WHITE DOT SYNDROMES
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The white dot syndromes (WDS) are a collection of diseases characterized by localized, circumscribed whitish lesions in the RPE or choroidal layers. They are of unknown etiology but are suspected to be inflammatory in nature and can be associated with uveitis. We present here selected representative cases of WDS seen by the Ocular Immunology and Uveitis Service. While many entities are easily distinguishable, some cases of overlapping signs and symptoms may occur. It is important to make the proper diagnosis as this has significant implications in terms of treatment and prognosis.

Multiple evanescent white dot syndrome (MEWDS)

Case: CG, a 28 year old, white female consulted for a 5 day history of decreased vision, photopsias, floaters of the right eye. There was no history of prodromal symptoms. The visual acuities were 20/40 OD and 20/20 OS. Slit lamp examination of the right eye revealed rare anterior chamber cells and 1-2+ vitreous cells; funduscopy showed slight optic nerve swelling, multifocal yellow-white dots about 1/5 disc diameter in size located mostly in the posterior pole but extending to the midperiphery (**Figure 1**). The left eye was normal.
Fluorescein angiography revealed early hyperfluorescence from these lesions with late staining. (**Figure 1**) A diagnosis of MEWDS was made. The patient was carefully observed and recovered 20/20 visual acuity after one month. There were no reported recurrences.

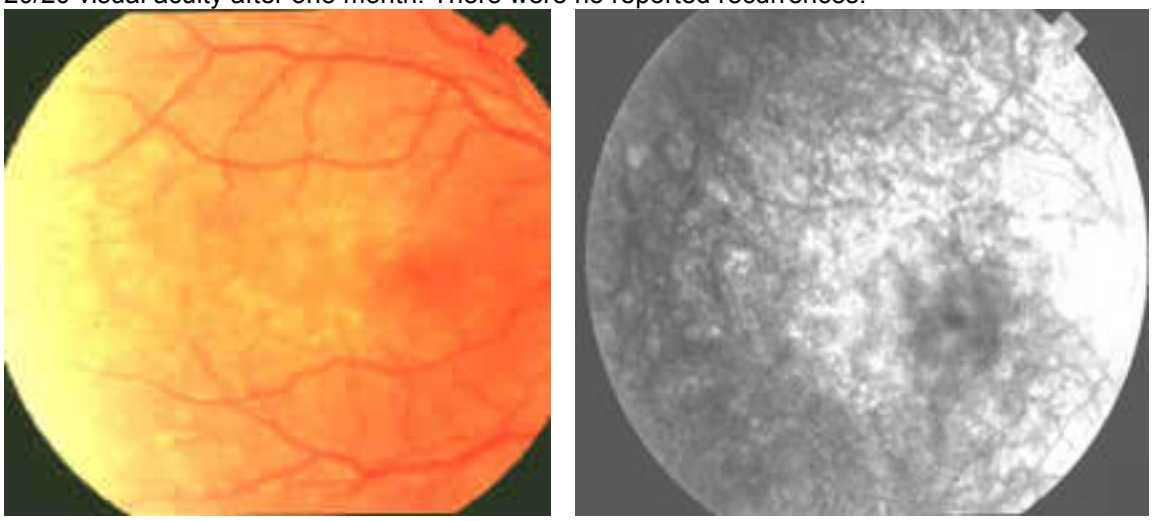


Figure 1. (Left) Multifocal shite dots at level of RPE. (Right) Hyperfluorescence and late staining from lesions

FEATURES OF MEWDS:

