Multimodal Imaging of the White Dot Syndromes and Related Diseases
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Abstract
The white dot syndromes encompass a group of rare posterior uveitis conditions that are characterized by outer retinal and/or choroidal hypopigmented lesions that are thought to be inflammatory in nature. The size, shape, and location of lesions in the fundus aid in differentiating these conditions. Multimodal imaging, including modalities such as fundus autofluorescence, optical coherence tomography, fluorescein angiography, and indocyanine green angiography, among others, has become integral in diagnosing and monitoring many of the white dot syndromes. Furthermore, multimodal imaging modalities have provided insights into the pathogenesis and exact sites within the retina and choroid affected by white dot syndromes.

Keywords: Uveitis; White dot syndromes; Multimodal imaging

Introduction
The white dot syndromes (WDS) comprise a group of diseases characterized by lesions of the outer retina, retinal pigment epithelium, choriocapillaris, choroid or a combination of these sites [1,2]. The WDS are hypothesized to have an inflammatory etiology, and this is more evident for certain conditions, such as birdshot chorioretinopathy (BCR), in which vitreous inflammation and retinal vasculitis often accompany the choroidal birdshot lesions. In many of the other WDS, inflammation of the anterior chamber and vitreous cavity may be lacking. While the WDS often present with symptoms of blurred vision, floaters, photopsias, and scotomata, fundus examination and imaging reveal distinct findings, including the specific location, size, and configuration of the lesions, allowing distinct classification of the disease.

Continuing advancements in ocular imaging technologies now allow for detailed assessment of both the anatomy and function of many posterior segment structures through multimodal imaging. These imaging modalities include fundus autofluorescence (FAF; structure and function of RPE), optical coherence tomography (OCT; cross-sectional view of vitreoretinal and choroidal structure), fluorescein angiography (FA; assessment of retinal vasculature), indocyanine green angiography (ICGA; assessment of choroidal vasculature), as well as wide-field technologies that encompass many of these modalities. Combining the information provided by these various modalities allows the clinician to identify the particular site of pathology aiding in diagnosis and gauge the severity of disease.

Multimodal imaging is often useful in the diagnosis and management of posterior segment disease. This is especially true for WDS. This review will focus on the characteristic multimodal imaging findings for several WDS in which multimodal imaging is especially useful.

Birdshot chorioretinopathy
Birdshot chorioretinopathy (BCR), which has also been referred to as vitiligino us chorioretinitis, is an inflammatory posterior uveitic syndrome characterized by deep small-to-medium-sized round or oval hypopigmented choroidal lesions radiating from the optic nerve in a pattern similar to birdshot from a shotgun (Figure 1) [3,4]. Birdshot lesions are easily detected by the 635 nm laser on Optos’ imaging as perivascular choroidal lesions (Figure 1) [5]. ICGA shows characteristic hypofluorescent choroidal spots that correspond to and are typically greater in number than the clinically apparent lesions during active disease (Figure 2) [6]. Hypoautofluorescent ICGA lesions may resolve with immunosuppressive treatment.

Vitreous inflammation and retinal vasculitis are often present as well, and FA is used to diagnose and monitor the vasculitic component. Furthermore, FA may demonstrate optic nerve hyperfluorescence, macular edema, retinal non-perfusion, or retinal neovascularization in advanced cases. OCT is most useful in evaluating for macular edema, which is the most common cause of vision loss in patients with BCR [7]. FAF abnormalities are not uncommon in birdshot chorioretinopathy, but interestingly, they do not often overlap with underlying choroidal inflammatory birdshot lesions (Figure 1) [8-10]. This suggests that inflammatory damage may be occurring separately in the choroid and overlying outer retinal structures. Macular hypofluorescence, indicative of atrophy, is associated with poor visual acuity [9].

Acute posterior multifocal placoid pigmentary epitheliopathyp
Acute posterior multifocal placoid pigmentary epitheliopathy (APMPPE) is characterized by large plaque-like posterior pole lesions at the level of the RPE and inner choroid [11]. APMPPE generally affects young (typically <30 years but can be older) otherwise healthy individuals often following a viral illness [2]. APMPPE seems to develop in women and men equally and is usually, but not always, bilateral. Lesions may resolve spontaneously without treatment; however, in more severe cases, outer retinal disruption with corresponding scotomata is permanent.

