Focal choroidal excavation: a preliminary interpretation based on clinic and review

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Abstract

• AIM: To describe the clinical and imaging characteristics associated with focal choroidal excavation (FCE), analyze the possible complication, and interpret its probable etiopathogenesis.

• METHODS: Retrospective descriptive case series of 37 eyes of 32 patients with FCE. Findings of spectral-domain optical coherence tomography (SD–OCT), fluorescein angiography, indocyanine green angiography, and clinical features were analyzed.

• RESULTS: All patients were Chinese. Five patients (15.6%) were bilaterally involved. Patients’ ages ranged from 7 to 66 y. Refractive error ranged between +2.0 D and 11.0 D. Mean best–corrected visual acuity was 0.6 (range, 0.1 to 1.2). Fundus examinations exhibited mild–moderate localized pigmentary disturbances in the corresponding area of 17 eyes. Fluorescein angiography performed in 18 patients showed varying degrees of hyperfluorescence and hypofluorescence related to a range of retinal pigment epithelium (RPE) alterations. Indocyanine green angiography performed in 7 patients showed hypofluorescence at the excavation. SD–OCT demonstrated choroidal excavation in all 37 eyes. Twenty–nine eyes showed a single lesion of FCE, and three eyes showed 2–3 separated lesions. Fifteen eyes showed separation between the photoreceptor tips and RPE consistent with nonconforming FCE. Central serous chorioretinopathy (CSC, n =1) and choroidal neovascularization (CNV, n=1) developed during follow-up.

• CONCLUSION: FCE could be interpreted as congenital focal choroidal dysplasia involving the RPE, choriocapillaris, and photoreceptor associated with the faulty anatomy. The abnormal anatomy of FCE was similar to anatomy at risk of CSC and CNV.

• KEYWORDS: focal choroidal excavation; dysplasia; optical coherence tomography; etiology

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INTRODUCTION

In 1959, Klien [1] was the first to described a focal concave-shaped chorioretinal anomaly with an undifferentiated retinal pigment epithelium (RPE) and choriocapillaris in histopathological images of the cadaver eye of an infant. In 2006, a similar chorioretinal change was the first observed in vivo using optical coherence tomography (OCT), and Jampol et al [2] defined it as a new entity using the term "choroidal excavation". In 2010, Liu et al [3] initially proposed the disease may result from the minor, imperfect closure of the embryonal fissure in view of the clinical observation, and Abe et al [4] hypothesized that choroidal excavation might stem from a microcyst in the superficial choroidal layer. In 2011, the entity was first named as focal choroidal excavation (FCE) [5]. According to the separation between the photoreceptor tips and RPE, FCE was classified into nonconforming and conforming FCE. In this report, malformative, dystrophic, and inflammatory hypotheses were briefly noted to explain the etiopathogenesis [5]. In 2012, FCE accompanied by choroidal neovascularization (CNV) were presented [6–7], and it was suggested that more attention to follow-up was warranted even if the lesion seemed stable. In 2013 and 2014, two reports of FCE with central serous chorioretinopathy (CSC) [8] and CNV [9]
contributed to our new understanding of FCE and other reports provided further detailed clinical and imaging characteristics\cite{10,11}.

Thus far, only limited cases of FCE detected by OCT have been documented \cite{2-13}, even though the morphological abnormality of choroidal excavation has been well described. The etiologic and pathologic mechanisms underlying this condition remains unclear, and further observation and interpretation is needed.

We present an expanded spectrum of 32 cases (37 eyes) with FCE detected by spectral-domain OCT (SD-OCT). We show new imaging findings of clinical and imaging features, give a novel hypothesis for the probable mechanism for this entity based on our literature review, and propose focusing attention on the abnormal anatomy of FCE similar to the risk of CSC and CNV.

**SUBJECTS AND METHODS**

All the procedures were approved by the Ethics Committee of Wenzhou Medical University, carried out in accordance with the Declaration of Helsinki. All patients undergoing fluorescein angiography (FA) or indocyanine green angiography (ICGA) provided written informed consent. A retrospective review of 37 eyes was performed in 32 patients with FCE. All patients were Chinese and were examined at the Affiliated Eye Hospital of Wenzhou Medical University and China-Japan Friendship Hospital. The patients were followed up for 2 to 43 mo. None of the patients had a history of trauma, posterior uveitis, or prior retinal or choroidal infection.