MEWDS is a relatively new disorder which was first described by Jampol and colleagues in 1984. [1] At least 60 cases have been reported. It is characterized by the following features:
1. Epidemiology
    a. Young patients aged 15 to 44 with a mean of 28 years
    b. Female predominance, original series, all women; 3:1
    c. No racial predilection
2.
Clinical Features
    a. Acutely decreased VA: 20/300-20/25
    b. Unilateral predominantly
    c. Viral prodrome in 25%

d. Occasional mild anterior chamber
e. Mild vitreous reaction in about 50%
f. LESION: White dots, discrete ,multiple, small 100-200, m m (1/10-1/5 DD), located in deep retina or RPE, each dot is made up of aggregates of many smaller white dots; distributed mainly in perifoveal and peripapillary regions, rarely involving the fovea, extending to mid-periphery
g. Asymmetric if bilateral
h. Macular granularity "grainy"
i. Irregular ILM reflex
j. Hyperemia or edema of optic disc common
h. Retinal splinter hemorrhages and venous sheathing rare1

3. VF [2]:
Enlarged Blind Spot
Paracentral and central scotomas

4. FA:
Early hyperfluorescence + late staining of lesions at RPE level
60% with disc capillary leakage with staining
Findings return to normal with residual subtle RPE defects [3,4]

5. ICG
Early, barely visible lesions; late hypofluorescence more than visible lesions which disappear on recovery

6. Electrophysiologic Tests: reversible [5]
Reduced ERG a-wave = photoreceptor dysfunction
Abnormal focal ERG = abnormal macular ERG, retinal dysfunction [6]
Prolonged Early receptor potential = RPE and outer retina dysfunction
Abnormal EOG = reduced light-to-dark ratio, impaired RPE function, reversible
Abnormal VER = decreased P100 component and prolonged latency suggestive of optic nerve dysfunction, reversible

7. Laser Densitometry
Areas of absent visual pigment not always corresponding to lesions. Partial recovery = RPE-photoreceptor complex abnormality [7]

8. Etiology
Undetermined = RPE-photoreceptor dysfunction
Infectious = associated with viral prodromes
Immunologic = case report of elevated IgG, IgM [8]; post Hep B vaccination [9]

9.Treatment: None, spontaneous recovery is the rulen [1]

10.
Prognosis
Excellent = most back to 20/20; 20/25-20/30 also possible
Recover time 1-16 weeks, average7
Rare recurrences [1]

Multifocal choroiditis and panuveitis

Case: LG, 61 year old from Massachusetts consulted for blurred vision, OU. She presented with a 6 months history of bilateral blurred vision and floaters. Existing medications included topical and oral steroids and Cyclogyl but experienced recurrent bouts of uveitis. Vision was 20/40 OU. Bilateral 2-3+ anterior chamber and vitreous cells were present as well as 1+ nuclear sclerosis.

Ophthalmoscopy revealed normal discs, bilateral macular edema and multiple deep, yellow retinal lesions especially in the periphery. (**Figure 2**) Lab work ups were negative for antinuclear antibodies, HLA-A29, Lyme, sarcoid, FTA-ABS, VZV. Raji cells and Epstein Barr titers were normal (1:40, ref. 1:10). Fluorescein angiography revealed hyperfluorescent lesions with late staining (**Figure 2**); electroretinograms showed generally depressed amplitudes suggesting widespread destruction. A trial of acyclovir (because of elevated VZV IgG) did not lead to improvement. Prednisone was then elevated to 60 mg daily with resolution of inflammation. However, while tapering, uveitis flare ups would develop. Cyclosporin A was then started at 200 mg by mouth daily with subsequent control of inflammation. The patient was followed up over 7 years and had relatively good control of his MCP. Final visual acuity was 20/30, OU.

