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White dot syndromes: a 20-year study of incidence, clinical features and outcomes

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Abstract

Purpose—To measure the incidence of white dot syndromes (WDS) in a community-based population and to report clinical features and outcomes.

Methods—Multi-center retrospective study using the Rochester Epidemiology Project medical records linkage system of Olmsted County, Minnesota. Databases were searched to identify all patients with WDS from January 1, 1988 through December 31, 2008.

Results—Mean ophthalmic follow-up was 4.5 years and mean general medical follow-up was 9.1 years. The incidence of WDS was 0.45 per 100,000 per year (95% CI 0.19 - 0.71). Incidence rates for specific disease entities were also calculated. We report some associated autoimmune diseases in our series. Multiple evanescent white dot syndrome (MEWDS) was more common in females and acute posterior multifocal placoid pigment epitheliopathy (APMPPE) was more common in males. Both MEWDS and APMPPE generally carried a good visual prognosis. Fifty percent of cases with APMPPE in our series had a positive history of psoriasis. The only punctuate inner choroidopathy (PIC) case carried that diagnosis as well.

Conclusions—WDS are rare diseases, and may be associated with other autoimmune diseases. Further studies with more patients and longer follow up periods are needed to draw conclusions about visual prognosis, development of other ocular conditions and associated medical diseases.

Keywords

Acute posterior multifocal placoid pigment epitheliopathy; incidence; multiple evanescent white dot syndrome; uveitis; white dot syndromes

Introduction

“White dot syndromes” (WDS) is a term that is used to describe a group of non-infectious retinal, retinal pigment epithelial and choroidal inflammatory conditions that include the following diseases:¹

- ☐ Acute posterior multifocal placoid pigment epitheliopathy (APMPPE)
- ☐ Serpiginous choroidopathy

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- ❑ Multiple evanescent white dot syndrome (MEWDS)²
- ❑ Birdshot retinochoroidopathy
- ❑ Multifocal choroiditis and panuveitis syndrome (MCP)³
- ❑ Punctuate inner choroidopathy (PIC)
- ❑ Acute zonal occult outer retinopathy (AZOOR)⁴

These entities are diagnosed based on medical history and clinical examination,⁵ often presenting the clinician with a significant diagnostic challenge,⁶ with some entities exhibiting interesting clinical and/or laboratory associations.⁷ Management options and outcomes are also variable. In addition, treatment of these diseases is diverse,⁸ and treatment options include:⁹ observation, immunosuppressive therapy, laser photocoagulation, topical or systemic steroid therapy, photodynamic therapy, and, most recently, anti-vascular endothelial growth factor agents.¹⁰ Some entities can occur simultaneously, possibly indicating a common causal entity.¹¹ AZOOR, for example, can follow MEWDS, carrying a worse outcome.¹²

The incidence of white dot syndromes is unknown.¹³ We conducted a population-based study using the resources of the Rochester Epidemiology Project database¹⁴ to evaluate more accurately the incidence, clinical features, and outcome of WDS in a well-defined community-based population.

Methods

All of the authors were involved in design and conduct of the study; data collection; data analysis and interpretation; and preparation and review of the manuscript. The protocol was approved by the Institutional Review Boards of the Mayo Clinic and Olmsted Community Hospital. All research complied with the Health Insurance Portability and Accountability Act and was carried out according to the principles of the Declaration of Helsinki.

We reviewed 20 years of data (January 1, 1988 through December 31, 2008) from the medical records of the Mayo Clinic and the Rochester Epidemiology Project. The Rochester Epidemiology Project is a unique database that combines the inpatient and outpatient medical records of the Mayo Clinic Rochester, its affiliated hospitals (St Mary's Hospital and Rochester Methodist Hospital), the Olmsted Medical Group, Olmsted Community Hospital, and a number of individual practitioners. Together, these facilities encompass all major medical facilities within Olmsted County. Because Olmsted County is a well-defined community, relatively isolated from other urban centers, the data include more than 90 % of medical encounters and 96% of hospitalizations of local residents.¹⁴

The computerized medical record index system was searched for all patients with a diagnosis of APMPPE, Serpiginous choroidopathy, MEWDS, birdshot retinochoroidopathy, MCP, PIC and AZOOR. Furthermore, all cases with a diagnosis of uveitis, vitritis, retinitis, choroiditis, retinochoroiditis, white dot syndrome, acute idiopathic blind spot enlargement syndrome¹⁵ and eye disease non-otherwise specified (NOS) were searched.