FCE was defined as a reflex curve alteration of the RPE-choriocapillary band in a 2D image or as a choroidal excavation in a 3D image detected in a SD-OCT scan analyzed by a single investigator, without the evidence of a posterior staphyloma or scleral ectasia. All patients underwent a detailed clinical examination, including best-corrected visual acuity (BCVA), refraction, slit-lamp, intraocular pressure, ophthalmoscopy, and fundus photography. SD-OCT was performed with a Topcon 3D-OCT-1000 (Topcon, Tokyo, Japan) and Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany) using 3D-macula or a 99-horizontal line protocol (6 x 6 mm area). The depth of FCE was manually measured. FA and ICGA were performed using the Heidelberg retina angiography 2 (HRA2; Heidelberg Engineering, Heidelberg, Germany).

**RESULTS**

The patients' demographic and clinical features are summarized in Table 1. Seventeen of 37 eyes were right eyes and 20 were left eyes. Nineteen eyes were myopic. Nine eyes achieved a BCVA of 1.0 or better. CSC was observed in 4 eyes and one case developed during the follow-up since our first examination for FCE. CNV was observed in 7 eyes and 1 of them developed during the follow-up. No patient had any other significant ocular manifestations. None of the patients had a history of any medical illness or medication use that seemed relevant to their choroidal and retinal findings, and none of the patients reported a family history of retinal disease. Twelve of the eyes were identified during routine eye examinations. Eleven eyes presented with retinal diseases and 7 with metamorphopsia or decreasing visual acuity. Six eyes were referred from an optometry clinic because their BCVA was less than normal, and one eye was found incidentally in one of our staff.

In most patients, the presence of FCE was not clearly evident on routine clinical examination. B-scan ultrasonography showed no microphthalmia. Funduscopy and color photography showed mild-moderate localized pigmented disturbances in the corresponding area of 17 eyes, while 9 of the eyes had no remarkable changes (Figures 1-5) and 11 eyes had fundus manifestations corresponding with CSC and CNV. Fluorescein angiography was performed in 18 patients and showed varying degrees of hyperfluorescence and hypofluorescence relating to a range of pigmentation alterations (Figures 2, 3). ICGA was performed in 7 patients and showed hypofluorescence at the excavation (Figure 3).

For all patients, the use of SD-OCT imaging was necessary to detect FCE. All the 37 eyes demonstrated reflex curve changes of the RPE-choriocapillary band in 2D image or choroidal excavation in 3D image. Twenty-nine eyes showed one lesion of the FCE, and 2 eyes showed 2 separate lesions (Figure 5). The remaining one eye showed 3 separate lesions (Figure 1).

All the excavations were located around the horizontal raphe. Thirty-seven of the 41 lesions were found in the fovea or juxta-fovea region, and the normal foveal contour was maintained, except in patients who also had CSC or CNV. Four lesions, which were the 2nd or 3rd lesion in the involved eye, were located extrafoveally (Figures 1, 5).
Figure 1  A 24-year-old woman with bilateral FCE was observed in the clinic for a pre-pregnancy physical examination and presented with BCVA of 1.2 in both eyes A, E: Fundus photographs showed normal pigment in the fovea. B, F: Fluorescein angiography showed irregular slight hyperfluorescence in the macula. C, G: The OCT images of the topographic map showed a bowl-shaped choroidal excavation with a depth of 182-210 μm. C, D: OCT showed three choroidal excavations in the macula of the right eye. One appeared in temporal to the fovea and the other appeared in inferotemporal to the fovea, with a reflex curve alteration of the RPE-choriocapillary band and IS/OS junction. The third was located just beneath the fovea. The band of the OS and IS/OS junction was blurred at the excavation, while the bands of ELM were fairly preserved. The hyporeflective space between the RPE and photoreceptors suggests it was nonconforming. H: The choroidal excavation was under the fovea and involved the outer retinal layer up to the ONL. The band of OS tips disappeared at the excavation, while the bands of ELM and IS/OS junction were preserved. The retinal layers from the OPL to RNFL were almost undisturbed. High reflex, with a density similar to fibrosis, was observed beneath the RPE-choriocapillary band at the excavation. (A, B, C, D: Right eye. E, F, G, H: Left eye).