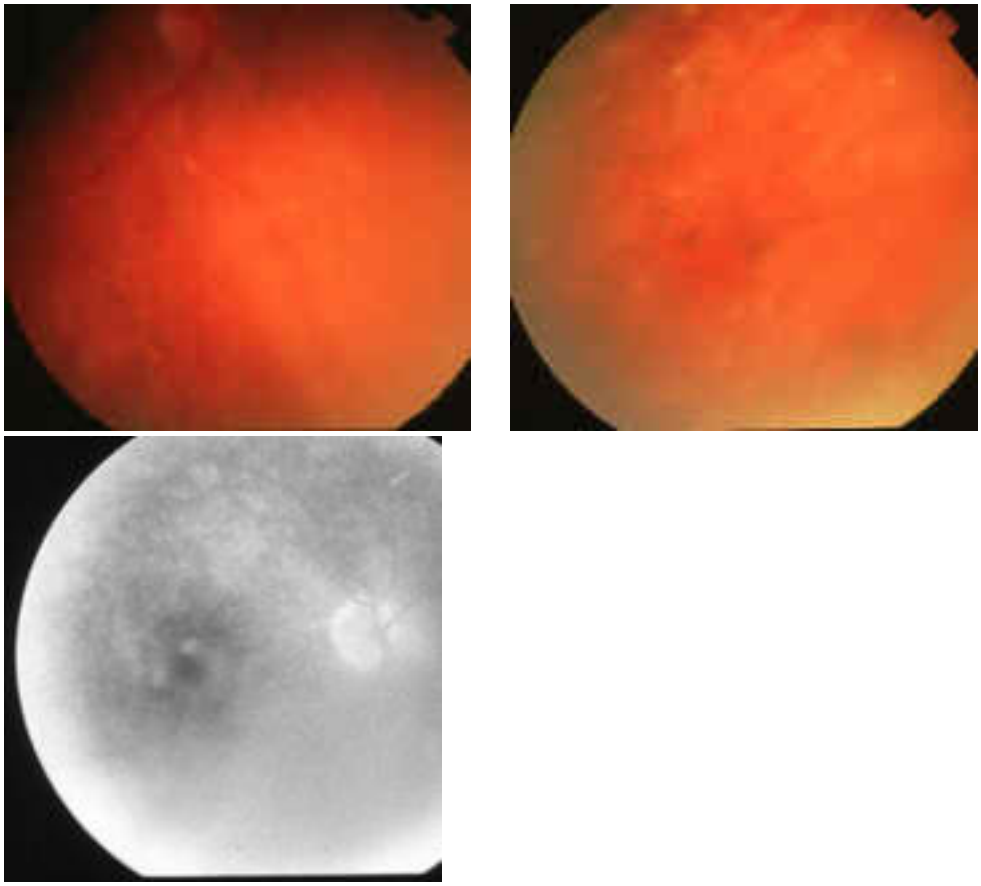


Figure 2: (Left & Center) Multifocal yellow lesions at the level of choroid and overlying vitritis. (Right) Hyperfluorescence and staining from lesions with associated cystoid macular edema.

FEATURES OF MCP:
First described by Nozik and Dorsch in 1973 [10], about 104 patients have been described in literature.
1. Epidemiology:
Age range 6-74 years old
Women comprise 80%
No racial predilection
Most patients are found in the histoplasmosis belt [10-12]
2.
Clinical Features
Bilateral in 80-96% though one eye often asymtomatic

Myopia associated with 88% of patients
Symptoms: blurred vision, metamorphopsia, floaters, scotomas, photopsia
VA range from LP to 20/20 though most patients worse than 20/100
Anterior segment has mild cells and flare in more than 2/3 of patients
1-3+ Vitreous cells found in > 90%
The lesions are typically small discrete spots about 200 micrometer in diameter but vary from 50 to 1000 um. They are usually round but sometimes polyglonal. Lesions are more concentrated in the periphery but posterior pole clustering has been reported. The lesions may number from a few to several hundred. Multiple active lesions may be present simultaneously. Active lesions are gray-yellow; resolving lesions are yellow-white. Inactive lesions are atrophic and "punched-out" in appearance with hyperpigmented rims. Over time, new lesions may evolve even in the absence of overt inflammation. Subretinal fibrosis may occur. (**Figure 3**) Histoplasma-like lesions are typically smaller and fewer. [10-12]

