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Foveal hypoplasia and optical coherence tomographic imaging

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Abstract:

Foveal hypoplasia is a retinal disorder in which there is a lack of full development of the morphology of the fovea. The optical coherence tomography (OCT) and functional findings are presented in relation to the underlying genetic and developmental conditions. Recent advancements of high-resolution OCT imaging have unveiled characteristics of foveal hypoplasia that were not detected by conventional imaging methods. An absence of a foveal pit does not necessarily imply poor visual acuity, and the maturation of the cone photoreceptors is important for the visual acuity. Regardless of the degree of the development of the inner retinal layers, the visual acuity can be preserved as in diseases such as Stickler syndrome that is a newly identified retinal disorder associated with foveal hypoplasia.

Keywords:

Achromatopsia, albinism, aniridia, familial exudative vitreoretinopathy, foveal avascular zone, foveal hypoplasia, incontinentia pigmenti, optic nerve hypoplasia, optical coherent tomography, retinopathy of prematurity, Stickler syndrome

Introduction

In humans and some primates, the central retina has a specialized structure called the foveal pit which is referred to as the fovea centralis. The pit is formed by the migration of the inner retinal neurons peripherally, and the underlying cone photoreceptors elongate and are densely packed. Foveal hypoplasia is a condition in which the foveal pit does not fully develop.[1] It is manifested by a reduction or absence of a foveal pit and a foveal avascular zone (FAZ). Foveal hypoplasia has been associated with poor vision and nystagmus,[1] and various diseases are known to be associated with foveal hypoplasia including albinism and aniridia.[2] However, the mechanism causing the lack of development of the foveal pit has not been definitively determined, and the genetic and nongenetic factors, such as prematurity of birth, can affect the development of the fovea. Foveal hypoplasia has been identified by ophthalmoscopy, fluorescein angiography, and histology before the advent of optical coherence tomography (OCT).[3,4]

Advances of high-resolution spectral-domain OCT and swept-source OCT have allowed ophthalmologists to obtain detailed views of the morphology of the retina and to investigate the morphology of normal and pathological maculas.[5,6] Recently, a new imaging method called OCT angiography (OCTA) has allowed clinicians and researchers to obtain detailed information on the retinal microvasculature in en-face images of different layers of the retina.[7] Owing to the progress of OCT imaging, foveal hypoplasia has been identified as a novel feature that is associated with known retinal diseases.

The aim of this review is to present the characteristics of diseases associated with foveal hypoplasia and to present the OCT images and functional assessments in relation to the underlying genetics or development conditions. The diseases can be characterized by their frequency of foveal hypoplasia, the underlining genetic and

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nongenetic conditions, and the presence or absence of vision impairments [Table 1].

Development of Normal Fovea

Foveal avascular zone

In humans, the normal development of the fovea begins at fetal week 25 and is completed by 15–45 months after birth.[20] The location of the future fovea is determined by fetal week 11.[21] The formation of the pit does not take place until the FAZ is formed.[22,23] Therefore, the morphology of the foveal pit is correlated with the FAZ, i.e. larger FAZs are associated with deeper and broader foveal pits.[24] Dubis *et al*.[24] analyzed the relationship between the FAZ and size of the foveal pit by OCT and other devices, and they reported that the size of the FAZ in normal participants is highly variable with the area ranging from 0.05 to 1.05 mm^2 and the diameter ranging from 0.2 to 1.08 mm.

