated, while the retinal arteries were straight and appeared narrow (Figure 1, left). Isolated venous tortuosity has, to our knowledge, not previously been reported in children with ONH. Interestingly, a review of ocular fundus photographs of patients with septo-optic dysplasia published in the literature illustrates similar findings,10-18 although this finding has never been commented on.

Spertus et al19 demonstrated that experimental carotid occlusion caused disruption of the retinal capillary bed pattern and tortuosity of the retinal veins. It can be speculated that the isolated venous tortuosity in our material may be caused by arteriovenous shunting, resulting from reduced oxygen demand and capillary blood flow in an eye with a reduced nerve fiber layer.
In addition to the above-mentioned ocular fundus findings, all children with ONH in the present study demonstrated a markedly reduced optic disc size, small cup and neuroretinal rim area, and few vascular branching points. A small optic disc was expected in the children with ONH, as this diagnosis is usually associated with a small optic disc area and a reduced number of nerve fibers, although a small optic disc is not a prerequisite for the diagnosis.20

It was recently proposed that loss of function of netrin-1 (molecules that guide growing axons21) resulted in failure of the retinal ganglion cell axons to exit the optic disc and thus resulted in ONH.22 It may be speculated that ONH in association with hormone deficiencies is the result of a common prenatal lesion, simultaneously affecting the retinal ganglion cells and the adjacent hypothalamic-pituitary region. Alternatively, the mechanism could be a preexisting midline lesion in the pituitary region (Figure 1, right) that “disturbs” and prevents the outgrowing axons from the retina to travel to the posterior parts of the brain and form appropriate connections in the visual cortex, ie, secondary retrograde degeneration.16,23 The latter hypothesis is supported by Taylor,24 who demonstrated ONH in patients with congenital suprasellar tumors.

Further analysis of the present material demonstrated an association between thin anterior visual pathways and lesions in the hypothalamic-pituitary region.25 This indicates early prenatal damage, since the retinal ganglion cells begin to form at 5 to 6 weeks of gestation (after fertilization)26 and the major development of the pituitary occurs at 8 weeks of gestation (after fertilization). In addition, the midline brain structures, such as the septum pellucidum and the corpus callosum, are formed during the first trimester.27 Another factor supporting early embryological damage in children with ONH and midline brain anomalies is the recent finding of associations between septo-optic dysplasia and mutations in the homeobox gene HESX1/Hesx1.28

It has been shown that alcohol abuse during pregnancy might be associated with ONH and tortuosity of the retinal vessels,29,30 as well as brain lesions such as migration disturbances31 and agenesis of the corpus callosum.32 In the present study, 1 mother admitted binge drinking of alcohol in the sixth week of gestation (after menstruation) and gave birth to a son with septo-optic dysplasia. In

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Visual Acuity</th>
<th>Refraction†</th>
<th>Motility</th>
<th>ONH Abnormal MR Imaging Findings</th>
<th>Pituitary Region</th>
<th>Other</th>
<th>Hormone Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/2.8</td>
<td>LP/LP</td>
<td>+5/+4</td>
<td>Nystagmus</td>
<td>Bil</td>
<td>Small</td>
<td>... ‡</td>
<td>...</td>
</tr>
<tr>
<td>2/F/4.0</td>
<td>NLP</td>
<td>0/0</td>
<td>...</td>
<td>Bil</td>
<td>Small</td>
<td>Absent‡</td>
<td>ASP, temporal cyst</td>
</tr>
<tr>
<td>3/M/4.8</td>
<td>20/50/20/50</td>
<td>−3/−3</td>
<td>Nystagmus</td>
<td>Bil</td>
<td>Small</td>
<td>Small</td>
<td>ASP</td>
</tr>
<tr>
<td>4/M/5.2</td>
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<td>Bil</td>
<td>Small</td>
<td>Absent‡</td>
<td>ASP</td>
</tr>
<tr>
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<td>NLP</td>
<td>0/0</td>
<td>...</td>
<td>Bil</td>
<td>Small</td>
<td>Absent‡</td>
<td>ASP</td>
</tr>
<tr>
<td>6/M/7.1</td>
<td>20/50/NLP</td>
<td>0/0</td>
<td>Exotropia</td>
<td>Uni</td>
<td>Small</td>
<td>Absent‡</td>
<td>ASP</td>
</tr>
<tr>
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<td>0/0</td>
<td>...</td>
<td>Bil</td>
<td>Small</td>
<td>Ectopic</td>
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</tr>
<tr>
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<td>20/50/NLP</td>
<td>0/0</td>
<td>Nystagmus, esotropia</td>
<td>Bil</td>
<td>Small</td>
<td>Ectopic</td>
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</tr>
<tr>
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<td>Nystagmus, esotropia</td>
<td>Bil</td>
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<td>...</td>
<td>ASP</td>
</tr>
<tr>
<td>10/F/0.9</td>
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<td>+1/+1</td>
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<td>Bil</td>
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<td>...</td>
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<td>...</td>
<td>PVL</td>
</tr>
<tr>
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<td>+2/+2</td>
<td>Nystagmus, esotropia</td>
<td>Bil</td>
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<td>...</td>
<td>PVL, delayed myelinization</td>
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<tr>
<td>13/M/3.8</td>
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<td>−2/−2</td>
<td>Nystagmus</td>
<td>Bil</td>
<td>...</td>
<td>...</td>
<td>ASP</td>
</tr>
<tr>
<td>14/F/6.0</td>
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<td>+3/+3</td>
<td>Nystagmus</td>
<td>Bil</td>
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<td>...</td>
<td>PVL</td>
</tr>
<tr>
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<td>...</td>
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<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>16/F/10.0</td>
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<td>−18/−19</td>
<td>...</td>
<td>Bil</td>
<td>...</td>
<td>...</td>
<td>Wide ventricles, gliosis, pachygyria</td>
</tr>
<tr>
<td>17/F/13.0</td>
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<td>+4/+3.5</td>
<td>Nystagmus</td>
<td>Bil</td>
<td>...</td>
<td>...</td>
<td>ASP</td>
</tr>
</tbody>
</table>

