Concentric Macular Rings Sign in Patients With Foveal Hypoplasia

Kurt Spiteri Cornish, FRCOphth; Aravind R. Reddy, FRCOphth; Vikki A. McBain, PhD

**IMPORTANCE** We describe a sign that can be used as a rapid and noninvasive adjunct to aid in the diagnosis of foveal hypoplasia.

**OBJECTIVE** To describe a concentric macular rings sign found on infrared reflectance (IRR) images in patients with foveal hypoplasia.

**DESIGN, SETTING, AND PATIENTS** We studied 13 patients with foveal hypoplasia (7 with ocular albinism [OA], 5 with oculocutaneous albinism [OCA], and 1 with aniridia) at a tertiary ophthalmology center with access to electrodiagnostic services from February 18, 2009, through April 9, 2013.

**MAIN OUTCOMES AND MEASURES** All patients and an age-matched control participant underwent a complete clinical examination, electroretinography (full field and pattern), visual evoked potentials, fundus autofluorescence IRR, and optical coherence tomography (OCT). One patient with OA and the control participant also underwent scanning laser polarimetry with variable corneal compensation (GDx VCC).

**RESULTS** Thirteen patients (6 girls and 7 boys), with a mean age of 5.8 years (range, 3-11 years), were included in the study. Seven patients were diagnosed as having OA and had minimal clinical signs (fine nystagmus in 2 patients and subtle iris transillumination in 5 patients). Five patients with OCA and 1 with aniridia were also included. In 12 patients, OA and OCA were confirmed with 5-channel visual evoked potentials (optic nerve misrouting). Whenever OCT was performed, foveal hypoplasia was indicated by the lack of foveal dip. The macula lacked the foveal attenuation normally seen with fundus autofluorescence, and a concentric macular rings reflex was seen with IRR in all 13 patients and with GDx VCC in 1 patient. A normal bowtie reflex was seen with IRR and GDx VCC in the age-matched control participant.

**CONCLUSIONS AND RELEVANCE** Our findings suggest that concentric macular rings seen on IRR or GDx VCC can occur in patients with foveal hypoplasia and can therefore aid in the diagnosis, especially in patients with minimal clinical signs (mild OA) or in cases in which OCT cannot be performed (young patients or patients with high-amplitude nystagmus).
Foveal hypoplasia is a condition that is commonly associated with diseases, such as aniridia and albinism. Isolated cases have also been documented. The condition has been studied with optical coherence tomography (OCT), fundus fluorescein angiography, and fundus autofluorescence (FAF). Scanning laser polarimetry can also be used to determine foveal position, but to our knowledge, the appearance of foveal hypoplasia with infrared reflectance (IRR) has never been documented. We present a unique case series of 7 patients in whom a concentric macular rings (CMR) sign was observed on IRR and who subsequently had foveal hypoplasia associated with ocular albinism (OA). We also report the occurrence of this macular reflex in 6 patients with known foveal hypoplasia (5 with oculocutaneous albinism [OCA] and 1 with aniridia). We conclude that this reflex can be used as a rapid and useful adjunct for the diagnosis of foveal hypoplasia.

Methods

This study followed the tenets of the Declaration of Helsinki, and written informed consent was obtained from all patients. The North of Scotland Research Ethics Service concluded that institutional review board approval was not required for this research. All investigations were performed as part of routine clinical care from February 18, 2009, through April 9, 2013, and included visual acuity (VA) assessment, electrophysiologic testing, and imaging. Distance VA was measured using logarithm of the minimum angle of resolution or Snellen charts. The IRR and FAF images were taken with the Heidelberg retina angiograph 2 (HRA2; Heidelberg Engineering). The HRA2 confocal scanning laser ophthalmoscope uses an 830-nm diode laser for IRR and a 488-nm laser for FAF. The OCT images were taken using the Spectralis (Heidelberg Engineering) and scanning laser polarimetry with variable corneal compensation (GDx VCC; Zeiss). Refractive error and presence of iris transillumination and nystagmus were also determined for each patient. Visual evoked potentials (VEPs), 5-channel VEP pattern electroretinography, and full-field electroretinography were conducted according to international standards of clinical electrophysiology in vision where possible.

