White-Spot Syndromes of the Retina

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Objectives
At the conclusion of the program, the attendees will be able to:
1. recognize the various white-spot syndromes of the retina
2. initiate appropriate diagnostic tests of patients with the white-spot syndromes
3. initiate treatment, if appropriate, of patients with white-spot syndromes

Questions
I. The AZOOR complex includes all of the following except:
   1. MEWDS
   2. MFC
   3. AZOOR
   4. Acute idiopathic blind spot enlargement
   5. Unilateral idiopathic acute maculopathy

II. All of the following have a female predominance except:
   1. MEWDS
   2. MFC
   3. AZOOR
   4. APMPPE
   5. AIBSE

III. Corticosteroid therapy is indicated for patients for which two of the following?
   1. Serpiginous choroiditis
   2. MEWDS
   3. AIBSE
   4. AZOOR
   5. Birdshot chorioretinopathy

Introduction
Many infectious and noninfectious inflammatory conditions of the eye are characterized by the development of white spots in the retina and choroid. After thorough investigations for systemic diseases and infectious causes there are a variety of apparent autoimmune inflammatory diseases that are idiopathic and are called the white-spot syndromes. We will review the following conditions: multiple evanescent white-dot syndrome, multifocal choroiditis and panuveitis, punctate inner choroidopathy, acute macular neuroretinopathy, acute idiopathic blind spot enlargement syndrome, acute zonal occult outer retinopathy, acute posterior multifocal placoid pigment epitheliopathy, serpiginous choroidopathy, relentless placoid choroiditis and birdshot chorioretinopathy. Some of these entities have been lumped together by Dr. Gass and called the AZOOR Complex. This concept will be reviewed as well. In addition, a recent theory has suggested that these apparent inflammatory diseases are related to autoimmune phenomenon. The common genetic hypothesis of autoimmune inflammatory diseases suggests that there are in the human genome greater than 20 loci that predispose to immune dysregulation (but are non-disease specific) and lead to autoimmune diseases such as diabetes Type I, demyelinating disease, autoimmune thyroiditis, inflammatory bowel disease, diabetes Type I, and others. The application of this hypothesis to the white-spot syndromes will be described.

MEWDS
The multiple evanescent white-dot syndrome (MEWDS) was first described in 1984, and is an acute multifocal retinopathy that involves the outer retina and the pigment epithelium and probably to some extent the choroid. The disease is almost always unilateral although rarely it may be bilateral but asymmetric. The course is almost always uniphasic and heals over a period of one to two months. In rare cases, a chronic recurrent variety of the condition is seen which may be unilateral or bilateral. About three-quarters of the patients are female. They are usually young, healthy females between the age of 15 and 47. They complain of unilateral loss of vision, photopsias, usually in the temporal visual field, and they may complain of enlarged blind spot in the temporal visual field. The characteristic appearance in the fundus is multiple 100-200 micron white dots that appear to be at the level of the outer retina and pigment epithelium. These dots are usually most marked in the perifoveal area and become less prominent outside the vascular arcades. They usually do not reach the fovea. However, the fovea is often abnormal with a finding of granularity consisting of multiple small yellow-orange or whitish granules in the fovea itself with a loss of foveal reflex. There may be vitreous cells and there may be very mild anterior chamber reaction. Optic disc edema, retinal vascular sheathing and confluent opacification of the retina involving the peripapillary zone, or more rarely other areas of the fundus are seen. Some patients when they first present may have pigmented chorioretinal scars in the fundus. Other patients may develop these scars as they are followed with chronic, recurrent disease. The involved eye often has an afferent pupillary defect and substantial temporal visual field loss with a very enlarged blind spot. Fluorescein angiography shows focal areas of punctate hyperfluorescence often in a “wreath-like” configuration corresponding to the visible white dots.
Indocyanine angiography shows hypofluorescence of the majority of lesions with many more lesions seen than are observed clinically. These lesions often cluster around the nerve, probably accounting for the blind spot enlargement. With fluorescein dye, the optic disc often is hot and leakage from the deep retina may be seen. Classic, cystoid macular edema is not seen. In the acute phase, the electroretinogram and the early receptor potential are markedly diminished.

