Title: Novel Spectral Domain Optical Coherence Tomography Findings Leading To New Insights Into The Pathogenesis Of Acute Posterior Multifocal Placoid Pigment Epitheliopathy.

Abstract
Novel spectral Domain optical coherence tomography findings leading to new insights into the pathogenesis of Acute Posterior multifocal placoid pigment epitheliopathy.

Purpose
To analyze the spectral Domain optical coherence tomography (SD-OCT) findings in acute posterior multifocal placoid pigment epitheliopathy (APMPPE) and to correlate it with the pathogenesis of the disease.

Methods
Prospective observational case series of 8 eyes of 5 consecutive patients diagnosed with acute posterior multifocal placoid pigment epitheliopathy. All patients underwent complete ophthalmic examination, fundus photography, fluorescein angiography (FA) and SD-OCT at initial visit. During the course of the disease and after resolution, ophthalmologic examination and SD-OCT were repeated. The SD-OCT scans were taken through the lesions seen clinically and on FA.

Results
In the acute stage all the 8 eyes had Inner Segment-Outer Segment (IS-OS) junction abnormalities in the form of undulations, thickening and irregularity at the edge of the lesion which got separated from the retinal pigment epithelial (RPE) layer towards the centre of lesion. The IS/OS junction was elevated as a dome in 4 eyes where there was significant sub-retinal pooling of dye on FA. 5 eyes had retinal pigment epithelial (RPE) changes in the form of irregularity, thickening or undulations. All the 8 eyes had involvement of outer plexiform layer (OPL) with splitting of the same at the edge of dome shaped elevation in two eyes. On resolution all eyes had prominent changes in the IS/OS junction in the form of irregularity, discontinuity and thinning at the site of lesion. There was decrease in thickness of outer nuclear layer (ONL) in all cases. Significant RPE abnormalities were seen only in 2 eyes. Eyes with significant thinning of outer retinal layers showed falling of inner retinal layers into the area of thinning.

Conclusion
In the acute and healed stages of APMPPE most significant changes appeared in the IS/OS junction of the retina in all 8 eyes. RPE changes were less significant compared to that of photoreceptors pointing to the primary involvement of photoreceptors in the pathogenesis of disease. Based on these we conclude that in APMPPE early and primary insult may occur in the photoreceptors.

Acute Posterior multifocal placoid pigment epitheliopathy is an idiopathic bilateral self limiting inflammatory disorder of the retina and choroid affecting young healthy adults as described originally by Gass. Visual disturbances are caused by multiple round to oval yellowish white placoid lesions located at the posterior fundus. This is usually associated with a viral prodrome and typically resolves in 2-3 weeks leaving discrete pigment epithelial scars. Recently a few case reports have described atypical features like serous retinal detachment, unilaterality and papillitis which are intermediate between APMPPE and Haradas disease. The purpose of this article is to describe the SD-OCT findings in APMPPE in the acute stage and after resolution.

Material and Method
This was a prospective observational study of 8 eyes of 5 consecutive patients diagnosed with APMPPE. The patients were evaluated at the uveitis service of Giridhar Eye Institute between July 2011 and March 2012.

Reduction of vision was the chief complaint in all patients. Multiple cream colored placoid lesions were present in the deep retina in all patients at the posterior pole. 2 patients had subretinal fluid at the macula and one patient had significant disc edema with hemorrhages. All patients at presentation underwent complete ophthalmic examination including best corrected visual acuity, slit lamp examination, fundus examination, color fundus photography (FF450 plus IR fundus camera; Carl Zeiss Meditec, Inc, Jena, Germany), fluorescein angiography(FF450 plus IR fundus camera; Carl Zeiss Meditec, Inc, Jena, Germany) and Heidelberg Spectralis
SD-OCT (Heidelberg Engineering, Heidelberg, Germany).

All patients were treated with oral prednisolone which was tapered according to the clinical response over a period of 4 to 6 weeks. Fundus examination and SD-OCT were repeated at 1 month follow up. The retina was first scanned with fast macular line scanning protocol. Single high resolution scans were taken along the vertical and horizontal axis through the center of the fovea and on the affected retinal areas. For OCT after resolution, follow up acquisition mode was used which automatically placed the follow up scans in exactly the same location as that of initial scan.