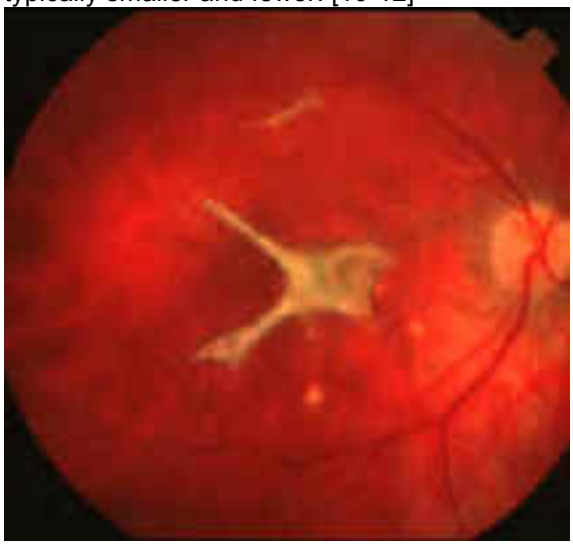


Figure 3. Subretinal fibrosis in MCP

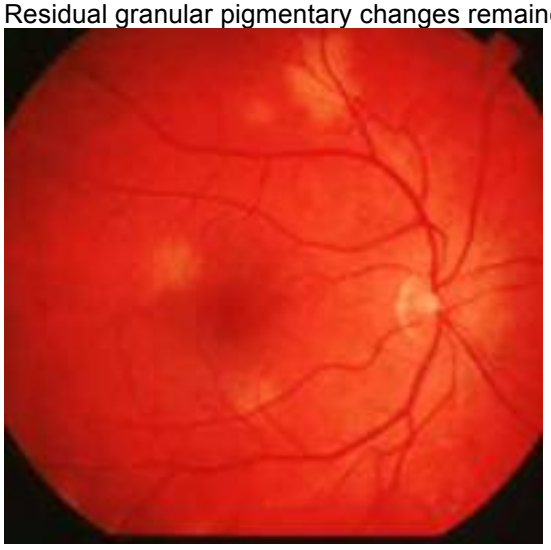
3. Visual Fields
Scotomas corresponding to lesions; blind spot enlargement [13]
4. FA:
Punched-out scars = RPE window defects, early hyperfluorescence with late fading
Active lesions = Early hyperfluorescence with late staining; cystoid macular edema (CME) may be present.
5. Electrophysiology
ERG = abnormal in half, may be mild or extinguished
EOG = usually normal
6. Etiology
Unknown
Suspected infectious causes: Epstein Barr virus, VZV, HSV, Histoplasma. An infection may also result in molecular mimicry and subsequent autoimmune disease
Immunologic abnormalities such as HLA-DR2 association suggest an autoimmune etiology. On histopathology, B cells and plasma cells are seen with complement and immunoglobulin deposition.
7.
Treatment
Steroids
Immunosuppressive therapy (CSA 4 mg/day)
8. Prognosis:
Guarded; VA is 20/200 or worse in 46% of patients; 51% are 20/80 or better
Causes of decreased vision include formation of choroidal neovascular network and cystoid

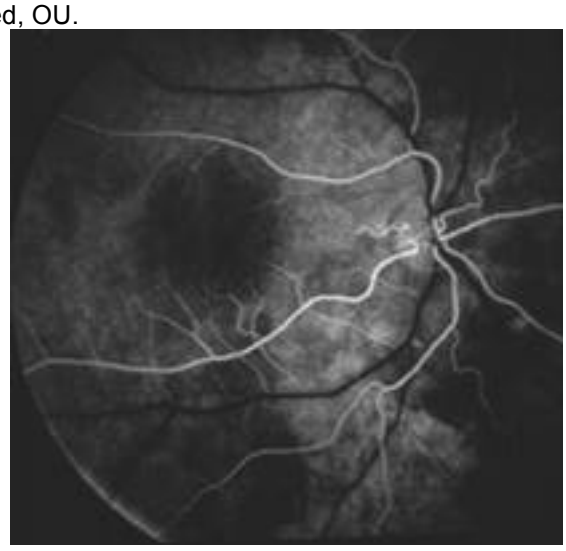
macular edema. [10-12]