The macular pigment appears at about 17 weeks of gestational age and is believed to drive the formation of the FAZ.[25] Its spatial distribution is correlated with the size of the FAZ.[26] The fovea is made up of the cone photoreceptors and Müller cells, and the rod photoreceptors are absent from the central fovea.[27] The Müller cells inhibit the migration of astrocytes into the central fovea so that an astrocyte-free zone is formed.[26] The astrocyte-free zone plays an important role in forming the FAZ because astrocytes induce the migration of retinal vessel cells across the retina.[28]

Development of the foveal pit

The development of the foveal pit involves the bidirectional movement of the neurons in the inner and outer retina [Figure 1].[22] The cells of the inner retina are displaced centrifugally to form the foveal pit, and the cone cells are displaced centripetally so that the density of cones in the foveal pit increases.[22]

During the third trimester and after birth, the ganglion cells and cells in the inner nuclear layer continue to be displaced away from the foveal pit and the FAZ.[29] The pit depth is reported to be 137.56 ± 4.3 μm, and the foveal pit diameter is 1.12–2.57 mm according to the analysis using spectral-domain OCT images.[24] Postnatally, the outer retinal layers mature as cone cells migrate centripetally and appear as a multicellular layer.[27] This phenomenon is referred to as cone specialization that includes a thinning of the individual cones and an increase in the density of foveal cones. The inner and outer segments (OSs) elongate, and the axonal processes lengthen and bend to form the "fibers of Henle."[22,29] The lengthening of the OSs and development of the rod-free zones are believed to be associated with good visual acuity. The rod-free zone is >1000 μm in diameter before birth and becomes reduced to 650–700 μm by 45 months of age.[27] At 14 fetal weeks, the cone density at the fovea is <15,000/mm^2 and it reaches 108,000/mm^2 by 4 years of age.[29]

Thomas *et al*.[30] proposed a structural grading system of foveal hypoplasia based on the cross-sectional OCT images: Grade 1, a shallow foveal pit and presence of a thick outer nuclear layer (ONL) and presence of OSs in the foveal pit; Grade 2, absence of foveal pit; Grade 3, absence of OS lengthening; and Grade 4, absence of ONL widening. Grades 1 and 2 represent deficient foveal pit formation with intact cone specialization, while Grades 3 and 4 represent a failure of cone specialization [Figure 2].

Table 1: Diseases associated with foveal hypoplasia

Diseases	Factors (genes; roles)	Type of foveal hypoplasia	Frequency of foveal hypoplasia	Nystagmus and poor vision	Reduced macular pigment
Albinism	Genetic (albinism genes;[8] melanin synthesis)	I + O	Frequent	Common	Found
Aniridia	Genetic (*PAX6*; pan-ocular genesis)	I + O	Frequent	Common	Found
Idiopathic foveal hypoplasia	Genetic (*PAX6, GPR143, SLC38A8*; special forms of albinism or aniridia)	I + O	Frequent	Common	Found
Retinopathy of prematurity	Nongenetic (retinal vascularization)	I + O	Frequent in severe cases	Uncommon for isolated foveal hypoplasia	Not evident
Incontinentia pigmenti	Genetic (*IKBKG*; genesis of ectoderm)	I	Infrequent	Uncommon for isolated foveal hypoplasia	Not evident
Achromatopsia	Genetic (achromatopsia genes;[9] cone genesis)	I + O	50%-80%[10-12]	Common due to cone dysfunction	Found (complicated as hyper-FAF with progressive retinal degeneration
Optic nerve hypoplasia	Genetic (*PAX6, PAX2*, and others;[13] ganglion cell genesis)	I	24%-82%[14,15]	Common due to dysgenesis of retinal ganglion cells	Not evident
Familial exudative vitreoretinopathy	Genetic (Wnt signaling genes:[16] Retinal vascularization)	I	20%[17]	Uncommon for isolated foveal hypoplasia	Not evident
Stickler syndrome	Genetic (procollagen genes[18])	I	82%[19]	Uncommon	Not evident

FAF=Fundus autofluorescence, I=Persistence of the inner retinal layer, O=Failed cone specialization in the outer retinal layer