The affected structures in the excavation generally included the RPE-choriocapillary band, the inner segment/outer segment (IS/OS) junction, the external limiting membrane (ELM), and the outer nuclear layer (ONL), which followed the contour of the choroidal excavation. In most of these cases, the layer from the outer plexiform layer (OPL) to the retinal nerve fiber layer (RNFL) was undisturbed (Figure 1). However, in 1 eye, the excavation involved the OPL besides the retinal structures mentioned above. In the areas that were affected, the OPL appeared thickened compared with the
Figure 2  A 29-year-old man with a nonconforming FCE in the left eye  A: The lesion showed mild pigment disturbance. B: Fluorescein angiography demonstrated punctiform hyperfluorescence. C: The RPE, IS/OS junction, ELM, ONL, OPL, and INL followed the curve of the choroidal excavation, with separation between the photoreceptor tips and RPE. The sclerochoroidal junction appeared smooth and undisturbed. High reflex, with a density similar to fibrosis, was observed beneath the RPE-choriocapillary band at the excavation.

Figure 3  A 26-year-old man with FCE associated with CNV in the right eye  A: A color photograph showing a macular hemorrhage. B: Fundus autofluorescence imaging revealed irregular hypo-autofluorescence in the fovea and speckled hyper-autofluorescence inferior to the fovea. C, F: Fluorescein angiography demonstrated irregular hyperfluorescence inferior to the fovea that was related to classic CNV in the early phase, with dye leakage in the late phase. D, E: Indocyanine green angiography showed hypofluorescence at the fovea. G, H, I: The OCT images demonstrated increased thickness at the macula, with a focal choroidal excavation in both the vertical (H) and horizontal (I) scans.
unaffected retina. The inner nuclear layer (INL) above the excavation was also part of the excavation and followed the alteration of the reflex curve in this eye (Figure 2).

There was a separation between the photoreceptor tips and the RPE in 15 eyes (nonconforming FCE). For two patients, the conforming lesion and the nonconforming lesion...
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cooexisted in the same eye (Figures 1, 5), an unusual finding that has not been reported previously. In other 4 cases, four eyes with CSC had a serous neuroepithelial detachment over the excavation (Figure 4). Seven eyes with FCE had CNV originated from the vicinity of the margin of excavation. None of the eyes showed any staphyloma of sclerochoroidal bands on the OCT scan, which appeared smooth. In some cases, high reflex, with a density similar to fibrosis, was observed beneath the RPE-choriocapillary band at the excavation (Figures 1, 2).

DISCUSSION

The etiologic and pathologic mechanism underlying FCE remains unclear. Based on clinical data and review, we hypothesized FCE could be an entity arising from the focal faulty differentiation of the chorioretina, a developmental disorder, because of the lack of a history of any related ocular disease and the occurrence of a new case in a child. As documented in the embryology literature [14], the RPE and presumptive sensory retina appear in the 5wk, followed by the occurrence of the chorioidal vasculature in the 7wk and photoreceptors in 3mo. The RPE is one of the earliest retinal structures to develop and differentiate [14], and is believed to be involved in the development and differentiation of the choroid and retina later [15]. It has been demonstrated in a mouse [16,17] and in the human [18] that the RPE is necessary for the normal morphogenesis of the sensory retina and choroid. Most notably, in 1959, Klein [1] reported a case of suspected retinoblastoma in a 2-month-old infant. Aside from 2 large flat white lesions around the optic disk, additional 6 small whitish retina lesions in her right eye were observed clinically. When 19 months old, she died from bronchopneumonia and her right eye was analyzed histopathologically. The final pathological diagnosis of the large lesions was atypical choroidal coloboma. The small lesions revealed a circumscribed concave-shaped chorioretinal anomaly, in which the RPE was poorly differentiated, the choriocapillaris underlying the RPE was rudimentary, and the neural retinal layers overlying the RPE, particularly the photoreceptors, had some degeneration. To our knowledge, Klein's [1] is the only histopathological report of focal concave-shaped chorioretinal anomaly reported in an infant up to now, and shows most similar chorioretinal alteration with FCE.