The striking thing about MEWDS is that patients recover. Over a period of several weeks to one to two months, an improvement in central vision is seen with a decrease in photopsias and a shrinking of the enlarged blind spot. Patients return to a normal blind spot although this may take a very long period of time. The electoretinogram also shows recovery. The extensive involvement of the ERG and of the multifocal ERG shows that this is a diffuse involvement of the photoreceptors. Although some authors have suggested primary choroidal vascular involvement, there is very little evidence to support this. There are one or two cases of choroidal neovascularization as a late complication of this inflammatory condition.

The cause of MEWDS is unknown. No therapy is necessary as the patients show healing and have an excellent visual outcome. A few patients go on to develop a chronic, recurring disease for which there is no treatment to date.

**AMN**

Because of the association of MEWDS with acute macular neuroretinopathy, I will next review this entity. Acute macular neuroretinopathy is a rare disease first described in 1975. It is seen in young adults, mostly women. It may be unilateral or bilateral. The patients complain of decreased vision, and testing with an Amsler grid shows small, pericentral scotomas that are reproducible and can be drawn easily in the macular area. The patients may also complain about an enlarged blind spot in the involved eye.

Examination reveals an absence of obvious inflammation or white spots. Dark red or brownish lesions are seen in the perifoveal area. The lesions may be circular or wedge-shaped. There has been much debate about the location of the changes. They appear to be deep, although there is some controversy as to whether they involve the retina, the pigment epithelium or other structures in the eye. The fluorescein angiographic picture is usually normal. The electoretinogram is usually normal. The patients do not evolve into another white-spot syndrome. However, the patients do show a gradual improvement and the lesions may become less prominent, although they may not disappear completely. It is classically said that recurrences do not occur in this condition, but we have seen one patient with multiple recurrences affecting both eyes.

The cause of acute macular neuroretinopathy is uncertain. It has been associated with the use of adrenergic medications. There is a similarity of the changes to the depressions in the retina seen with ischemia, but acutely cotton-wool spots are not observed. It has been suggested that AMN may be the result of occlusion of the deep layer of retinal capillaries.

Gass and Hamed described two patients who demonstrated MEWDS and acute macular neuroretinopathy at different times in their clinical courses. Both diseases are seen in young females and so this makes the occurrence of these two rare diseases in a single individual of great interest.

**MFC**

The commonest of these white-spots syndromes in our practice is the multifocal choroiditis and panuveitis syndrome. We believe that this is the same entity as punctate inner choroidopathy as patients may have lesions resembling punctate inner choroidopathy in one eye and multifocal choroiditis in the other eye. This entity also is called pseudo-ocular histoplasmosis and consists of multiple foci of choroiditis scattered in the post pole and periphery of the eye. When the lesions predominate in the macular area, there is very little intraocular inflammation and there are serous detachments in the areas of active choroiditis, it is called punctate inner choroidopathy. When the lesions cluster elsewhere in the fundus, then the entity is often called multifocal choroiditis. The patients show a variable amount of vitreous inflammation and sometimes mild anterior chamber inflammation. There may be retinal vascular sheathing and obliteration. Multiple foci of choroiditis are usually seen. These may be old and pigmented or active. Subretinal fibrosis develops between chorioretinal scars. Patients develop a napkin-ring type of scarring around the optic nerve in many cases. The patients complain not only about blurred vision, but they also may complain of an enlarged blind spot in the temporal field with photopsias. The patients may be difficult to differentiate from the presumed ocular histoplasmosis syndrome. In both conditions, there may be peripapillary scarring, multiple chorioretinal scars, choroidal neovascularization and peripheral Schlaegel lines. However, the lesions in multifocal choroiditis are often clustered. They are often signs of intraocular inflammation and the amount of subretinal scarring and bridging of chorioretinal scars is much greater with multifocal choroiditis than POHS. Choroidal neovascularization is a common complication of both conditions, but is very marked in multifocal choroiditis and may result in loss of vision. Indocyanine angiography shows multiple hypofluorescent lesions.
clumped around the optic nerve in some patients. The ERG shows a widespread photoreceptor dysfunction in many cases and, in fact, the visual loss may be much greater than can be expected from looking at the scars. The loss of vision in patients with multifocal choroiditis may be due to active choroiditis or choroidal neovascularization. It may be difficult to distinguish the two when the lesion is new and it may be necessary to treat it with steroids or follow the patient closely to determine if choroidal neovascularization is present in the lesion. Often there is both inflammation and choroidal neovascularization. The treatment of the inflammation is usually systemic or periocular corticosteroids, whereas the treatment of the choroidal neovascularization may be a combination of steroids and thermal laser (if the lesion is extrafoveal), or photodynamic therapy if the lesion is subfoveal.