Acute posterior multifocal placoid pigment epitheliopathy

Case: KB, 34 y.o. female consulted for "spots in vision whether eyes closed or open". 2 weeks PTC, spots in vision associated with severe headaches, nausea and vomiting which prompted hospitalization. CT Scans were negative. Patient diagnosed as "migraine". After a week, visual acuity worsened to 20/200 OD and 20/80 OS. She consulted with eye doctor who found increased IOP to 40 mm Hg OD and 36 mm Hg OS. Tobradex q 2 and Timoptic bid were started and the patient referred to the Ocular Immunology Service on 8/5/93.
VA: OD: 20/200 and OS: 20/70. Both cornea exhibited keratic precipitates. There was 3+ anterior chamber cells and flare, OU and 1/2+ vitreous cells, OU. Funduscopy revealed, OD: Slight blurring of nasal disk margins, arteriolar attenuation, retinal opacification in perpapillary area deep whitish spots at level of choroid and pigmentary disturbance of the macula; OS: Blurred nasal disk margins with inferior disc hemorrhage; deep well-demarcated yellow dots in the fovea, pigmentary disturbance in the macula having a "beaten-metal appearance". (**Figure 4**)

A fluorescein angriogram showed early blockage from the lesions and late hyperfluorescence. (**Figure 3**) Impression: APMPPE with neurologic symptoms R/O Bechet's, PAN, viral disorders. Workups were negative for FTA-ABS, Rickettsia, Lyme, ACE, RPR, ANCA, ANA. There were normal complement, Raji cell levels in the serum. Lumbar puncture revealed CSF pleiocytosis. The patient was started on Prednisone 80 mg with vision back to 20/20 in 2 weeks. A few new spots formed but lesions disappeared along with AC and vitreous cells. Residual granular pigmentary changes remained, OU.





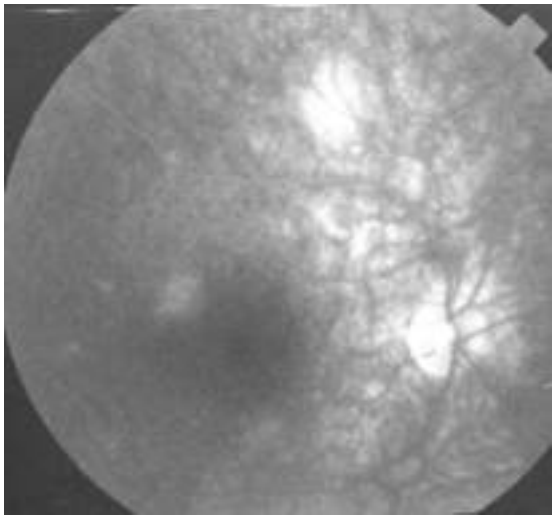


Figure 4: (Left) Multiple deep, 1/2-1 disk diameter white lesions. (Center) FA shows early blocked fluorescence and (Right) late hyperfluorescence form these lesions.

FEATURES OF APMPPE:

APMPPE was first described by Gass in 1968 [14]. Over 200 cases have been reported. Its clinical features have been well characterized while its etiology, like many of the WDS disorders is unclear:

1. Epidemiology

3rd decade of life, age range 8-66
no sex predilection
no race predilection

2.