During the acute phase of the disease, APMPPE presents with creamy deep placoid lesions on fundoscopy (Figure 3). FA during acute disease shows early hypofluorescence with progressive irregular staining of lesions (Figure 3) [11]. ICGA shows early hypofluorescence that persists into the late frames (Figure 3) and often is larger in area than the visible lesions on exam [12]. OCT demonstrates outer retinal and RPE disruption corresponding to the
lesions, and in some cases, outer retinal cysts have been described [13,14]. FAF imaging may reveal a spectrum of abnormalities ranging from mostly hypoautofluorescent lesions to a mottled signal of mixed hyper- and hypo-autofluorescence, at times with a hyperfluorescent halo surrounding the lesion (Figure 3) [9,15,16]. Debate continues as to whether the primary site of pathology lies in the RPE or choriocapillaris (i.e. early hypofluorescence on FA may be due to blockage from inflamed RPE or choriocapillaris non-perfusion). As suggested by ICGA studies twenty years ago, [17] emerging studies using OCT angiography (OCTA) have demonstrated choriocapillaris non-perfusion in APMPPE [18].

The acute phase of APMPPE generally resolves over the course of weeks to months [1,2]. Smaller lesions may resolve spontaneously with little evidence of prior pathology on ophthalmoscopy. However, larger lesions often evolve into areas of coarse deep retinal pigmentary changes (Figure 4). Areas of ICGA hypofluorescence, both early and late, generally improve with time. OCT may show some reconstitution of outer retinal structures, but FAF often remains abnormal in the area of previous lesions (Figure 4). OCT and FAF are especially useful in monitoring APMPPE because they provide rapid non-invasive assessment of lesion size and activity.
Serpiginous choroiditis

Serpiginous choroiditis, also known as geographic helicoid peripapillary choridopathy, classically presents with helicoid or geographic white-to-grey peripapillary lesions that extend outward from the disc in a serpentine configuration [19,20]. Vision is lost when the fovea becomes involved. A variant referred to as macular serpiginous choroiditis presents with similar lesions predominantly affecting the macula, often with a poorer prognosis given the high frequency of foveal involvement [21,22]. Serpiginous choroiditis is characterized by periods of disease activity and remission with recurrent activity often occurring at the edge of previous lesions [19,20]. With time, lesions evolve into chorioretinal atrophy. Given the recurrent nature of the disease, lesions often appear to have areas in multiple stages of activity with some areas appearing more active or atrophic than others. Serpiginous choroiditis has been associated with tuberculosis (TB) infection in endemic areas [23]. In patients who are not infected with TB, serpiginous choroiditis is thought to be driven by an autoimmune inflammatory reaction, and immunosuppression is often employed in an attempt to preserve vision by halting progression and preventing recurrent disease [24].

During active disease, serpiginous choroiditis typically presents with large peripapillary hypopigmented helicoid lesions extending outward from the disc in a serpentine configuration (Figure 5) [24]. FAF imaging reveals hypoautofluorescence in areas of atrophy, while more active areas are typically hyperautofluorescent (Figure 5) [9,25,26]. OCT shows disruption of the outer retinal structures and RPE (Figure 5). Intra- and sub-retinal fluid may be present, especially at the edges of active lesions. FA shows early hypofluorescence with progressive staining of the lesions later in the angiogram (Figure 6). As with APMPPE, OCT and FAF are especially useful in monitoring serpiginous choroiditis because they provide rapid non-invasive assessment of lesion size and activity [9].

Ampiginous chorioretinitis

Ampiginous chorioretinitis, also known as relentless placoid chorioretinitis, presents with extensive deep amoeboid-shaped lesions similar to APMPPE but has a progressive course akin to serpiginous chorioretinitis with lesions often extending through the posterior pole and into the peripheral retina [2,27]. As in APMPPE, a viral prodrome is often observed; however, the precise pathogenesis of this disease is unknown. Given the severe presentation of these patients, immunosuppression with systemic corticosteroids is often employed during acute disease and long-term steroid-sparing therapy may be required [2].

