Brief Report

Structural Abnormalities of the Inner Macula in Incontinentia Pigmenti

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IMPORTANCE This report presents evidence from spectral-domain optical coherence tomography and fluorescein angiography of inner foveal structural abnormalities associated with vision loss in incontinentia pigmenti (IP).

OBSERVATIONS Two children had reduced visual behavior in association with abnormalities of the inner foveal layers on spectral-domain optical coherence tomography. Fluorescein angiography showed filling defects in retinal and choroidal circulations and irregularities of the foveal avascular zones. The foveal to parafoveal ratios were greater than 0.57 in 6 eyes of 3 patients who had extraretinal neovascularization and/or peripheral avascular retina on fluorescein angiography and were treated with laser. Of these, 3 eyes of 2 patients had irregularities in foveal avascular zones and poor vision.

CONCLUSIONS AND RELEVANCE Besides traction retinal detachment, vision loss in IP can occur with abnormalities of the inner foveal structure seen on spectral-domain optical coherence tomography, consistent with prior descriptions of foveal hypoplasia. The evolution of abnormalities in the neural and vascular retina suggests a vascular cause of the foveal structural changes. More study is needed to determine any potential benefit of the foveal to parafoveal ratio in children with IP. Even with marked foveal structural abnormalities, vision can be preserved in some patients with IP with vigilant surveillance in the early years of life.

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Incontinentia pigmenti (IP), or Bloch-Sulzberger syndrome, is a rare X-linked dominant disorder mainly seen in females because a single allele in male embryos is usually fatal.[1,2] Incontinentia pigmenti usually presents with a characteristic skin rash that leaves hypopigmented patches on the trunk and limbs.[3] The most serious events involve the retina and central nervous system (CNS) in 18% to 30%.[2-5] Loss-of-function mutations in *IKBKG/NEMO* impair nuclear factor-kappa B (NF-κB) signaling and are responsible for most cases of IP.[6,7] Although NF-κB signaling is ubiquitous, effects from the *IKBKG/NEMO* mutation do not manifest in all tissues.

Vision loss has been associated with vascular occlusions, secondary extraretinal neovascularization (NV), tractional retinal detachments,[2,5,8] and foveal hypoplasia.[8] Herein, we report findings from spectral-domain optical coherence tomography (SD-OCT) in children with IP examined before age 5 years. Poor visual behavior corresponded with inner retinal structural abnormalities.

Methods

Institutional review board approval was obtained from the University of Utah. Owing to the retrospective nature of the study, the human study committee deemed it exempt from the requirement for informed consent. All children had biopsy-proven IP and were seen by the pediatric ophthalmology and retina services between May 2010 and August 2014.

Data from clinical visits and examinations under anesthesia (EUAs) included images from wide-angle fluorescein angiography (FA; RetCam; Clarity Inc) and macular SD-OCT (Bioptigen Inc) (**Table**). Retinal thickness measurements were taken at the fovea from the inner limiting membrane to the retinal pigment epithelium, the parafoveal retina 1000 µm from the nasal and temporal fovea as visualized on SD-OCT slices, and the choroid under the fovea (**Figure 1**B and **Figure 2**B) using the caliper measurement tool provided with the Bioptigen software. The foveal location was estimated as 0.5 disc diameter inferior to the center of the optic nerve and 2 disc diameters temporal to it. We measured retinal thickness as reported by Vajzovic et al[9] and included the inner limiting membrane to the inner aspect of the retinal pigment epithelium. The nasal and temporal parafoveal measurements were averaged and divided by the central foveal thickness to create a ratio.[9] The FAs were reviewed and analyzed qualitatively for vascular filling defects during transit phases and leakage from extraretinal NV in late phases.

PubMed searches were done without limitations on date using the terms *incontinentia pigmenti*, *eye*, *ocular*, *optical*, *optical coherence tomography*, and *fovea* to ascertain current literature on SD-OCT methods, IP, and foveal development.

Results

Patients were girls examined by age 5 years (Table). Two had poor visual development, inner foveal structural abnormalities, and retinal thinning that increased through 2 years of follow-up. Both had magnetic resonance imaging (MRI) abnormalities consistent with IP and extraretinal NV requiring laser treatment. In these 2 patients and in patient 3 with extraretinal NV, foveal to parafoveal ratios on SD-OCT were greater than 0.57.[9]