During the acute phase of multifocal choroiditis, in addition to chorioretinal scars, there may be whitish lesions present in the outer retina. These lesions do not have the wreath-like pattern of hypofluorescence on FA seen in MEWDS. These lesions can disappear completely or evolve into chorioretinal scars. Healing of the lesions is accelerated by the use of corticosteroids and the lesions can disappear dramatically. A frequent complication however is the development of choroidal neovascularization. Therapy of multifocal choroiditis consists of immune suppression using corticosteroids or other agents during acute episodes. Treatment of choroidal neovascularization can include corticosteroids, photodynamic therapy or thermal laser. Patients often have multiple recurrences and relapses and choroidal neovascularization will often be a major problem.

No definite etiology of multifocal choroiditis has been demonstrated, although viral causes have been suggested. However, it appears as though it is autoimmune as immune suppression suppresses the disease.

**AIBSE**

The neuro-ophthalmology community uses the term acute idiopathic blind spot enlargement (AIBSE). These are young, healthy patients, often females, who present with an enlarged blind spot without associated retinal or choroidal or disc findings. It has been my experience and others that these patients often have either MEWDS or multifocal choroiditis, and the acute lesions may have faded or be very subtle. In particular, MEWDS lesions can be extremely subtle and can disappear within several weeks leaving behind the enlarged blind spot. In addition, during the early phase of multifocal choroiditis, the chorioretinal disease may be rather unimpressive, but the blind spot enlargement may be rather marked. It seems likely that the entity of acute idiopathic blind spot enlarge-

**AZOOR**

Acute zonal occult outer retinopathy (AZOOR) occurs in young, healthy individuals who develop unilateral or bilateral areas of dysfunction of the peripheral outer retina. They may have photopsias along the margins of these scotomas. The retina in the area of involvement often appears normal initially. Even with evolution of the lesions, the retinal abnormalities are often subtle. There may be pigmentary mottling, which can be very mild but may eventually resemble segmental retinitis pigmentosa. Patients may have relapsing episodes of loss of vision in the peripheral retina of one or both eyes. Electroretinogram is usually abnormal in the involved eyes. Patients may show recovery of visual function in this area, but in a few patients, relentless progression is seen with loss of peripheral vision. However, bilateral blindness is extremely rare. Patients who develop segmental, episodic areas of loss of peripheral vision should be suspected of having AZOOR. A patient who has had multiple episodes may begin to resemble other diffuse photoreceptive dysfunctions such as retinitis pigmentosa, diffused unilateral subacute neuroretinitis, cancer associated retinopathy and other diffuse photoreceptive abnormalities.

Patients with AZOOR have been treated with corticosteroids and antiviral drugs in hopes of affecting the course of AZOOR, but they do not seem to help. Fortunately, most cases stabilize after six months of activity and bilateral severe loss of vision is the exception in this condition. The fundus findings may be very impressive with large segmental areas of bone spicule pigmentation. There often are peripapillary pigmentary changes as well. These patients do not show the white dots of MEWDS or the punched out scars seen with multifocal choroiditis.

**AZOOR Complex**

Because of similarities in their clinical presentation, Gass has suggested that the entities of MEWDS, multifocal choroiditis (and PIC), acute idiopathic blind spot enlargement and AZOOR may represent part of the spectrum of the same disease. He calls this the AZOOR complex. Evidence in favor of this hypothesis includes the presence of photopsias, the presence of blind spot enlargement, occurrence in young, healthy patients, often females. The presence of pigmented scars in some patients with MEWDS and white lesions in some patients with multifocal choroiditis are taken as further evidence that these conditions may be related. The occurence of
acute macular neuroretinopathy in patients with MEWDS has also resulted in this being included in the AZOOR Complex, although the clinical findings are different. Electroretinographic abnormalities are also present in many of these patients.

Because of the distinct, clinical courses with these various conditions, I have maintained that these are separate entities, although they are overlapping in a few patients and have similarities in their symptomatology. The presence of the photopsias indicates photoreceptor abnormalities. The presence of the electroretinographic abnormalities indicates diffuse photoreceptor abnormalities, sometimes more severe than suspected from the white dots. This is true of MEWDS and multifocal choroiditis. However, the clinical courses are different. MEWDS patients get better and do not evolve into multifocal choroiditis or AZOOR. Multifocal choroiditis patients sometimes have a relentless ongoing course with scarring and in the end stage may have a diffuse loss of field and vision, but are distinguishable by the clinical appearance from AZOOR. AZOOR patients do not develop obvious chorioretinal scars or white dots. Because these entities are distinguishable clinically, it is of value until we understand their etiologies to separate them into the various categories. In addition we know, for example, that MEWDS patients require no treatment whereas patients with multifocal choroiditis may need antiinflammatory therapy or treatment of choroidal neovascularization.