Clinical data collected included best-corrected Snellen visual acuity and details of ocular exam and description of lesions and angiograms. Medical records were scrutinized looking for the presence and/or occurrence of autoimmune diseases during the period of follow up.

The annual age- and gender-adjusted incidence rates were calculated by using the age-specific and gender-specific populations' figures for Olmsted County, Minnesota, from the United States Census Bureau. Age-specific and gender-specific denominators for individual

years were generated from linear interpolation of the census figures and by using statistical demographer data projections of the Olmsted County population. The 95% confidence intervals (CIs) were calculated for the rates with assumptions based on the Poisson distribution.

Results

Review of the computerized record system revealed 2293 patients with the above diagnoses. The number of cases of WDS was 13. One patient declined research authorization.

Sixteen eyes in 12 patients were included for analysis in the study. Charts, color photographs and fluorescein angiograms were reviewed separately by two researchers (NEA and JSP) to determine the diagnosis. If there was a doubt or disagreement a third opinion (SJB) was sought. There were 4 males and 8 females. Mean follow-up in the ophthalmology clinic was 4.5 years (range, 0.76 to 9.0 years) and mean of general medical follow up was 9.1 years (range, 1 to 21 years). The condition was bilateral in 4 and unilateral in 8 patients. Age of onset ranged from 11 to 52 years (mean, 27.2 years). All patients were white.

The annual incidence rates per 100,000 Olmsted County residents for males, females, and combined are presented in Table 1. The annual incidence rate per 100,000 population adjusted to the age and gender distribution for the 2000 United States White population was 0.45 per 100,000 persons (95% CI, 0.19-0.71). Although there appears to be a difference, the numbers of patients were too small to determine statistically significant differences between males and females.

Table 2 summarizes the 12 cases according to diagnosis, gender, age, laterality and visual acuity (VA) at presentation and at last evaluation.

Of the 12 cases, 6 cases carried the diagnosis of MEWDS (5 females and one male). Four cases were diagnosed with APMPE (one female and three males). One woman was diagnosed with MCP and one woman had PIC. No cases of the other white dot syndromes were identified in this study. The first 2 cases in chronological order presented in 1989. Five cases presented in the year 2000 alone and 8 cases presented between 2000 and 2002. There were no cases identified between 2003 and 2008.

Table 3 outlines the age- and gender adjusted incidence rate per 100,000 persons for the 4 white dot syndromes identified in this study population.

In 20 years between 1988 and 2008, we found no cases of serpiginous choroidopathy, birdshot retinochoroidopathy or AZOOR in Olmsted County, Minnesota.

Table 4 outlines the 12 cases according to diagnosis and certain clinical features at presentation.

All six cases of MEWDS were unilateral, five of which occurred in females. This is consistent with previous reports about the disease.¹⁶ Presenting visual acuity ranged from 20/20 to 20/50 in the involved eye. Two cases (33%) presented with photopsias as the chief complaint. Only one case (16.5%) had a concomitant upper respiratory tract infection at presentation, an occurrence previously described in the literature.^{17,18} One case had fibromyalgia and developed scleroderma. One case had slightly elevated antinuclear antibody (ANA). All MEWDS cases were observed with no medical intervention and all eyes maintained 20/20 visual acuity (VA) at the end of follow up.

We found four cases of APMPE, of which three cases (75%) had bilateral involvement. Two cases (50%) had or developed psoriasis and a third case had eczema. In all the bilateral cases, presenting VA ranged between 20/20 and 20/60 and all of these cases were observed to a final VA of 20/20 in all eyes. APMPE carries a relatively benign prognosis, but some patients may experience incomplete visual recovery.¹⁹ Incidentally, the presenting VA in the unilateral case was 20/20 but this patient ended up with 20/400 VA and a central scotoma. No intervention was done in this case. This same patient developed tonsillar carcinoma and was treated successfully.