Patient 2

A girl diagnosed as having IP by skin biopsy at age 2 months underwent EUA at age 2.5 months. The FA transit in the right eye showed patchy choroidal filling defects, delayed filling of retinal veins, and irregularities in the foveal avascular zone (FAZ). There was avascular peripheral retina but no extraretinal NV. One month later, extraretinal NV developed in the right eye and the peripheral avascular retina was treated with laser. Spectral-domain optical coherence tomography of the right eye showed irregularity of the contour of the nasal right fovea with thinning of the inner retinal layers and a normal-appearing outer retina and inner segment-outer segment line. Findings on SD-OCT of the left eye were normal (Figure 1). On subsequent EUAs between ages 6 and 27 months (Table), laser treatment was performed for extraretinal NV in the left eye, and SD-OCT of the right eye showed thinning of the temporal retinal layers, irregularity of the foveal contour, and loss of definition of the inner retinal layers throughout the fovea. The foveal to parafoveal ratio was increased (Table).[9] The findings on SD-OCT, foveal to parafoveal ratio, and FAZ were normal in the left eye. At age 23 months, the child was treated with patching for intermittent exotropia and a fixation preference of the left eye. Brain MRI and magnetic resonance angiography at age 6 months showed a reduced corpus callosum volume and patchy white matter lesions.

Patient 4

A girl was diagnosed as having IP on day 4 of life. Clinical examination findings at 2 weeks of life were normal, but foveal reflexes were reduced and brain MRI showed an immature myelin pattern at age 4.5 months. Ensuing visits with the pediatric ophthalmology service were made for poor visual development, worse in the left eye than in the right eye, and the patient was treated with patching therapy. At age 21 months, EUA with FA revealed peripheral avascular retina in each eye with extraretinal NV in the left eye, managed with laser treatment. Follow-up EUAs with SD-OCT and FA at ages 27 and 29 months showed disorganized inner retinal layers in each eye, irregularities of both FAZs (Figure 2), and extraretinal NV in the right eye that was treated with laser. At age 5 years, visual acuity was 20/60 OD and 20/100 OS. The foveal reflex was reduced in the right eye and nearly absent in the left eye, and SD-OCT showed loss of the foveal depression with irregularities and thinning of the inner nuclear, inner plexiform, and nerve fiber and ganglion cell layers in both eyes. Outer retinas and inner segment-outer segment lines appeared normal. Foveal to parafoveal ratios were elevated (Table).

At a Glance

- Foveal hypoplasia occurs with inner foveal abnormalities seen on spectral-domain optical coherence tomography.
- Foveal abnormalities include inner foveal thinning that progresses, disorganized inner retinal layers, and increased foveal to parafoveal ratios.
- Vascular filling defects and foveal structural abnormalities do not necessarily respect the horizontal raphe in incontinentia pigmenti.
- Foveal disorganization on spectral-domain optical coherence tomography is associated with reduced vision but not necessarily with peripheral avascular retina and peripheral extraretinal neovascularization.
- More study is warranted to determine possible associations between the foveal to parafoveal ratios and any retinal abnormalities in incontinentia pigmenti.

Discussion

To our knowledge, we present the first SD-OCT findings of children with IP, highlighting 2 with abnormal inner foveal structure, abnormal FAZ, and decreased vision. The 3 infants with extraretinal NV did not all have foveal layer disorganization, but all had increased foveal to parafoveal ratios (>0.57)[9] in at least 1 eye.

Prior to wide-angle FA and handheld SD-OCT, vision loss in IP was associated with vitreous hemorrhage, tractional retinal detachment, and retinal ischemia from vascular occlusions. Foveal hypoplasia was reported on fundus photographs and FA as lack of a foveolar pit, pigmentary changes, and abnormal FAZ.[3] The genetic mutation in IP involves the gene expressing NF-κB. The NF-κB signaling pathway affects all cells, but our patients had inner retinal layer disorganization and thinning reflected in increased foveal to parafoveal ratios and did not manifest outer retinal abnormalities. These findings suggest that the genetic defect leading to abnormal NF-κB signaling manifested in vascular events with secondary neural structural changes. Loss of vascular support in vein occlusions can lead to thinning of the parafoveal retina,[10] but the structural changes in our patients did not respect the horizontal raphe, suggesting a broader effect than in an occlusion of a branch retinal arteriole or vein.

The most serious manifestation of IP involves the CNS. Patients 2 and 4 both had abnormal MRI findings that are reported in IP.[11] The cause of the CNS anomalies in patients with IP is unknown but believed to be from vaso-occlusive events.[12,13] Lee et al[11] and Goldberg[14] emphasized that CNS imaging can be lifesaving in patients with IP and retinal manifestations because stroke-like events can occur.