Results

An 8-year-old girl with slightly reduced VA (Snellen 20/35) and absent foveal reflex on fundal examination was referred by her optometrist. Her VA did not improve despite hypermetropic correction, and she did not have nystagmus or iris transillumination. Standard electrodiagnostic test results were all within normal limits; however, the OCT revealed complete absence of foveal dip in both eyes (Figure 1A and B), and the CMR sign was seen bilaterally on IRR (Figure 1D and E). This reflex had not been observed previously and is not seen in an 8-year-old patient with normal eye examination findings (Figure 1F). In addition, FAF revealed loss of the normal typical attenuation at the fovea (Figure 1G-I). Subsequent 5-channel VEPs revealed contralateral predominance, confirming optic nerve misrouting. GDx VCC imaging of the retinal nerve fiber layer (RNFL) revealed the same CMR sign as seen on IRR (Figure 1J and K), where a bowtie reflex is normally seen (Figure 1L).

Another 6 patients (3 boys and 3 girls), with a median age of 5.5 years (range, 4-8 years), were examined and subsequently diagnosed as having OA. They all presented with reduced VA and mild or no nystagmus and/or iris transillumination (Table). In all cases, the standard electrophysiologic test results were within normal limits, but 5-channel VEPs revealed optic nerve misrouting. In all patients, foveal hypoplasia was seen on OCT and the CMR sign seen on IRR images taken with the HRA2 (Figure 2A-F). Five patients with a confirmed diagnosis of OCA had foveal hypoplasia on OCT and the CMR sign on IRR images taken with the HRA2 (Figure 2G-I; poor-quality OCT in 2 patients). Furthermore, a 2½-year-old patient with confirmed aniridia had a similar CMR sign on IRR images taken with the HRA2 (data not shown).

The CMR sign was seen on IRR images taken with the HRA2 but not on the IRR images taken with the Spectralis. The focal plane of the lenses used to acquire the images varied between the 2 instruments, where a mean lens diopter (D) power of +7.52 D was used on the HRA2 compared with +4.75 D on the Spectralis.

Preliminary Pearson correlation coefficient analysis revealed a positive correlation between VA and the grade of foveal hypoplasia ($r = 0.627$); however, the number of patients in the sample was not high enough to prove statistical significance ($P = .09$). No correlation was found between VA and central retinal thickness ($r = -0.085, P = .85$) or largest ring diameter on IRR ($r = 0.169, P = .69$).

Discussion

In this study, a previously unreported sign was observed on IRR imaging in 7 patients with unexplained VA reduction (Figure 1D and E and Figure 2A-F). It was subsequently found to correspond with foveal hypoplasia in OA, OCA, and aniridia. This sign, to our knowledge, has been seen in only patients with foveal hypoplasia and has not been observed in other macular diseases.

Foveal hypoplasia is a disease in which a foveal pit is absent or reduced. It can occur as an isolated finding or associated with other diseases, such as OA, OCA, or aniridia. Michaeides et al reported a continuum of foveal maturity and cone specialization in cases of OA and OCA. Consequently, milder forms of the disease can also manifest themselves with less obvious clinical signs, such as seen in the patients in our case series, some of whom had only subtle or even absent iris transillumination defects. Our finding with IRR can be particularly useful in the diagnosis of these patients. Foveal hypoplasia has been graded into 4 groups based on structure, and although there was an association between VA with the different OCT-based grades of foveal hypoplasia in our study,
A and B, Optical coherence tomogram shows foveal hypoplasia with complete absence of a foveal dip (arrows) in the right and left eyes, respectively. C, Optical coherence tomogram from an age-matched control participant highlights the foveal dip. D and E, Infrared reflectance image shows the concentric macular rings sign (dashed circles) described in this study in the right and left eyes, respectively. F, Infrared reflectance image in an age-matched control participant shows the bowtie reflex (dashed bowtie pattern). G and H, Fundus autofluorescence image shows loss of normal central attenuation at the fovea in the right and left eyes, respectively. I, Fundus autofluorescence image in an age-matched control participant shows the central attenuated signal due to increased macular pigment. J and K, Scanning laser polarimetry with variable corneal compensation image shows the concentric macular rings sign in the right and left eyes, respectively. L, Scanning laser polarimetry with variable corneal compensation image in an age-matched control participant shows the bowtie reflex.