Clinical Features

Acute visual loss in one eye over a few days, Metamorphopsia, scotomas, Other eye affected within a few days or weeks (delay of up to 3 years has been reported); bilateral in 75%. Common gastrointestinal or respiratory viral prodrome or may result after ampicillin and sulfonamide therapy with presenting VA, 20/20 to count fingers

LESION: flat, multiple, gray, cream or yellow "placoid" post-equatorial lesions, 1/8 to 1/4 disc diameter in size, occasionally confluent, usually starts at posterior pole and arise more peripherally to the original ones; new lesions may appear for up to three weeks after onset occasional associated vitreous cells, retinal edema or hemorrhage, retinal vasculitis and papillitis; rare serous retinal detachment; very rare CNVM has been associated with episcleritis, iritis, and PUK [14,15]

Systemic associations:

i. CNS: cerebral vasculitis, meningoencephalitis, and CSF pleocytosis with a[16]

ii. Others: erythema nodosum, microvascular nephropathy, platelet aggregation abnormalities, hearing loss or tinnitus, thyroiditis, sarcoidosis, mycobacterial infection, group A Streptococcus, Hep B vaccination

iii. Mortality due to cerebral vasculitis in a patient [17] spontaneous resolution of lesions in 2-5 weeks. Lesions start to heal centrally. Pigment clumping and depigmentation are observed. VA improvement follows but may lag weeks to months after resolution of lesions.

3. FA :Early hypofluorescence of placoid lesions (possible RPE masking) with hyperfluorescence and staining in late venous phase (damaged RPE and BRB); occasional prolonged choroidal phase and filling of choriocapillaries seen in hypoF patches ; after healing, window defects remain without leak

4. ICG: Profound delay in choroidal filling and extensive choroidal non-perfusion even outside visible lesions. These defects decrease over time. Evidence of choroidal vasculitis: infiltration around some larger choroidal vessels [18.19,20]
5. VF:
Scotoma, may be permanent; central defects in 2/3
6. Electrophysiologic:
Usually normal, transient ERG, dark adaptation and cone pigment studies: EOG: markedly abnormal
7. Etiology: Unknown etiology. Originally, RPE dysfunction because lesions seen at RPE level and masking of choroidal fluorescence and abnormal EOG. However, currently believed to be a choroidal vasculitis with resulting ischemia.
a. Evidences for this a choroidal problem include:
i. ICG shows choroidal non-perfusion and choroidal vasculitis; the placoid lesion may correspond to choroidal lobule with secondary RPE swelling over it [18-20]

ii. Association with systemic vasculitides
b. Evidences for a possible Immunologic involvement include:
i. Anterior uveitis and vitritis may occur

ii. Prodrome suggests that a virus may be an inciting antigen with resulting Arthrus reaction and blockage of vessels

iii. Hypersensitivity reaction suspected due to relation to completion of antibiotic therapy
iv. DTH raction due to association with other DTH diseases such as sarcoid, TB; CSF pleocytosis, CNS vasculitis with arterial narrowing, fibrinoid necrosis and granulomas; granulomatous rxn

v. HLA-B7 and -DR2 have 3 fold risk

vi. Association with erythema nodosum, episcleritis, neurosensory hearing loss
7. **Treatment** No proven treatment. Corticosteroids may be tried for extensive disease. MRI should be done when patient has headaches (multifocal white lesions), always present when there is cerebral vasculitis which may need high-dose corticosteroids and long-term immunusuppression with azathioprine
8.**Prognosis:** 90% have 20/25 vision in series of Wolf however, 2/3 with visual complaints of blurred vision, metamorphopsia or scotoma. 80% have 20/40 vision or better; recurrences are rare and occur usually within 6 months but may relapse up to 3 years after original episode [21]

Punctate inner choroidopathy

Case: BS, 49 y.o. female consulted for "blue haze" and vision described as "like a film negative", OD, incidentally discovered (7/9/87) VA OD: 20/125 and OS: 20/20. The anterior segments were normal. Funduscopy showed: OD, In and around fovea, multiple, yellow, round to elongated patches at the level of the RPE or choroid; normal periphery and OS, deep yellowish lesions and RPE changes similar to right eye but smaller and less extensive. A fluorescein angiogram revealed OD: RPE window defects with early hypofluorescence and late punctate staining consistent with PIC and Drusen, OS. (**Figure 5**)