Table. Clinical History and Findings on SD-OCT and FA

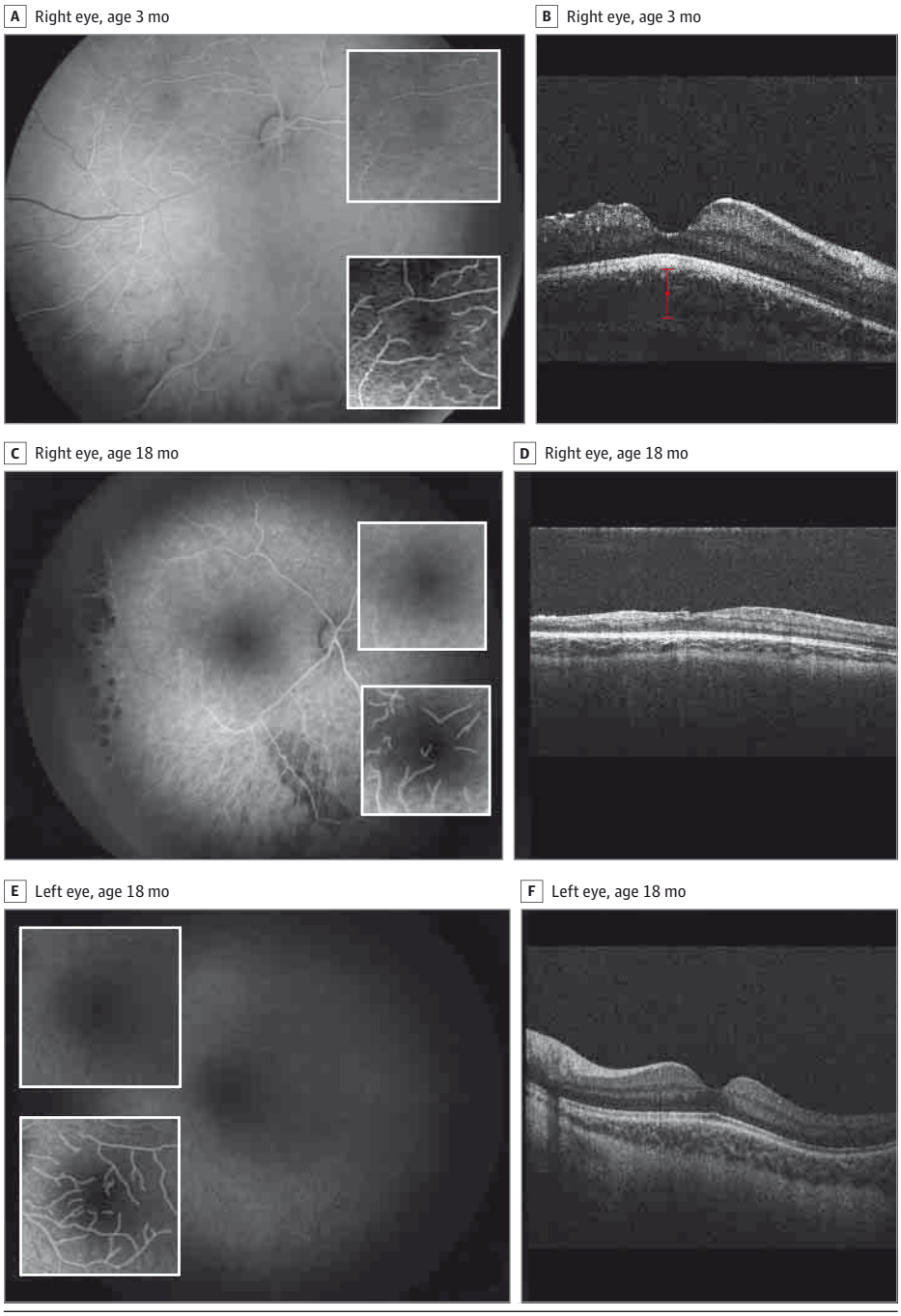
Variable	Patient No. 1	2	3	4	5
MRI	…	Thin corpus callosum and patchy subcortical and periventricular white matter disease	No MRI, normal neurologic examination	Immature myelination consistent with age, otherwise normal	…
IKBKG/NEMO mutation	Positive[a]	…	…	…	…
BCVA					
Age at testing	13 mo	2 y	21 mo	5 y	12 mo
OD	Fix and follow	Unmaintained fixation	Fix and follow	20/60	Fix and follow
OS	Fix and follow	Fix and follow	Fix and follow	20/100	Fix and follow
Strabismus and amblyopia	Not noted	Present	Not noted	Present with nystagmus	Not noted
Foveal hypoplasia					
OD	None	Present	None	Abnormal	None
OS	None	None	None	Present	None
Extraretinal NV					
OD	None	Present	Appeared as regressed	Present	None
OS	None	Present	Appeared as regressed	Present	None
Vascular abnormalities noted on FA	FAZ normal OU; peripheral retina vascularized OU	Irregular FAZ with vessel entering FAZ OD, normal FAZ OS; peripheral nonperfusion OU; extraretinal NV OU	FAZ normal OU; peripheral nonperfusion OU; extraretinal NV OD	Irregular FAZ OS > OD; peripheral nonperfusion OU; extraretinal NV OU	FAZ normal OU; peripheral retina vascularized OU
Laser treatment	None	OU	OD	OU	None
Follow-up, mo	11	31	17	61	<1
Features on SD-OCT					
Central foveal thickness					
Age at first testing, mo	6	3	25	28	…
OD, μm	128	162	210	656	…
OS, μm	132	125	190	808	…
Age at second testing, mo	15	18	…	54	…
OD, μm	144	228	…	270	…
OS, μm	145	180	…	191	…
Foveal to parafoveal ratio					
Age at first testing, mo	6	3	25	28	…
OD	0.48	0.26	0.65	0.98	…
OS	0.53	0.40	0.60	0.96	…
Age at second testing, mo	15	18	…	54	…
OD	0.51	0.81	…	0.86	…
OS	0.52	0.63	…	1.00	…
Inner segment-outer segment junction	Normal OU	Normal OU	Normal OU	Normal OU	…
Choroidal thickness					
Age at first testing, mo	6	3	25	28	…
OD, μm	361	197	NA[b]	633	…
OS, μm	265	241	NA[b]	607	…
Age at second testing	15	18	…	54	…
OD, μm	441	166	…	317	…
OS, μm	259	233	…	184	…