The RPE, choriocapillaris, and photoreceptor are three substructures involved in FCE [2,12]. Based on Klein's [1] "neuroectodermal" theory, we speculated that the development of FCE may be due to the faulty differentiation of the choroiretina. However, it is difficult to explain the localization of FCE, which is typically located in the perifovea around the horizontal raphe. An alternative possibility we suggested was that FCE may be regarded as atypical coroidal coloboma that arises due to the minimal defective closure of the embryonal fissure. When there is a good apposition in a normal-sized optic cup, the failure of closure, accompanied by the aberrant differentiation of the RPE, can lead to a small defect in a normal-sized eye [19]. The failure of RPE differentiation can result in lesions in which multiple structures are malformed [16,17]. Histologically, these lesions may be deficient in the RPE, the overlying sensory retina, the underlying choroid [1,20], or even the whole retina. Clinically, the subtype and visual prognosis of the lesion varies and depends on the severity, location, and other complications. A large lesion involving the macula may lead to severe impairment of vision. A small lesion involving limited tissue may interfere less with vision and may show minimal thinning of the choriocapillaris or varying degrees of pigment clumping along the line of fissure closure [19].

Mini lesions beneath the RPE are difficult to detect by conventional examination. The OCT, especially SD-OCT, provides high quality images of the retina and choroid with an axial resolution of approximately 5 μm [21]. In the FCE cases reported in our study and the previous literature [2,12], the choroidal excavation involved the choriocapillaris and RPE in the foveal or perifoveal region, and the lesions had a thickened photoreceptor cell layer and the attenuation or absence of IS/OS junction and photoreceptor cell tips [4]. We recently noted that OPL following the contour of the excavation appeared thickened, while the layers from OPL to RNFL were previously reported to be normal [3,12]. The alterations observed by OCT have been confirmed by other imaging modalities. Hypo-autofluorescence indicates the loss of RPE activity in the lesion, and hypofluorescence of ICGA suggests the presence of impaired choroidal circulation [5,12].

Based on the shapes of the lesions of the structures involved, Margolis et al. [19] defined two types of choroidal excavation, conforming and nonconforming. He suggested the possibility of progressing from the conforming to nonconforming type when the normal choroid becomes thinner with age and the stress between the photoreceptor chips and RPE increases with time. However, no association between the diameter or depth of the excavation and the patients' ages was presented, and apparently none of the cases progressed from the conforming to nonconforming type during the 6-66mo of follow-up [11]. Additionally, in our study, we observed different phenotypes of this defect with greater age diversity. In the current report, this age-related interpretation may not be able to accurately illustrate the occurrence of the nonconforming type in children, especially the co-occurrence of the
Table 2 Literature review of the clinical features of choroidal excavation\(^{[2-13,19]}\)

<table>
<thead>
<tr>
<th>Author</th>
<th>Eyes/Cases (n)</th>
<th>Age range</th>
<th>Sex (M/F; n)</th>
<th>Race (n)</th>
<th>Myopia cases (n)</th>
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<td>29</td>
<td>1/0</td>
<td>Asian (Japanese)</td>
<td>1</td>
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<tr>
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<td>22-62</td>
<td>4/8</td>
<td>White; Asian 4; Hispanic 1; Black 1</td>
<td>$\geq 7$</td>
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<td>26-64</td>
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<td>25-70</td>
<td>10/7</td>
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<td>33-38</td>
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<td>2</td>
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<td>Savastano et al(^{[13]})</td>
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<td>49-60</td>
<td>1/2</td>
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<td>$\geq 2$</td>
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<td>0/1</td>
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<td>19-76</td>
<td>35/40</td>
<td>Non-Asian; Asian 62</td>
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conforming and nonconforming FCE in the same eye of a child (Figure 5). Alternatively, it is plausible that dysplasia leads to various degrees of lesions and that choroidal excavation can demonstrate the various phenotypes inherent to it.

Aside from developmental and age-related origins, inflammation and infection as possible etiologies were proposed for FCE \(^{[5,13]}\), but FCE lacks a history of any related ocular diseases and keeps relatively stable course, its OCT manifestation resembles the histopathological images of Klein's case \(^{[1]}\) and one case occurred in early childhood. In view of that, congenital focal choroidal dysplasia would be a more appropriate name for the entity if earlier onset age is collected and longitudinal study is evidenced in the future.