**Results**

Table 1 shows patient's demographic and clinical characteristics. Of the 5 patients 3 were males and 2 were females. Average age at presentation was 36 yrs. The disease was unilateral in 2 and bilateral in 3 cases. Preceding fever was present in 2 cases and 1 patient had head ache. All the patients were otherwise healthy. Laboratory examination included negative titers for Toxoplasmosis, a negative quantiFERON TB Gold for tuberculosis and a negative fluorescent treponemal antibody absorption test. There was no associated anterior uveitis or vitritis in any patient. Multiple cream colored placoid lesions were present in the deep retina at the posterior pole in 3 patients (patients 1,2,3) (typical APMPPE) and 2 patients in addition had sub retinal fluid(patients 4,5)(atypical APMPPE) and one patient had significant disc edema with hemorrhages similar to Vogt-Koyanagi-Haradas Disease(VKH)( patient 5).

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LE-left eye; RE-right eye; VA-visual acuity; M-male; F-female.

**Case Report (patient 1;Representative of typical APMPPE)**

This was a 35 yrs old female patient with history of decrease in vision of LE of 3 days duration. She had a viral prodrome 5 days prior to this. Her best corrected visual acuity (BCVA) in BE was 20/30,N6. Fundus examination showed multiple cream colored placoid lesions in the deep retina at the posterior pole(figure-1A). FA showed the classic pattern of initial hypo fluorescence with late phase hyperfluorescent staining of the placoid lesions(figure-1B&C). Patient was diagnosed to have APMPPE and was treated with oral prednisolone (1mg/kg) which was tapered over a period of one month.

SD-OCT demonstrated similar characteristic features in the acute stage in all 3 patients(patiens1,2,3). At the edge of the placoid lesions the IS-OS junction was irregular with undulations which got separated from the RPE layer more
towards the centre of the lesion (figure-1D). Then this layer became thickened and more hyper reflective with increase in hyper reflectivity of the overlying ONL. There was increase in reflectivity and irregularity of the OPL as well (figure-1E). As the lesion progressed more towards the centre the thickened IS-OS line got elevated partly from the underlying RPE and formed a dome shaped elevation that had a hyper reflective membrane lining all around it. Roof of the dome had a few hyper reflective points like echoes hanging down (figure-1F). At all levels changes in photoreceptors were more prominent than that of RPE.

Figure 2. Fundus picture of RE(A). Early FA picture showing hypo fluorescent lesions and large area of submacular hypo fluorescence(B). Late FA showing hyperfluorescence of the initial hypofluorescent lesions and macular dye pooling(C). Black on white SD-OCT image at the edge of the lesion with IS-OS irregularity and undulations and separation from the RPE layer(D). Hyper reflectivity of ONL and OPL(E). Dome shaped elevation of partly separated IS-OS junction with splitting of OPL at the edge and hyper reflective echoes from the roof are seen clearly(F). The fluid collection is above the partly separated IS-OS junction(F). RPE elevation and undulations(G).

Figure 4. Disc edema, peripapillary hemorrhages and large area of subretinal fluid collection in the RE of patient 5(A). Mid FA picture(B). Late FA picture showing disc leakage, large area of sub retinal pooling of dye and pin point hyper fluorescent dots within the area of dye pooling(C). Black on white SD-OCT image showing 3 compartments of fluid with more hyper reflective elements in the central one(D).
Figure 3. Black on white SD-OCT image of patient 4 after resolution showing irregular hyper reflectivity, thinning and discontinuity of IS-OS junction and RPE layer. The external limiting membrane is thinned out nasal to the fovea. There is thinning of ONL. Irregular reflectivity of OPL is also seen nasal to fovea(A). OCT section through a different site showing thickening, increased reflectivity and elevation of RPE. The IS-OS junction is absent on a major area within the lesion(B).