Abbreviations: BCVA, best-corrected visual acuity; FA, fluorescein angiography; FAZ, foveal avascular zone; MRI, magnetic resonance imaging; NA, not available; NV, neovascularization; OD, right eye; OS, left eye; OU, each eye; SD-OCT, spectral-domain optical coherence tomography; ellipses, not done.

[a] Testing performed at Casey Eye Institute, Oregon Health and Science University, Portland.

[b] Unable to discern the posterior aspect of the choroid to obtain accurate measurement.

Figure 1. Fluorescein Angiographic Images and Spectral-Domain Optical Coherence Tomographic Images of Patient 2

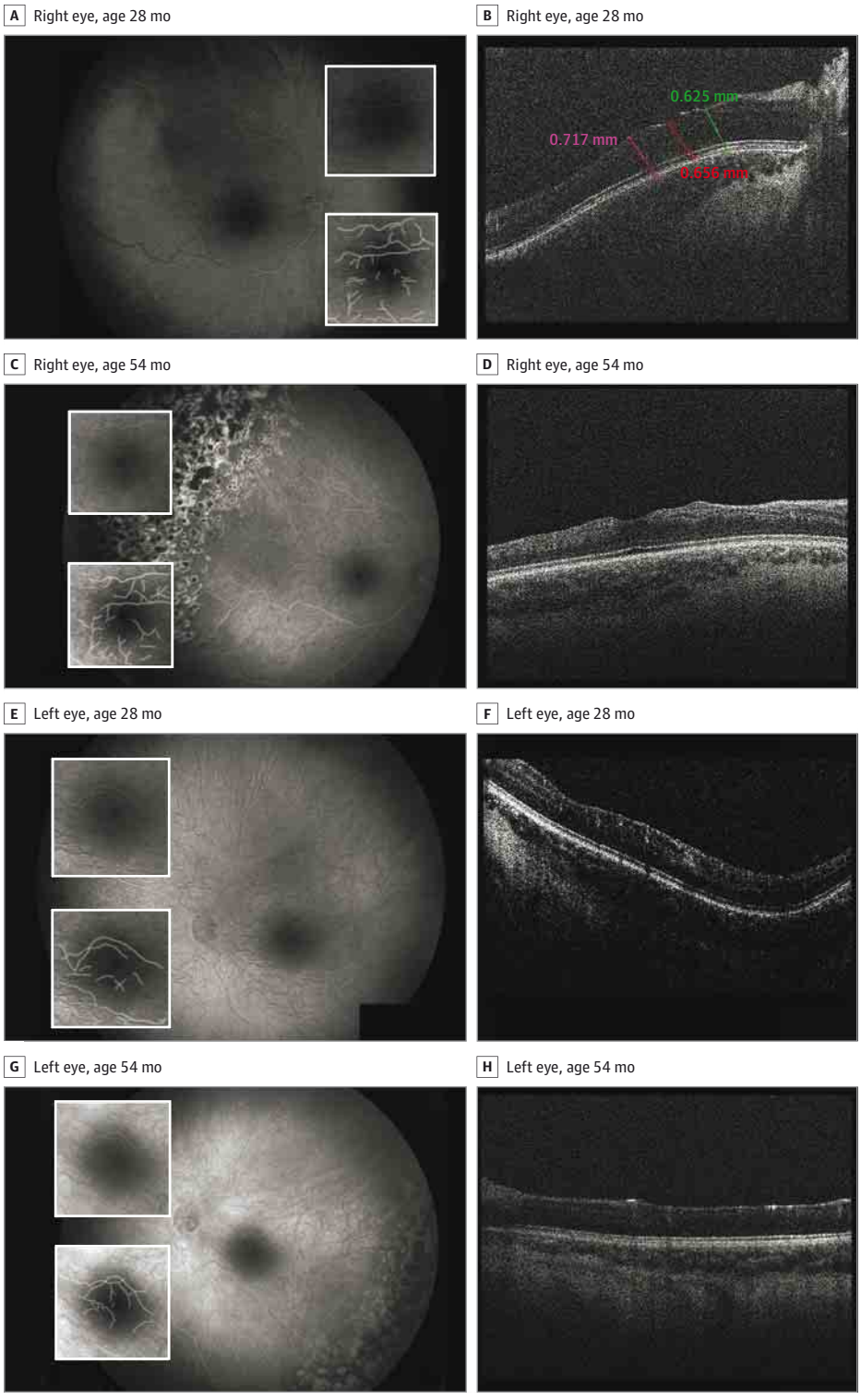


A, Fluorescein angiographic image (main image), foveal avascular zone (top inset), and computer-enhanced foveal avascular zone (bottom inset) of the right eye at age 3 months. B, Spectral-domain optical coherence tomographic image of the right eye at age 3 months. Red line indicates the line of measurement of choroidal thickness at the foveal center. C, Fluorescein angiographic image (main image), foveal avascular zone (top inset), and computer-enhanced foveal avascular zone (bottom inset) of the right eye at age 18 months. D, Spectral-domain optical coherence tomographic image of the right eye at age 18 months. E, Fluorescein angiographic image (main image), foveal avascular zone (top inset), and computer-enhanced foveal avascular zone (bottom inset) of the left eye at age 18 months. F, Spectral-domain optical coherence tomographic image of the left eye at age 18 months.

Conclusions

In summary, we describe inner foveal abnormalities in children with biopsy-proven IP and vision loss. Coordination among ophthalmologists, dermatologists, and pediatric neurologists is important. Also, it is important to use EUA with FA to detect extraretinal NV, laser to treat avascular peripheral retina, SD-OCT to assess the macular structure, and clinical examination to identify and treat strabismus and amblyopia. Extraretinal NV can occur in the absence of foveal structural abnormalities, and more study is warranted regarding the potential importance of the foveal to parafoveal ratio in association with peripheral retinal abnormali-