The single MCP case we encountered was a 19 year-old female with bilateral involvement and 20/20 acuity. At her last ophthalmic examination her eyes were quiet with no change in VA. No intervention was needed. The single PIC case was a 52 year-old lady with blurring of vision and a black spot in one eye (VA 20/30). Visual field testing revealed an enlarged blind spot. This patient was started on high dose prednisone and tapered over 4 months. She subsequently developed ocular hypertension in both eyes and was diagnosed with psoriasis and eczema. VA was 20/25 at the last follow-up visit. Information about her visual field defect was not available.

Table 5 summarizes the 12 WDS cases according to diagnosis and associated autoimmune disease(s).

Discussion

To our knowledge, this is the first study to try to determine the incidence of white dot syndromes. We found 6 cases of MEWDS, 4 cases of APMPE, one case of PIC and one case of MCP in 20 years in Olmsted County, Minnesota. WDS is a heterogeneous group of diseases and its prevalence among uveitis patients is unknown. Spital et al estimated the relative frequency of white dot syndromes in pediatric uveitis patients to be between 1 – 5 per cent.¹³

MEWDS is unilateral in 80% of the cases and affects women more than men in the second to fifth decades. A viral prodrome is reported in 50% of the cases. In our series, the female preponderance was clear, while only one case had a documented flu-like illness prior to presentation.

APMPPE has no sex predilection and usually involves both eyes. Some case reports pointed to an association with central nervous system vasculitis.²⁰ Three of our four cases occurred in male patients, and three of the four cases were bilateral. Most of MCP and PIC cases are young women. Birdshot retinochoroidopathy occurs more in women and 90% of patients are HLA A29 positive. AZOOR also occurs more in women whereas in serpiginous choroidopathy, men and women are equally affected.

WDS are non-infectious syndromes and an underlying autoimmune mechanism is presumed. Treatment includes, but is not limited to, steroids and immune-suppressants. The association with other autoimmune diseases is an interesting link to explore. In this series, half the cases of APMPE had or developed psoriasis, and the single PIC case carried the same diagnosis as well. The small number of cases precludes establishing a statistically significant association. Because the majority of the population in Olmsted County is white and the diseases are very rare, we cannot extrapolate the data to other ethnic groups.

This study shares the limitations common to all retrospective research. WDS can pose a real diagnostic challenge and many cases can be mild or asymptomatic, thus the calculated incidence most accurately represents symptomatic cases. It is possible that some patients may have been missed because of inaccurate coding or because patients sought care outside

of Olmsted County, although all cases diagnosed as uveitis were reviewed. Previous data showed that 99% of Olmsted County residents did their cataract surgeries locally indicating the tendency to seek eye care near home (Gray D, unpublished data, 1997).²¹ Our incidence figures most likely represent an underestimation of the true frequency of WDS, but it is the best data available to this date. However, the design of this study to measure incidence probably could not be improved, unless all Olmsted County residents underwent ocular examinations. The small number of cases makes it difficult to draw powerful correlations with clinical findings.

In this population-based, 20-year study of WDS, the annual incidence of WDS adjusted to the age and gender distribution for the 2000 United States white population was 0.45 per 100,000 population per year. MEWDS was more common in females and APMPPE was more common in males, with both diagnoses carrying a good visual prognosis. We reported some associated autoimmune diseases. Further studies with longer follow up periods are needed to draw conclusions about visual prognosis, development of other ocular conditions and associated medical diseases.

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TABLE 1

Incidence Rates of white dot syndromes (WDS), Olmsted County, Minnesota, 1988 through 2008 (Adjusted for 2000 United States White population)

	Incidence Rate per 100,000 Persons	95% Confidence Intervals	
		Lower	Upper
Age- and gender-adjusted, females	0.60	0.18	1.01
Age- and gender adjusted, males	0.30	0.004	0.59
Age- and gender-adjusted, total	0.45	0.19	0.71

TABLE 2

Summary of the 12 cases according to diagnosis, gender, age, laterality and visual acuity (VA) at presentation and at last evaluation.