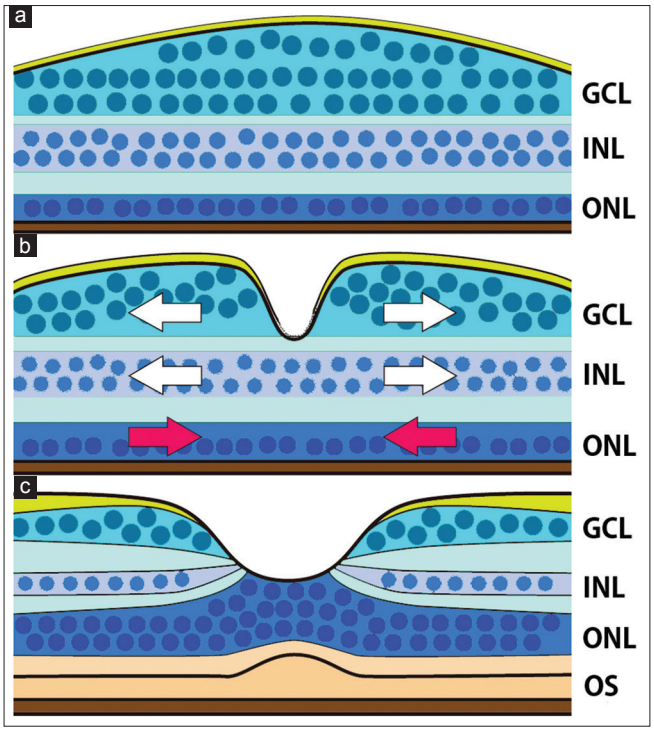

Figure 1: Schematic diagram showing the development of the foveal structure. (a) At the end of the second trimester, a thickened ganglion cell layer is found, however, a foveal pit is not present. The outer nuclear layer is a single-cell layer. (b) A foveal pit forms in the ganglion cell layer and inner nuclear layer. The cells in the ganglion cell layer and inner nuclear layer are displaced centrifugally to form the foveal pit (white arrows), and cone cells in the outer nuclear layer are displace centripetally (red arrows). (c) In the adult retina, the cone cells form a multicellular layer, and the inner and outer segments become prominent. The schema is based on references Springer and Hendrickson[23] and Hendrickson[29]