**Birdshot Chorioretinopathy**

This is a chronic inflammatory condition affecting the posterior segment. In its early stages it may be difficult to distinguish from an intermediate uveitis. However, with the development of the cream-colored lesions in the fundus, resembling birdshot lesions, the patients do become distinguishable from other forms of uveitis. In addition, there is a strong association with HLA-A29, with this being present in greater than 90% of patients and in only 5% of the population. Patients with birdshot are often middle-aged and present with vitreous debris, retinal vascular leakage, cystoid macular edema, and disc leakage.

The patients note floaters, decreased vision, photophobia, color vision problems and even night blindness. The electroretinogram, in advanced cases, is abnormal. The patients have only mild anterior segment inflammation, variable vitritis, no clear-cut snow banks, but they have retinal vascular leakage and the birdshot lesions. The uveitis can be suppressed with corticosteroids or other immune suppressive agents. This can result in a dramatic improvement of vision. However, when these agents are tapered, the condition often will return. A low level of corticosteroids or another agent may be required to suppress the condition, and we often have the patient on low doses of steroids and cyclosporine.

Patients with birdshot chorioretinopathy may develop chronic cystoid macular edema, epiretinal membranes, choroidal neovascularization and occasionally retinal vascular occlusions with neovascularization of the retina or optic disc.

**APMPPE**

Acute posterior multifocal placoid pigment epitheliopathy was first described by Gass in 1968. The disease is seen in young patients and unlike many of these other conditions is seen equally in males and females. The patients usually present with bilateral visual loss; they develop acute lesions that appear over a period of several weeks and then heal over a period of several weeks. Late recurrences are extremely rare, but do occur. The lesions are geographic and scattered throughout the posterior pole and sometimes just outside the arcades. The fovea may be involved. Cream-colored lesions that are placoid are seen at the level of the outer retina or pigment epithelium. The fluorescein angiogram is characteristic in showing hypofluorescence of the acute lesions, which has been attributed either to blockage by swollen RPE or hypoperfusion of the choriocapillaris. Indocyanine green also demonstrates acute hypofluorescence of the lesions. The patients may rarely show scleritis, or iritis and may have optic disc edema and retinal vascular sheathing. Patients may also have meningeal symptoms including stiff neck, headache, hearing loss, and may have elevated protein levels and cells in the spinal fluid. This is a meningoencephalitis in addition to being an inflammatory chorioretinopathy.

The lesions heal rapidly over a period of several weeks and pigment. There is a recovery of vision so that even when the fovea is involved the foveal visual acuity is usually pretty good. Most patients improve to 20/30 or better, but there may be some permanent loss of vision and a few patients can get late choroidal neovascularization.

The cause of APMPPE remains uncertain. A viral cause has been suggested in clinical cases but some patients develop APMPPE-like syndromes in the setting of autoimmune disease such as polyarteritis or lupus or in response to drugs that may precipitate an immune complex disease. It seems likely that APMPPE is immune mediated.

A few patients have been reported to die from cerebral vasculitis. Severe cases are sometimes treated with corticosteroids, although the outcome is good without corticosteroids and there is no evidence to date that the short-term or long-term outcome is affected by corticosteroids.
Some patients with APMPPE-like lesions continue to develop fresh choroidal lesions over long periods of time extending for months or even years. In addition, they develop hundreds of lesions that extend all the way from the posterior pole to the far periphery. The lesions are similar in appearance to the APMPPE lesions, but we have called this syndrome relentless placoid chorioretinitis. It appears to respond to corticosteroids and other immune suppressive agents (e.g., cyclosporine).