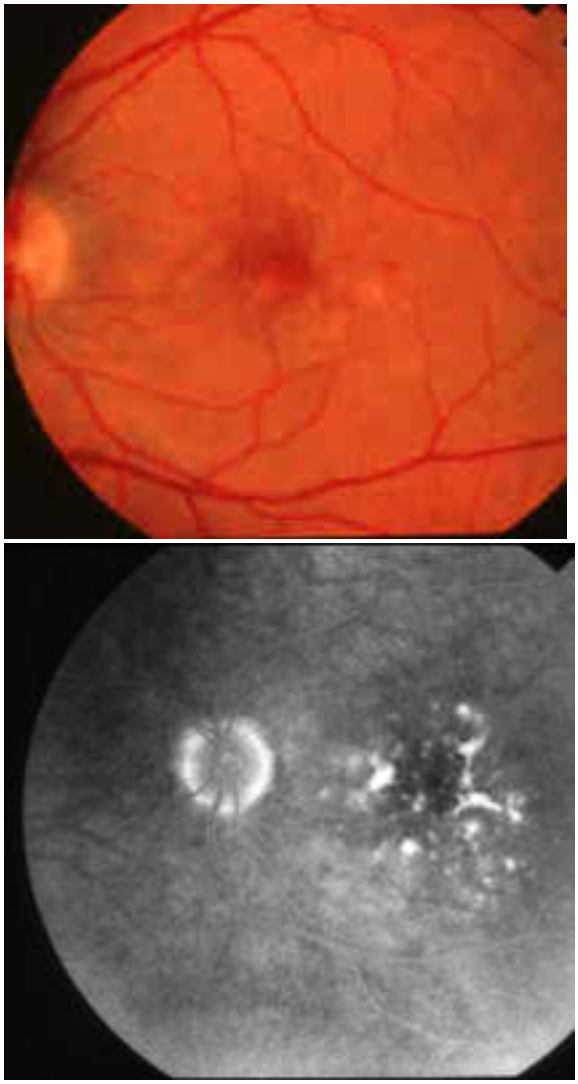


Figure 5 (Left) Punctate yellow lesions at RPe and choroid level. (Right) Window-defect type hyperfluorescence

Lab results showed:
EBV + EBV nuclear antigen, early antigen: Positive (1:40 Ref < 1:10)
HSV IgG Positive
FTA-ABS: Negative
ANA, RF: Negative

After 1 week, vision spontaneously improved to 20/40 then to 20/20. Repeat episodes aaround 2-3 times a year occurred in the right eye over the following year with worst VA of 20/50 recovering to 20/20 within a week of flareup.

2 years later, flare up, OD with VA down to 20/50. Right eye (4/7/89) showed discrete RPE defects, ill-defined yellowish, white, deep lesions with 1/4 DD greenish subretinal lesion with subretinal hemorrhage located superotemporal to foveal center. OS has RPE defects and several lesions. A subretinal hemorrhage is seen just temporal to fovea. FA OD revealed multiple hyperF lesions and hypoF lesions in macula. Two discrete hyperF lesions increase in intensity and size throughout transit views and shows some leakage on late views FA OS: window defect. Imp: Bilateral maculopathy consistent with PIC. Discrete lesions which leak in delayed views suggestive of SRNV in OD. Possible occult membrane due to hemorrhage. The hemorrhages resorb and never return. . (Possible spontaneous regression of a membrane) Over next 7 years, occasional flare-up of either eye with vision returning to normal. Final VA 20/15, OU.

FEATURES OF PIC:
Originally reported by Watzke and others in 1984 [22], some consider this to be a variant of multifocal choroiditis.