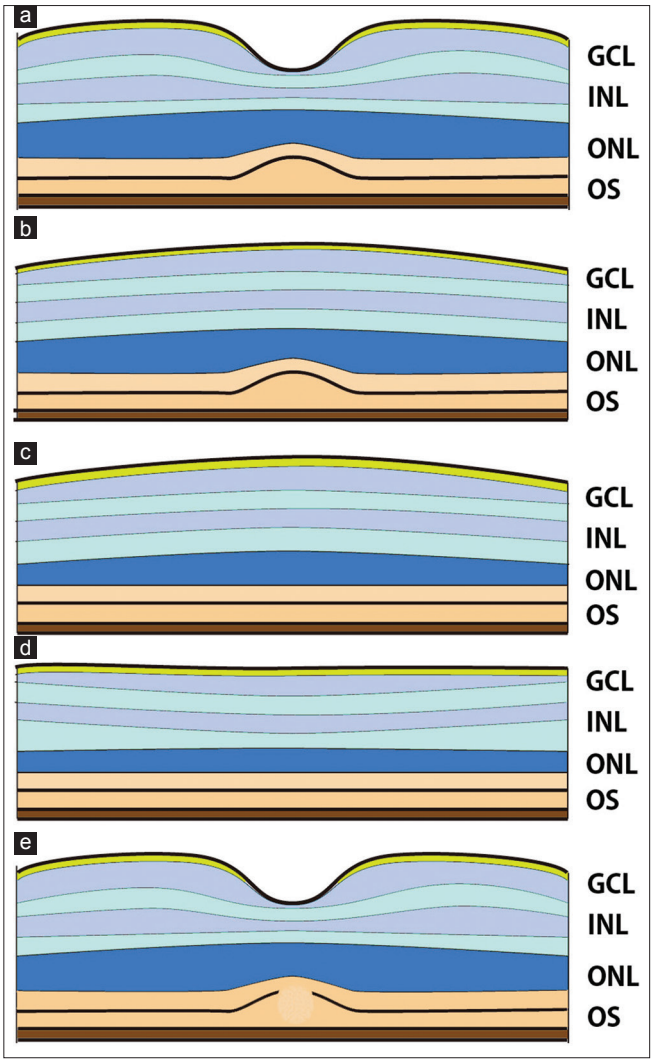

Figure 2: Structural grading system of foveal hypoplasia using cross-sectional optical coherence tomography images after Thomas *et al*.[30] (a) Grade 1, a shallow foveal pit and presence of outer nuclear layer and outer segment in the fovea. (b) Grade 2, absence of foveal pit. (c) Grade 3, absence of outer segments lengthening. (d) Grade 4, absence of outer nuclear layer widening. (e) Atypical form of foveal hypoplasia with disruption of the inner and outer segments of photoreceptor, a sign of photoreceptor degeneration. Grades 1 and 2 represent deficient foveal pit formation without affecting the cone specialization while Grades 3 and 4 represent a failure in the cone specialization

Diseases Known to be Associated with Foveal Hypoplasia Before Optical Coherence Tomography Imaging

Before the advent of OCT imaging, several diseases were known to be associated with foveal hypoplasia. These include albinism, aniridia, isolated foveal hypoplasia, retinopathy of prematurity, and incontinentia pigmenti (see below). In addition, foveal hypoplasia was also reported to be associated with microcornea and familial and presenile cataract; however, the details have not been published.[2]

Albinism

Oculocutaneous albinism (OCA) is a group of autosomal recessive disorders that is characterized by hypopigmentation of eyes, skin, and hair due to an impairment of melanin synthesis.[8] Ocular albinism (OA) is an X-linked recessive disorder that only affects the eyes. Ocular symptoms in OCA and OA include poor visual acuity, nystagmus, strabismus, hypopigmentation of the uvea, and foveal hypoplasia. Optic nerve fibers misrouting is also a characteristic of OCA and OA.[31] Seven types of human OCA, OCA 1–7, have been identified and six genes have been found to be the cause of these OCAs.[8] In addition, there are several syndromic forms of albinism including the Hermansky–Pudlak and Chediak–Higashi syndromes.[8]

Despite the genetic heterogeneity of albinism, patients with albinism are believed to have foveal hypoplasia consistently. The relationship between the visual function and abnormal pit formation in albinism has been investigated by time-domain and spectral-domain OCT images.[32-36] It has been debated whether the degree of foveal pit formation is correlated with the visual acuity.[33-35] Mohammad *et al*.[36] showed that the visual acuity was not correlated with the presence of the inner

retinal layers, and the length of the photoreceptor layer was the best predictor of the visual acuity. This led to a conclusion that the pit formation is not required for cone specialization.[34,35]

It is not known whether the foveal hypoplasia in eyes with OCA and OA is related to the abnormal melanin synthesis.[31] Patients with albinism lack a rod-free zone that is essential for cone specialization.[37,38] Macular pigmentation is also deficient, and the phenomenon is believed to be associated with the poor vision.[39,40]

Aniridia

Aniridia is caused by mutations in the *PAX6* gene.[41] Aside from the characteristic iris dysgenesis, the findings in eyes with aniridia include poor vision and nystagmus. The *PAX6* gene is a transcription factor that encodes a key regulator of ocular and neural development. As seen in eyes with albinism, a lack of macular pigment is also a characteristic in eyes with aniridia.[42]

Patients with aniridia are consistently associated with foveal hypoplasia with the exception of hypomorphic mutations in the *PAX6* gene. Yokoi *et al*.[43] analyzed 28 patients who had mutations in the *PAX6* gene or chromosomal abnormality including the *PAX6* gene region, and all but one case had foveal hypoplasia. Hingorani *et al*.[44] analyzed 43 patients with a *PAX6* mutation and found that 34 of 35 patients with foveal hypoplasia had gene truncation mutations, i.e., nonsense, frameshift, splicing, or C-terminal extension mutations, or gene deletions. However, foveal hypoplasia was not found in 6 of 9 patients who had missense mutations. The visual acuities in the better eye ranged from light perception to 20/80 in the patients with truncation mutations while the visual acuities in the better eyes in the patients with missense mutations ranged from 20/30 to 20/250 with a median of 20/60. Two patients lacked nystagmus.[44] Katagiri *et al*.[45] reported that different OCT images of Henle's fiber layer reflected different grades of foveal maturity with regard to the visual acuity in eyes with aniridia and isolated foveal hypoplasia.