Figure 2. Fluorescein Angiographic Images and Spectral-Domain Optical Coherence Tomographic Images of Patient 4



A, Fluorescein angiographic image (main image), foveal avascular zone (top inset), and computer-enhanced foveal avascular zone (bottom inset) of the right eye at age 28 months. B, Spectral-domain optical coherence tomographic image of the right eye at age 28 months. The purple and green lines indicate the lines of measurement of the parafoveal regions; red line, the line of measurement of the fovea. C, Fluorescein angiographic image (main image), foveal avascular zone (top inset), and computer-enhanced foveal avascular zone (bottom inset) of the right eye at age 54 months. D, Spectral-domain optical coherence tomographic image of the right eye at age 54 months. E, Fluorescein angiographic image (main image), foveal avascular zone (top inset), and computer-enhanced foveal avascular zone (bottom inset) of the left eye at age 28 months. F, Spectral-domain optical coherence tomographic image of the left eye at age 28 months. G, Fluorescein angiographic image (main image), foveal avascular zone (top inset), and computer-enhanced foveal avascular zone (bottom inset) of the left eye at age 54 months. H, Spectral-domain optical coherence tomographic image of the left eye at age 54 months.

ties. In patients with retinal involvement, monthly examinations for the first 3 to 4 months of life and then every 3 to 4 months are recommended for at least the first year.[15] Neurologic evaluations in all patients with IP and CNS imaging with retinal involvement are recommended.[11] With vigilant follow-up, vision can be preserved in patients with IP.

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Drafting of the manuscript: Basilius, Young, Michaelis, Jenkins, Hartnett.
Critical revision of the manuscript for important intellectual content: Basilius, Young, Michaelis, Hobbs, Hartnett.
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