Table. Demographics of the Study Patients*

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Diagnosis</th>
<th>RVA</th>
<th>LVA</th>
<th>Refraction Right Eye</th>
<th>Refraction Left Eye</th>
<th>Iris Transillumination</th>
<th>Nystagmus</th>
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<tr>
<td>1/F/8</td>
<td>OA</td>
<td>20/35</td>
<td>20/35</td>
<td>3.50</td>
<td>3.50</td>
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<td>No</td>
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<tr>
<td>2/F/4</td>
<td>OA</td>
<td>20/80</td>
<td>20/40</td>
<td>−1.25</td>
<td>0.25</td>
<td>Subtle</td>
<td>Fine rotary</td>
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<tr>
<td>3/M/5</td>
<td>OA</td>
<td>20/45</td>
<td>20/65</td>
<td>2.50</td>
<td>3.25</td>
<td>Subtle</td>
<td>Latent</td>
</tr>
<tr>
<td>4/M/4</td>
<td>OA</td>
<td>20/50</td>
<td>20/40</td>
<td>3.50</td>
<td>3.25</td>
<td>Subtle</td>
<td>No</td>
</tr>
<tr>
<td>5/M/7</td>
<td>OA</td>
<td>20/90</td>
<td>20/100</td>
<td>2.25</td>
<td>2.00</td>
<td>Subtle</td>
<td>No</td>
</tr>
<tr>
<td>6/F/6</td>
<td>OA</td>
<td>20/140</td>
<td>20/63</td>
<td>14.00</td>
<td>14.00</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>7/F/8</td>
<td>OA</td>
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<td>20/125</td>
<td>2.50</td>
<td>3.50</td>
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<td>8/F/5</td>
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<td>20/100</td>
<td>20/100</td>
<td>3.00</td>
<td>4.50</td>
<td>Mild</td>
<td>Yes</td>
</tr>
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<td>9/M/4</td>
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<td>20/90</td>
<td>20/83</td>
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<td>10/M/3</td>
<td>OCA</td>
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<td>20/38</td>
<td>−0.25</td>
<td>0.00</td>
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<td>11/F/11</td>
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<td>20/80</td>
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<td>2.00</td>
<td>Marked</td>
<td>Horizontal pendular</td>
</tr>
<tr>
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<td>OCA</td>
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<td>Marked</td>
<td>Mild</td>
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<td>13/M/3</td>
<td>Aniridia</td>
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<td>20/100</td>
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<td>5.00</td>
<td>Marked</td>
<td>Horizontal pendular</td>
</tr>
</tbody>
</table>

Abbreviations: LVA, left visual acuity; NA, not applicable; OA, ocular albinism; OCA, oculocutaneous albinism; RVA, right visual acuity.

* The LVA and RVA values are in Snellen equivalents.
the number of patients was too small to find a statistically significant correlation.

In the normal fovea, the cylindrically shaped axons of the photoreceptors are oriented radially in a symmetric pattern that forms the outer plexiform layer or Henle layer of the retina. The Henle layer exhibits form birefringence, the characteristic that is responsible for producing the bowtie or macular cross on GDx VCC and IRR images (Figure 1L and F). Birefringence in the eye is also exhibited by the RNFL and cornea but is dependent on thickness, so the bowtie reflex is believed to be formed by the Henle layer centrally with increasing influence of the RNFL more eccentrically and is dependent on the normal foveal architecture. This theory would explain the presence of the macular cross pattern in normal eyes on IRR and GDx VCC images.

In eyes with OA, Chong et al suggest that the normal centripetal displacement of inner retinal elements radiating from the foveola is absent. Therefore, the lack of a bowtie reflex seen in our patients could be explained by the lack of inner retinal displacement. There are various theories for the lack of cen-
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...triptetal inner retinal displacement in foveal hypoplasia, including the lack of a normal foveal avascular zone, which is believed to determine the extent of centrifugal migration of inner retinal layers. The absence of the foveal avascular zone has been described in isolated foveal hypoplasia.13,14

The underlying cause of the CMR sign is not yet fully understood. It is believed that a concentric regular ring of phase retardation is caused by the radially symmetric orientation of the axons (Henle layer) and RNFL around the fovea because these layers form a continuous regular layer in cases of foveal hypoplasia. This theory would explain why the CMR is present (and identical) on IRR and GDx VCC images. Corneal birefringence is completely compensated by the GDx VCC. The presence of our described sign on this instrument excludes any influence of the cornea in the formation of the concentric pattern.

The CMR was not seen on the IRR image taken with the Spectralis but was seen on the IRR image taken with the HRA2, despite using similar optic and incident light wavelengths of 830 nm. Only the degree at which the focal length varies when operating the HRA2 vs the Spectralis differs principally because the IRR is required for the former to obtain sharply focused FAF images.

Conclusions

The CMR sign appears to be a consistent finding in patients with foveal hypoplasia. On the basis of our case series, IRR (but not using the Spectralis) presents a rapid and useful imaging modality for the investigation of suspected foveal hypoplasia and albinism. Further studies are required to explain the pathophysiologic mechanism underlying this sign and to understand how it correlates with varying degrees of foveal hypoplasia and clinical phenotype.

REFERENCES