The macular pigment is also deficient in eyes with aniridia and is believed to be associated with poor vision.[40,42]

Isolated foveal hypoplasia

Isolated foveal hypoplasia is a condition that lacks any other ocular manifestations. Hypomorphic mutations of the *PAX6* gene are known to cause isolated foveal hypoplasia which has an autosomal dominant inheritance.[46,47] Patients with OA with a *GPR143* mutation can have isolated foveal hypoplasia.[48] Recently, mutations in the *SLC38A8* gene were identified to cause autosomal recessive, isolated foveal hypoplasia.[49,50] The gene encodes a putative sodium-dependent amino-acid/proton transporter. So far, 11 mutations in the *SLC38A8* gene from 11 families have been reported, and all cases showed typical foveal hypoplasia.[49-51]

Retinopathy of prematurity

Retinopathy of prematurity is an environmental disorder that is caused by hypoxia of the retina due to arrested development of the retinal vessels.[52] Secondary fibrovascular proliferation results in tractional retinal detachment that can lead to blindness. A pathological expression of vascular endothelial growth factor in the retinal tissues is associated with the progression of the disease process.

A disruption of foveal development is associated with retinopathy of prematurity.[53,54] Thus, morphological abnormalities in the macular region including retention of inner retinal layers and absence of a foveal pit as well as macular edema have been detected in the OCT images.[55-57] Perifoveal capillaries are formed during late gestation, and foveal development can be affected by the prematurity.[28] The photoreceptor layer is thin in the fovea of eyes of premature neonates.[55] The diameter of the FAZ is reduced in eyes with retinopathy of prematurity.[54] Villegas *et al*.[58] reported that an abnormal foveal pit was present in children between 2-and 18-years-of-age with a history of retinopathy of prematurity. Twenty-four of these eyes (64%) had a visual acuity of 20/40 or better. The reduction of the visual acuity was correlated with the presence of myopia but not with the structural changes seen in the OCT images.[58] The macular pigment is deficient in premature babies; however, its relevance to the visual acuity is unknown.[59]

Falavarjani *et al*.[60] showed that the FAZ area in 43 eyes with a history of prematurity was smaller than that of controls by OCTA. Twelve of these eyes totally lacked the FAZ. Nonobe *et al*.[61] found that the median FAZ area in 10 patients with a history of retinal coagulation therapy was 0.103 mm^2 by OCTA which was significantly smaller than that of normal participants.

Incontinentia pigmenti

Incontinentia pigmenti is an X-linked dominant retinal disorder characterized by pathognomonic skin rashes on the trunk and limbs.[62] The disease affects various tissues of ectodermal origin including the retina and the central nervous system. Mutations in the *IKBKG* gene cause incontinentia pigmenti.[62]

The disease is associated with occlusive changes throughout the retinal vasculature. The macular abnormalities include an abnormal vascular pattern in the parafovea and foveal hypoplasia.[63,64] However, more than 90% of patients with incontinentia pigmenti

have normal vision, and the consequences of the foveal hypoplasia remain unknown.[65] A small case series study (n = 4) using spectral-domain OCT showed that the foveal hypoplasia was associated with eyes with incontinentia pigmenti.[63,66] The eyes with reduced vision were associated with irregularities of the FAZ detected by fluorescein angiography and a persistence of inner retinal layer by OCT.[66] The frequency, severity, and visual impairments of the foveal hypoplasia are yet to be determined in patients with incontinentia pigmenti.