In addition to the changes observed by OCT, several clinical features have been assessed based on the present study and literature review \(^{[2,4-7,10-12]}\) that enable us to better understand FCE. The FCE generally presents unilaterally but can be observed bilaterally, with an approximately 16% bilateral occurrence (Table 2). The patients examined by routine eye examination may be asymptomatic \(^{[3]}\), but most patients presented to the clinic with complaints of visual disturbance. In FCE patients, the degree of metamorphopsia \(^{[4,5,7,10-12]}\), central scotoma \(^{[4]}\), or decreasing visual acuity \(^{[4,11]}\) varied. Ophthalmoscopy and fundus photography are nonessential for FCE diagnosis, even if some eyes show varying degrees of foveal or perifoveal pigmentary disturbances. Pigmentation within the lesion can range from a mild "reddish" or "yellowish" hypopigmentation to pigment motting in macula. In the previous reports of 86 eyes of 75 patients, all of the patients were adults when FCE was diagnosed (Table 2). This is similar to the present study, where 29 of our patients were adults. However, an earlier age of diagnosis was confirmed in a child aged 7 in our study (Figure 5), which suggests that FCE may occur in earlier age of childhood and the etiology of FCE may be due to a congenital factor since the lack of any acquired factors presented in this child and also in other FCE patients. FCE shows an ethnic predilection. All of our patients were Chinese, which was in accordance with the Asian preponderance (82%) reported in previous publications (Table 2). Kumano et al\(^{[10]}\) suggested that ethnic risk factors and inheritance patterns are related to FCE.

Although all the reported cases lack the relevant disease history and family history, at least 68% of FCE patients also had myopia (Table 2). Most of our patients also presented with myopia. However, it has been reported that the choroidal thickness of patients with hyperopic to moderately myopic eyes are not obviously different from that in healthy subjects when adjusted for age, refractive error, and/or race. The choroidal thickness was only greater than that of the control group in highly myopic eyes\(^{[13]}\). This may suggest that refractive error is a risk factor for the development of FCE or may be associated with FCE, rather than being an etiological factor for the condition.

So far, 7 patients of FCE had a concurrent diagnosis of CSC based on the previous study \(^{[5,10]}\). In our study, we presented additional 4 cases with co-occurred CSC. Although the generalized choroidal vascular disturbances of FCE, such as choroidal vascular dilation, choroidal vascular hyperpermeability, and multifocal hyperfluorescence and hypo fluorescence \(^{[10,13]}\), are believed to be similar to what are often observed in CSC\(^{[10,12]}\), the role of FCE in the occurrence of CSC is not confirmed at the present time. According to Ellabban et al\(^{[8]}\), none of their CSC patients showed new occurrence of FCE during the disease course, and none of the eyes showed resolution of FCE during their follow up. At
least, it suggests that CSC may not necessarily causatively relate to the onset of FCE. In our cases, 4 eyes were accompanied by CSC and 1 of them developed a secondary serous retinal detachment above the area of excavation 3mo after the first visit, which was consistent with CSC in OCT and the FA image. It seems that FCE has a possible role in the onset of this special concurrent CSC. Yet precise interpretations cannot be determined until further population-based studies are completed. While FCE generally maintains a stable natural course, a secondary CNV can be main cause for a visit to the clinic. In the current study, seven eyes with FCE had CNV and one of them developed CNV during the 28mo follow-up. The results emphasize the possibility of FCE as a risk factor for CNV. However, the reason for this risk is not clear. Commonly, CNV could be due to the degeneration of RPE in age-related macular degeneration and the break of Bruch’s membrane (BM) in other diseases, such as angioid streaks or pathologic myopia. In Klien’s case, absence of BM behind circumscribed areas of faulty differentiation of RPE was revealed. Previous studies of FCE have explored several changes in the choroidal excavation, such as the aberrant choroidal circulation defined by FA and ICGA, thinned choroid, and defects of the RPE-BM-choriocapillar complex defined by OCT, which share the anatomic features of CNV risk factors. So it is believed that besides bad circulation, a defect of the BM should also be considered a risk factor for the development of CNV in FCE. Due to the anatomic abruption of BM or anatomic disruption of RPE-BM-choriocapillar complex, CNV may develop. This type of CNV is similar to that which is secondary to PM and angioid streaks. It seems that cases frequently defined as idiopathic in many patients with FCE should be reconsidered, especially in younger patients. In view of the risk of developing CNV, it is suggested that more attention should be given to FCE patients over the long term.

In conclusion, FCE could reflect the aberrant differentiation of chorioretina, which involves the dysplasia of the RPE, choriocapillaris, and photoreceptors. However, our preliminary interpretation of FCE as congenital focal choroidal dysplasia is not conclusive and requires further support. It is notable that FCE present similarity with the anatomical risk of CSC and CNV. More histopathological studies are needed to further elucidate the pathogenesis of FCE and to define the long-term prognosis.

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