No.	Diagnosis	Gender (M,F)	Age at presentation	Laterality (U, B)	VA at presentation	VA at last ocular evaluation
1	MEWDS	F	42	U	20/20	20/20
2	MEWDS	F	24	U	20/20	20/20
3	MEWDS	F	32	U	20/20	20/20
4	MEWDS	M	11	U	20/50	20/20
5	MEWDS	F	13	U	20/50	20/20
6	MEWDS	F	23	U	20/20	20/400
7	APMPPE	M	29	U	20/20	20/20, 20/20
8	APMPPE	F	24	B	20/20, 20/40	20/20, 20/20
9	APMPPE	M	19	B	20/20, 20/20	20/20, 20/20
10	APMPPE	M	38	B	20/20, 20/60	20/20, 20/20
11	MCP	F	19	B	20/20	20/20
12	PIC	F	52	U	20/30	20/30

(M: male; F: female; U: unilateral; B: bilateral; MEWDS: Multiple evanescent white dot syndrome; APMPPE: Acute posterior multifocal placoid pigment epitheliopathy; MCP: Multifocal choroiditis and panuveitis syndrome; PIC: Punctuate inner choroidopathy)

TABLE 3

Incidence Rates of specific white dot syndromes (WDS), Olmsted County, Minnesota, 1988 through 2008.

White dot syndrome	Age- and gender- adjusted Incidence Rate per 100,000 Persons (total)	95% Confidence Intervals (Lower-Upper)	
MEWDS	0.22	0.04	0.39
APMPPE	0.15	0.002	0.30
MCP	0.03	0.0	0.10
PIC	0.04	0.0	0.13

(MEWDS: Multiple evanescent white dot syndrome; APMPPE: Acute posterior multifocal placoid pigment epitheliopathy; MCP: Multifocal choroiditis and panuveitis syndrome; PIC: Punctuate inner choroidopathy)

TABLE 4

Summary of the 12 cases according to diagnosis and clinical features at presentation

No.	Diagnosis	Anterior chamber cells	Vitreous cells	Photopsias at presentation	Other pertinent ocular findings
1	MEWDS	No	No	Yes	No macular edema
2	MEWDS	No	No	No	No macular edema
3	MEWDS	Trace	Yes	No	No macular edema
4	MEWDS	No	No	No	No macular edema
5	MEWDS	No	No	Yes	No macular edema
6	MEWDS	No	No	No	No macular edema
7	APMPPE	No	No	Yes	No macular edema
8	APMPPE	No	No	Yes	No macular edema
9	APMPPE	No	No	Yes	No macular edema
10	APMPPE	No	Yes	No	No macular edema
11	MCP	No	Yes	No	High myopia
12	PIC	No	No	No	Ocular hypertension

(M: male; F: female; U: unilateral; B: bilateral; MEWDS: Multiple evanescent white dot syndrome; APMPPE: Acute posterior multifocal placoid pigment epitheliopathy; MCP: Multifocal choroiditis and panuveitis syndrome; PIC: Punctate inner choroidopathy)

TABLE 5

Summary of the 12 WDS cases according to diagnosis and associated autoimmune disease(s).

No.	Diagnosis	Associated medical (autoimmune) condition(s)
1	MEWDS	Fibromyalgia, scleroderma
2	MEWDS	None
3	MEWDS	Elevated ANA
4	MEWDS	None
5	MEWDS	Seasonal allergy
6	MEWDS	None
7	APMPPE	None
8	APMPPE	Psoriasis/psoriatic arthritis, erythema nodosum
9	APMPPE	Eczema, seasonal allergy
10	APMPPE	Psoriasis, diabetes mellitus
11	MCP	None
12	PIC	Psoriasis, eczema, diabetes mellitus

(MEWDS: Multiple evanescent white dot syndrome; APMPPE: Acute posterior multifocal placoid pigment epitheliopathy; MCP: Multifocal choroiditis and panuveitis syndrome; PIC: Punctate inner choroidopathy)