Diseases Newly Identified to be Associated with Foveal Hypoplasia by Optical Coherence Tomography Imaging

With the advent of high-resolution OCT imaging, signs of foveal hypoplasia have been identified in eyes with achromatopsia, optic nerve hypoplasia, familial exudative vitreoretinopathy (FEVR), and Stickler syndrome. The signs are the persistence of the inner retinal layers as detected in the cross-sectional OCT images and reduced size of the FAZ by OCT angiography. In contrast to eyes with achromatopsia or optic nerve hypoplasia in which poor vision is essentially due to cone dysfunction or dysgenesis of retinal ganglion cells, eyes with FEVR and Stickler syndrome tend to have good visual acuities regardless of the severity of foveal pit malformation [Figure 3].

Achromatopsia

Achromatopsia is an autosomal recessive disorder with deficits of cone function.[9] The disease is characterized by low vision, photophobia, and nystagmus. The conventional photopic ERGs are essentially absent whereas the scotopic ERGs remain intact. Mutations in six genes, *CNGA3*, *CNGB3*, *GNAT2*, *PDE6C*, *PDE6H*, and *ATF6*, are known to cause achromatopsia.[9] These genes encode proteins in the cone photoreceptors involved in phototransduction except for the *ATF6* gene which is a transcription factor that regulates the unfolded protein response during endoplasmic reticulum maintenance.[9]

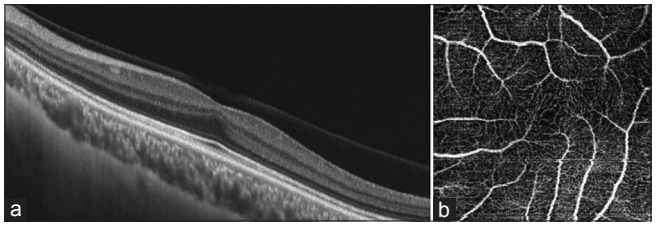

Figure 3: Eye in patient with Stickler syndrome showing foveal hypoplasia. The left eye of a 22-year-old male patient diagnosed with Stickler syndrome with a best-corrected visual acuity of 1.0. (a) Cross-sectional optical coherence tomography image showing persistence of inner retinal layers, and the presence of a widening of the outer nuclear layer and lengthening of the outer segments leading to the "foveal bulge."(b) Optical coherence tomography -angiographic image showing a lack of foveal avascular zone suggesting foveal hypoplasia

Foveal hypoplasia in eyes with achromatopsia was first reported by Thiadens *et al*. as a sign of impaired foveal pit formation using OCT imaging.[10] Foveal hypoplasia was found in 50%–80% of patients with achromatopsia.[10-12] Sundaram *et al*.[11] found no significant differences in the age, contrast sensitivity, retinal sensitivity, and fixation stability between patients with and without foveal hypoplasia. A thickening of the outer nuclear layer was not observed.[10] Notably, the photoreceptor layer in the fovea was disrupted including the absence of the inner segment ellipsoids, hyporeflective zone, and atrophy as seen in the OCT images [Figure 2].[11,12] Adaptive optics scanning light ophthalmoscopy revealed that the foveal cone density is significantly lower than that of normal eyes.[67] These signs in the outer retinal layers seem to progress while the morphology of foveal pit did not progress.[10] Abnormalities of the near-infrared fundus autofluorescence images were also reported in eyes with achromatopsia.[68] According to Greenberg *et al*.,[69] the degree and distribution of the fundus autofluorescence vary considerably among patients, and 53% (9/17) had reduced or absent autofluorescence. Hyperautofluorescence was also observed as a sign of progressive retinal degeneration.