SD-OCT after resolution (1 month) showed changes mainly in the IS-OS junction and photoreceptor layer in the form of irregularity, discontinuity and thinning at the site of lesion. There was decrease in thickness of ONL. RPE layer showed undulations, irregularity, thinning and focal increase or decrease in reflectivity in the area of the lesion. The area of involvement of RPE was much less compared to the involvement of photoreceptor layer in healed lesions also. Irregularities in the OPL were also seen at 1 month.

Case Report (patient 4)
This 28 yrs old gentle man complained of blurring of vision of both eyes of 1 day duration. His BCVA in the RE was 20/120, N36 and LE was 20/200, N36. Fundus examination showed sub macular fluid in addition to the typical placoid lesions(figure-2A). Both the eyes had macular pooling of dye on FA along with the typical features of placoid lesions(figure-2B&C). SD-OCT through the area of sub macular fluid showed a large dome shaped elevation which had a similar pattern of progression from the edge towards the centre as in patient 1(figure-2D&E). There was accumulation of fluid with hyper reflective material beneath the dome(figure-2F&G). There was splitting of OPL at the edge of the dome. At few places within the dome there were changes in the RPE layer in the form of irregular reflectivity, undulations, thickening and thinning which were much less significant compared to the involvement of photoreceptor layer(figure-2G). These changes did not happen at the edge of the lesion but more towards the centre.

SD-OCT findings of healed lesions were similar to patient 1 but the IS-OS junction and RPE layer abnormalities were much more prominent. The IS-OS junction was irregular and thinned with few undulations trough out the extent of the lesion with no area showing restoration of original architecture except at the edge(figure-3A). The IS-OS line and RPE layer were discernible as two separate layers only at few places within the area of initial dome shaped elevation(figure-3A&B).

Case Report (patient 5)
30 yrs old male patient presented with gross reduction of vision of RE of 2 days duration, 5 days following an episode of viral fever. His BCVA in the RE was counting fingers at 2 meters 20/400,N36. His LE was normal. There was a large area of subretinal fluid at the posterior pole and disc edema(figure-4A). Few placoid lesions were seen temporal to macula and below the major vascular arcade. FA showed pooling of dye in the area of subretinal fluid and a few pin point hyper fluorescent dots within this area. He also had disc leakage on FA(figure-4B&C).

SD-OCT showed large accumulation of fluid beneath the elevated IS-OS junction in 3 loculi. In the middle loculus corresponding to the yellowish area seen on fundus photograph, accumulation of hyper reflective material was significantly denser compared to the temporal and nasal compartments which had relatively clear fluid. In all the 3 compartments fluid collection was beneath the elevated IS-OS junction(figure-4D). The pattern of progression of the lesion was similar to patient 1 but the changes were more dramatic.

Healed lesions had features similar to patient 4. Area with significant thinning of outer retinal layers showed falling down of inner retinal layers into the area of thinning.

Discussion
In our study we analyzed the retinal structural changes in the acute and healed stages of APMPPE using Spectralis OCT. Based on our results we put forward a new proposal into the pathogenesis of the disease.

In all eyes structural alterations were seen in and external to the OPL with maximum changes occurring in the photoreceptor layer. SD-OCT findings of patients with typical
APMPPE showed similar characteristic features. At the edge of the placoid lesions the IS-OS junction was irregular with undulations which got separated from the RPE more towards the centre of the lesion. Then this layer became thickened and more hyper reflective with increase in hyper reflectivity of the overlying ONL. As the lesion progressed more towards the centre the thickened IS-OS line got elevated partly from the underlying RPE and formed a dome shaped elevation that had a hyper reflective membrane lining all around it. At the roof of the dome there were a few hyper reflective points like echoes hanging down. In the 2 patients with subretinal fluid, fluid was located beneath the elevated IS-OS junction. Patient 5 had accumulation of fluid beneath the elevated dome of IS-OS junction in multiple loculi. Presence of hyper reflective material beneath the dome points to an inflammatory pathology. Changes in the RPE layer were more prominent towards the centre of lesion than at the edges. We postulate that there is an initial inflammatory insult to the photoreceptors which produced some morphological alteration at the IS-OS junction which led to an increase in reflectivity and thickening of this layer. With further changes inflammatory materials and fibrin would have got attached to this resulting in further thickening and eventual partial separation and elevation of this layer. The OCT findings of RPE layer points to the involvement of this also in the disease process but to a lesser extent compared to photoreceptors as indicated by the less frequent and less area of involvement of RPE and by the appearance of these changes more towards the centre than edge of lesions. The origin of fluid is mostly probably from the choroid because the inner retinal layers were intact on OCT and all the retinal vessels were normal on FA. The changes in the photoreceptors would have produced initially functional and later morphological changes in the RPE and that the subretinal fluid would have swept across the functionally deranged RPE from the choroid (the changes in the RPE may be functional initially and not picked up by the OCT). Also changes in the RPE layer were more prominent in the eyes with subretinal fluid collection (patient 4 & 5) favoring our suggestion. The IS-OS junction and photoreceptor changes on SD-OCT after resolution were much less significant compared to the initial OCT pictures which favor the inflammatory etiology rather than a vascular one which would have produced more permanent changes. Residual IS-OS junction and RPE changes were more prominent in eyes with subretinal fluid collection indicating more extensive damage in these eyes.