*ONH indicates optic nerve hypoplasia; MR, magnetic resonance; LP, light perception; NLP, no light perception; Bil, bilateral; Uni, unilateral; ASP, agenesis of septum pellucidum; and PVL, periventricular leukomalacia. Visual acuity and refraction values are given as right eye/left eye.
†Spherical equivalent.
‡Not present.
§No identified bright spot.
addition to prenatal alcohol exposure, increased tortuosity of the retinal veins in combination with tortuosity of the retinal arteries has been described in children born preterm. However, all children with ONH and pituitary deficiency in the present study had a gestational age of more than 34 weeks.

Figure 1. Left, Fundus photograph of the left eye of a 5-year-old boy with septo-optic dysplasia (patient 4, Table 1), demonstrating optic nerve hypoplasia with increased tortuosity of the retinal veins and few vascular branching points. Right, T1-weighted coronal noncontrast magnetic resonance image. The chiasm is very thin (small white arrow). The pituitary stalk is thin (open arrow), and there was no sign of any bright spot corresponding to a neurohypophysis in the sella or in an ectopic location. No septum pellucidum is seen (large white arrow).

Figure 2. Individual values of index of tortuosity for arteries and veins and number of branching points in children with optic nerve hypoplasia (ONH) with and without pituitary deficiency. The shaded area depicts the fifth to the 95th percentile range, and the center line indicates the median for the healthy reference group.

Table 2. Ocular Fundus Variables in Children With ONH With and Without Pituitary Deficiency* 

<table>
<thead>
<tr>
<th>Ocular Fundus Variable</th>
<th>Children With ONH and Pituitary Deficiency (n = 8)</th>
<th>Children With ONH Without Pituitary Deficiency (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optic disc area, mm²</td>
<td>Median (2.67†) (range) 1.34 (0.70-2.30)‡</td>
<td>1.42 (0.79-2.21)‡</td>
</tr>
<tr>
<td></td>
<td>No. (%) below 5th percentile 7 (87)</td>
<td>7 (78)</td>
</tr>
<tr>
<td>Cup area, mm²</td>
<td>Median (0.41†) (range) 0 (0-0.25)</td>
<td>0 (0-1.04)</td>
</tr>
<tr>
<td></td>
<td>No. (%) where cup = 0§ 6 (75)</td>
<td>6 (67)</td>
</tr>
<tr>
<td>Index of tortuosity of arteries</td>
<td>Median (1.10†) (range) 1.08 (1.05-1.11)‡</td>
<td>1.08 (1.05-1.14)‡</td>
</tr>
<tr>
<td>Index of tortuosity of veins</td>
<td>Median (1.07†) (range) 1.15 (1.06-1.21)‡</td>
<td>1.08 (1.02-1.12)‡</td>
</tr>
<tr>
<td></td>
<td>No. (%) above 95th percentile 6 (75)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>No. of branching points</td>
<td>Median (23†) (range) 13 (9-18)‡</td>
<td>13 (8-15)‡</td>
</tr>
<tr>
<td></td>
<td>No. (%) below 5th percentile 7 (87)</td>
<td>9 (100)</td>
</tr>
</tbody>
</table>

*ONH indicates optic nerve hypoplasia.
†Reference group medians.
‡P < .001 (significant high proportion of observations outside the 90th reference interval [Figures 2 and 3]).
§In the reference group, 12% had cup = 0.

**Table:**

- **A**: Ocular Fundus Variables in Children With ONH With and Without Pituitary Deficiency.
- **B**: Graphs showing the variability of index of tortuosity for arteries and veins and number of branching points between children with ONH with and without pituitary deficiency.
- **C**: Variables and their respective medians, with significance noted for some comparisons.
than 35 weeks. Hence, prenatal alcohol exposure or preterm birth could not explain the isolated tortuosity of the retinal veins seen in the present study.

The low number of retinal vessels reflected in the low number of vascular branching points might be explained by the reduced number of retinal ganglion cells, since the neuroectoderm controls vascular development.34

**CONCLUSIONS**

Isolated tortuosity of the retinal veins in children with ONH and endocrinopathy may potentially help the ophthalmologist in early identification of the children who should undergo a thorough diagnostic workup of endocrine functions to prevent unnecessary life-long sequelae and even sudden death.8

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**REFERENCES**

23. Hoyt CS, Good WV. Do we really understand the difference between optic nerve hypoplasia and atrophy? Eye. 1992;6:201-204.