Optic nerve hypoplasia

Optic nerve hypoplasia is a congenital anomaly of the optic nerve caused by dysgenesis of retinal ganglion cells.[70] Optic nerve hypoplasia is manifested by a small-sized optic nerve head with a peripapillary hypopigmentation referred to as "double-ring sign."[70] The etiology is highly diverse, and mutations in genes, involved in transcription regulation (e.g., *PAX6* and *PAX2*), chromatin remodeling, a-dystroglycan glycosylation, cytoskeleton protein, RNA splicing, and MAP kinase signaling pathway, have been associated with optic nerve hypoplasia.[13,71] Optic nerve hypoplasia can be manifested by a thinner retinal nerve fiber layer and ganglion cell layer.[70] Foveal hypoplasia was found in a case with mutation in the *PAX2* gene.[72] Pilat *et al*.[14] reported that 82% (18/22) of eyes with optic nerve hypoplasia had a persistence of the inner retinal layers in the fovea in the spectral-domain OCT images. Katagiri *et al*.[15] reported that 24% (7/29) of eyes with optic nerve hypoplasia had foveal hypoplasia.

Familial exudative vitreoretinopathy

FEVR is a hereditary vitreoretinal disorder characterized by insufficient vascular development in the peripheral retina.[16] Secondary pathological processes lead to various forms of retinal detachments with fibrovascular proliferation. The genes causing FEVR are highly heterogeneous, and aside from very rare causative genes, four genes, *FZD4*, *LRP5*, *TSPAN12*, and *NDP*, are known to cause FEVR.[16,73] The main causative genes are related to Wnt signaling, a key regulator of cellular proliferation

and differentiation, and mutations in these genes account for ~50% of the FEVR cases.[16,73]

Eyes with FEVR have different degrees of severities of the retina, and the vascular system ranging from mild vascular abnormalities in the peripheral retina to total retinal detachment. Secondary proliferative changes in the periphery can affect the macular structure which is seen as an ectopic macula and falciform retinal folds. The deformed macular structures have hindered the detection of microstructural changes in eyes with FEVR. Yonekawa *et al*.[17] found various abnormal microstructural findings by spectral-domain OCT. Twenty-two (20%) of 52 eyes with Stage 1 and Stage 2 FEVR, i. e. milder forms not accompanied by a retinal detachment, had a persistence of the inner retinal layers in the fovea which is analogous to mild foveal hypoplasia. The persistence of the inner retinal layer did not appear to cause the reduced visual acuity when the underlying outer retinal structures remain intact.[17] As the majority of mild cases of FEVR are asymptomatic, it is difficult to estimate the exact frequency of foveal hypoplasia in FEVR patients.

Stickler syndrome

Stickler syndrome is an inherited connective tissue disease that affects the eyes, ears, joints, and midline facial structures.[18] The ocular features are high myopia, vitreous degeneration, cataracts, perivascular retinal degeneration, and a high incidence of retinal detachments.[74] The retinal detachments occur during childhood and can lead to blindness.[75] Stickler syndrome is caused by mutant procollagen genes in which mutations in the *COL2A1* gene account for more than 80% of the patients.[75]

Matsushita *et al*.[19] showed that 82% of eyes with Stickler syndrome had a persistence of the inner retinal layers with a reduced or absent foveal pit in the OCT images. In addition, the OCT angiography showed smaller FAZ areas and disarrangements of the capillary network around the fovea. All of the eyes in their cohort had fairly good visual acuity, and the foveae were limited to Grades 1 or 2 based on the criteria by Thomas *et al*.[30] There was not a significant correlation between the visual acuity and degree of foveal hypoplasia. Foveal hypoplasia had not been reported in patients with Stickler syndrome probably because these patients have fairly good visual acuity.[19]

Conclusions

Recent advancements of high-resolution OCT imaging have challenged the earlier concepts of the visual consequences of foveal hypoplasia. A lack of foveal pit does not simply indicate poor visual acuity as clinicians have observed cases with foveal hypoplasia with no visual impairments. On the other hand, the maturation of the cone photoreceptors is important for visual prognosis. The causes of foveal hypoplasia are highly heterogeneous, and other retinal disorders have been found unexpectedly to be associated with foveal hypoplasia as determined by OCT imaging. The en-face images of the FAZ could be useful in the identification of eyes with foveal hypoplasia. Future studies *in vivo* imaging by OCT will provide more evidence that will be helpful in understanding the physiology and pathology of the fovea.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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