1. Epidemiology
   Young, 2nd-3rd decade
   Mostly women
   Myopic
   Majority bilateral
2. Clinical Features [22]
   a. Symptoms: blurred vision, light flashes, paracentral scotomas
   b. Signs: small, yellow-white lesions of inner choroid and RPE, 100-300 um
   c. Located in posterior pole to mid-periphery
   d. Overlying serous detachment
   e. Vision not usually affected unless fovea is involved.
   f. Later, may form variably pigmented atrophic cylindric punched-out lesions
   g. CNVM may often arise, 30-50% of patients
   h. No AC or vitreous inflammation [in comparison to MCP]
   i. Recurrences are common
   j. Normal optic nerve
3. VF:
   Paracentral defects
4. FA:
   Hyperfluorescence in the arterial phase with AV phase staining; CNVM shows early leak
5. ICG:
   There is early hypofluorescence corresponding to the lesions; occasionally, larger vessels may be seen to cross these lesions and exhibit localised points of hyperfluorescence [23]
6. Etiology:
   The etiology is unknown but may be related to abnormalities of choroidal vasculature such as myopic cracks. The choroidal neovascular membranes are composed of fibrovascular tissue with lymphocytes, plasma cells, RPE cells.24
7. Treatment: There is no definite treatment for the lesions. VA has been reported to improve after steroid use (oral or periocular) in some eyes. Laser treatment or subretinal surgery with membrane removal are indicated if CNVM develops. CNVM in PIC has been identified to be of the type 2 variety and has been reported to respond relatively well to submacular surgery though may be associated with recurrence [24]
8. Prognosis:
   Final visual acuities are generally good with 70-77% having 20/40 or better. Decreased vision is associated with CNVM involvement of foveal area (1/3 of patients).

DIFFERENTIALS:
An important differential diagnosis of the different WDS is Birdshot chorioretinopathy, which is described more thoroughly elsewhere in the website. The differential list for WDS is briefly outlined here:

Diffuse Subretinal Fibrosis
The lesions are predominantly in the posterior pole and result in central visual loss. There may be mild vitritis as well. The most characteristic findings are that of subretinal fluid accumulation, subretinal fibrosis which may enlarge over time. These lesions are usually bilateral but may be asymmetrical

Acute Retinal Pigment Epitheliopathy or ARPE
Characterized by suddenly visual loss with appearance of round macular lesions arranged in discrete clusters of 1-4 spots surrounded by a yellow-white halo. These spots are in the RPE layer and over time, either darken or develop pigment migration. Fluorescein angiography reveals central dark spots with window-defect type hyperfluorescent halos. The visual fields may show central scotomas. The electroretinograms are relatively normal while the electrooculograms are

abnormal suggesting an RPE dysfunction. ARPE is a self-limited disease with visual recovery usually within 3 months.

Sarcoidosis
Ocular sarcoidosis frequently presents with Dalen-Fuchs nodules, choroidal granulomas, optic disc inflammation, and retinal vasculitis, pars planitis and vitreous snowballs. Diagnosis is by biopsy of sarcoid nodules or lungs. ACE, lysozyme and abnormal gallium scans may also establish the diagnosis.

Sympathetic ophthalmia

A type of granulomatous uveitis occurring after trauma or surgery to one eye with development of contralateral intraocular inflammation. The associated features include mutton-fat keratic precipitates, prominent vitritis, Dalen-Fuchs nodules, papillitis. Macrophages and CD8+ cells are found in the choroid.

In summary, we present selected cases of white dot syndromes seen at our clinic. While clinical features may overlap, careful examination and appropriate use of diagnostic tests may help establish the correct diagnosis. Early identification is important because while MEWDS is generally benign, APMPPE may be associated with systemic vasculitis. MCP has a chronic recurrent course and is responsive to anti-inflammatory therapy. PIC is associated with a significant risk of choroidal neovascular membrane formation and necessitates careful monitoring.

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