Patient 5 in addition to disc edema and pin point hyper fluorescent dots on FA and loculated subretinal fluid collection on SD-OCT pointing to the overlapping nature of APMPPE and Vogt-Koyanagi-Harada disease (VKH). Hyper reflective material in the central subretinal locusus seen in OCT in this patient was much more (corresponding fundus photo showed more yellowish discoloration of subretinal fluid) than in the temporal and nasal loculi (fundus photo showing clearer fluid collection). This may be because there is more inflammatory material and fibrin in the central loculus compared to the other two.

The hyper reflective dots seen hanging from the roof of the dome shaped elevation, not described earlier may represent the separated outer segments of photoreceptors. The splitting of OPL and falling down of inner retinal layers into the area of thinning were also not reported earlier and to the best of our knowledge this is the first report of an SD-OCT analysis from the edge towards the centre of the lesion in a systematic way.

We have measured the choroidal thickness of 3 patients (5 eyes) in the acute stage. The average choroidal thickness of RE (3 eyes) was 328 μm and that of the LE (2 eyes) was 302 μm which was not much higher than that of normals. Also there was no significant correlation between the choroidal thickness and presence or absence of subretinal fluid.

There are only a few published case reports on OCT findings of APMPPE in literature. Earlier reported OCT findings in APMPPE include increased reflectance of outer retinal layers without much increase in the retinal thickness at the site of placoid lesions, presence of subretinal fluid, focal disruptions of RPE and IS-OS junction. To the best of our knowledge there are only three case reports on SD-OCT findings in APMPPE to date. Lee et al8 has described presence of compartmentalized sub retinal fluid lined with septae at the macula and in the peripapillary retina in his patient at the time of presentation who had features similar to VKH. Two of our patients (patient 4, 5) had similar features. The fluid was not seen when OCT was repeated 5 days later in his patient. Our repeat scans were taken much later (1 month) and hence the time of disappearance of fluid would have been earlier. Partial reappearance of IS-OS junction and reorganization of OS/RPE region was demonstrated in the 3 month OCT in Lee’s series but similar changes were seen much earlier in our cases (1 month). Montero et al9 has described the location of fluid as intra retinal but the presence or absence of macular detachment was not specified. We could clearly demonstrate the location of fluid beneath the elevated IS-OS junction. Cheung et al10 demonstrated relatively well preserved RPE when changes occurred in the ONL and IS-OS junction in the early stages of the disease. Our cases had similar early changes in the IS-OS junction occurring before changes in the RPE layer.

**Conclusion:**

SD-OCT features in acute and healed stages of APMPPE
suggest primary insult of photoreceptor layer which may be triggered by an inflammatory mechanism rather than a vascular one. However more extensive studies with newer imaging modalities and larger number of patients and longer period of follow up are needed to confirm this hypothesis.

References

Dr. N. Sandhya joined Giridhar Eye Institute as Consultant in 2004. She underwent a short term training in Uvea in Sankara Nethralaya, Chennai, after her MS and DNB. Currently she is a Senior Consultant in Cataract, Uvea and Glaucoma services in Giridhar Eye Institute.