During acute disease, ampiginous lesions appear as creamy deep amoeboid-shaped lesions, similar to those in APMPPE, but often
dispersed throughout the posterior pole and extending into the retinal periphery (Figure 7). OCT shows outer retinal and RPE disruption corresponding to the lesions (Figure 7). Intra- and sub-retinal fluid may be present, especially at the edges of active lesions. FAF demonstrates a network of abnormal signal with areas of mixed hypofluorescence, often at the center of lesions, and hyperfluorescence, often at the lesion borders (Figure 7). FA shows early hypofluorescence with late staining. During convalescence, lesions often contract and become more pigmented on fundoscopy (Figure 7). On FAF, convalescent lesions appear more hypoautofluorescent reflecting permanent RPE derangement. As with APMPPE and serpiginous chorioretinitis discussed above, OCT and FAF imaging are useful for both diagnosis and monitoring of ampigious chorioretinitis.

Multifocal choroiditis and panuveitis & punctate inner choroidopathy

Multifocal choroiditis and panuveitis (MCP) is an idiopathic panuveitis characterized by discrete, variably sized, chorioretinal lesions throughout the fundus accompanied by an inflammatory reaction in the vitreous cavity and often in the anterior chamber. Punctate inner choroidopathy (PIC) is an uncommon idiopathic inflammatory chorioretinitis characterized by multiple, small (100-300 µm), discrete, yellow-white, posterior pole lesions [2,28]. Patients with PIC generally lack signs of inflammation in the anterior chamber and vitreous. MCP and PIC are more common in young moderately myopic females and are generally bilateral. Choroidal neovascularization (CNV) may develop and is an important cause of vision loss in MCP and PIC. Given these similarities, MCP and PIC may represent a spectrum of disease rather than independent disease processes [29]. Furthermore, disruption of outer retinal structures on OCT, similar to that seen in acute zonal occult outer retinopathy (described below), beyond the individual chorioretinal lesions has been reported in cases of MCP and PIC [30-32].

The chorioretinal lesions in MCP and PIC may have indistinguishable features on multimodal imaging [29]. FAF imaging of active lesions
tends to show a hypoautofluorescent center with surrounding hyperautofluorescence (Figure 8) [9,33,34]. Lesions become more uniformly hypoautofluorescent once scarred and inactive. FAF may show lesions not yet apparent by ophthalmoscopy [35]. Therefore, FAF is an important imaging tool in monitoring disease progression in patients with MCP. OCT typically shows hyper-reflective outer retinal nodular lesions corresponding to clinically apparent lesions with more widespread disruption in the surrounding outer retinal architecture.

Multiple evanescent white dot syndrome

Multiple evanescent white dot syndrome (MEWDS) is an idiopathic, presumed inflammatory condition characterized by multiple outer retinal white dots and foveal granularity (Figure 9) [36]. MEWDS is typically unilateral, affects women more commonly than men, and is often preceded by a viral prodrome. This disorder is commonly transient with resolution of visual symptoms and retinal anatomy over the course of weeks to months.

MEWDS lesions are typically hyperautofluorescent on FAF imaging (Figure 9) [37,38]. FA shows characteristic "wreath-like" hyperfluorescence of lesions that persists into late frames (Figure 9). ICGA typically shows hypofluorescent spots in late frames [39]. OCT shows disruption of photoreceptors, specifically the ellipsoid zone and outer segments, in areas corresponding to individual lesions (Figure 9) [25,38,40]. Reconstitution of outer retinal architecture may be seen with convalescence.

Acute zonal occult outer retinopathy

Acute zonal occult outer retinopathy is a rare condition characterized by acute zonal loss of outer retinal function with minimal ophthalmoscopic findings [41]. Photopsias and scotomata are commonly experienced by patients with AZOOR, and this condition predominantly affects young women. Electroretinography is often abnormal. The pathogenesis has been suggested to involve viral infection of the RPE with subsequent inflammatory insult.

Fundoscopy is often normal or may reveal subtle pigmented abnormalities, often in the peri-papillary region (Figure 10). FAF findings can be variable ranging from normal, to areas of stippled hyper- and hypoautofluorescence, to areas of sharply demarcated hypoautofluorescence (Figure 10) [42]. FA typically shows early hyperfluorescence from transmission defect that fades in later frames [43]. OCT of affected areas shows disruption of outer retinal structures, including the ellipsoid zone and photoreceptor outer segments (Figure 10).

Conclusions

As described above, many WDS have characteristic findings on multimodal imaging that aid in distinguishing the specific WDS. Additionally, multimodal imaging is important in monitoring for
progression and response to treatment in several of these conditions. Further advances in imaging technology, such as OCT angiography and adaptive optics in combination with either confocal scanning laser ophthalmoscopy or OCT, will undoubtedly provide additional information on the anatomic and functional nature of WDS.

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References