Serpiginous Choroiditis
This disease is seen in young to middle-aged patients, usually third to sixth decade. It often becomes bilateral, although acutely the lesions may be unilateral. The acute lesions may involve the macula or the peripapillary area. Patients present with placoid lesions that result in loss of visual function in that local area. The patients are healthy systemically and no family predisposition is apparent. They complain of loss of central vision or paracentral scotomas. Vitreous cells are seen. The fundus lesions vary in size from one to several disc diameters. The lesions that begin peripapillarily extend out in a serpentine fashion from the disc toward the periphery. The macular lesions are more geographic in appearance and may extend out to involve the midperiphery. The lesions appear gray-white or yellow or at times even have a greenish hue. There may be some subretinal fluid present. The lesions individually heal into chorioretinal scars with development of chorioidal atrophy. The amount of atrophy is usually greater than what is seen with APMPPE. There is also a more significant, permanent loss of vision that corresponds to the lesions. If the fovea is involved, the vision often does not recover. Patients often develop recurrences, usually in a satellite fashion adjacent to old, healed lesions. This is very different than the behavior of APMPPE. In addition, patients may develop choroidal neovascularization adjacent to areas of scarring. Visual loss may be due either to the choroiditis or the choroidal neovascularization.

Treatment of serpiginous choroiditis with corticosteroids or the immune suppressive agent does appear to result in more rapid healing of the lesions. In addition, the maintenance of a significant amount of systemic immune suppression seems to prevent recurrences. However, patients often flare up when the systemic medications are tapered. In addition, choroidal neovascularization is a major cause of visual loss. These lesions can be treated with thermal laser, if extrafoveal, or photodynamic therapy if subfoveal and occasionally subretinal surgery is indicated as well.

Serpiginous choroiditis may be immune mediated, but to date there’s very little evidence supporting this. It does respond to immune suppression. There are occasional patients where it is difficult to distinguish whether the patients initially have APMPPE or serpiginous choroiditis. In these occasional patients, the clinical cause will be quite distinct. The APMPPE lesions heal promptly and rarely show recurrences or relapses. The serpiginous choroiditis patients invariably have recurrences.

The Common Genetic Hypothesis of White-Spot Syndromes
The origin of these inflammatory, apparently autoimmune, conditions remains uncertain. There are examples of viral infections precipitating a white-spot syndrome. For example, MEWDS has been reported to follow varicella or adrenovirus infection. Similarly, APMPPE has been reported following viral infections. Yet there is no consistent viral cause of any of these conditions. In addition, the suggestion that these are autoimmune diseases is, so far, unproven. Many, but not all of them, appear to respond to immune suppression with corticosteroids or other agents. There are other features of the white-spot syndromes that must be explained by any theory of their pathogenesis. Many of them have a marked female predominance (often young, healthy myopic females). Some cases are apparently precipitated by vaccinations (e.g., hepatitis-B). Some cases appear to be precipitated by viral infections. Because of the similarity of these demographic factors to other autoimmune diseases, such as lupus and other acquired disease of connective tissue and inflammatory bowel disease, demyelinating disease, autoimmune thyroiditis, and Type I diabetes, it is suspicious that the white-spot syndromes may represent the same phenomenon, which are manifested primarily in the eye as the target organ. Kevin Becker, Ph.D., at the National Institutes on Aging has summarized the literature in regard to the human genome having non-disease specific loci that contribute to autoimmune disease. These genetic loci predispose to immune dysregulation and, depending upon interactions with other genes or environmental factors, the patient may develop a variety of autoimmune diseases, such as the conditions outlined above. This results in a familial clustering of these autoimmune diseases so that one finds not necessarily one specific autoimmune disease in the family, but examples of different autoimmune diseases. These diseases may be precipitated by a viral infection or a vaccination. These are probably interactions with other genes such as the HLA loci (for example, birdshot chorioretinopathy). We have hypothesized that these white-spot syndromes may represent autoimmune phenomena in the eyes. If we are correct, one would expect a higher incidence of autoimmune disease in families of patients with the white-spot syndromes. We have not done this study to date but on questioning several of these patients, it is apparent that they do come from autoimmune families. Because of this, we are
proposing a collection of data on patients and the first and second-degree relatives of patients with white-spot syndromes for familial hereditability studies. If this is productive, then familial studies looking for the genetic loci associated with white-spot syndromes can be done.

It seems likely that these will be the same loci as have been identified for more common systemic autoimmune diseases. It is interesting that in Gass’s recent review of AZOOR, 28% of his patients had other autoimmune diseases, particularly thyroiditis and demyelinating disease. It seems quite possible that the common genetic hypothesis of autoimmune inflammatory disease may explain the white-spot syndromes.

References

Answers to CME Questions
I. 5
II. 4
III. 1 and 5