Acute Zonal Occult Outer Retinopathy (AZOOR)

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Core Messages

- Acute zonal occult retinopathy is a syndrome first described by Gass [3, 7], who introduced the acronym AZOOR, which summarizes the typical clinical characteristics of a spectrum of retinal disorders:
- *Acute:* rapid loss of visual function in one or both eyes with photopsias in the area of visual field
- *Zonal:* visual loss occurring in one or more retinal regions with or without concomitant blind spot enlargement
- *Occult:* minimal initial ophthalmoscopic changes or absence of funduscopically visible alterations in the retinal area corresponding to the visual field loss
- *Outer:* affecting primarily the photoreceptor and retinal pigment-epithelial (RPE) layer with abnormal responses on electroretinographic (ERG) testing. Cones tend to be more affected than rods
- *Retinopathy*
- Similar changes described in patients with *multiple evanescent white dot syndrome* (MEWDS), *acute idiopathic blind spot enlargement syndrome* (AIBSES), *multifocal choroiditis and panuveitis* (MCP), and *acute macular neuroretinopathy* (AMN). Therefore, it has been suggested that these entities are not separate diseases but an overlapping spectrum of a single disorder (*AZOOR complex*)
- *Acute annular outer retinopathy,* which may be a variant of AZOOR

4.1 Aetiology

The aetiology of AZOOR is still unclear, but it is presumed to be of autoimmune inflammatory origin. Evidence for autoantibodies directed against retina-specific proteins is still lacking [10]. Gass speculated that AZOOR may originate from a viral infection latent in a region of the outer retina which becomes activated, resulting in acute retinal dysfunction and potentially death of the retinal receptors with no immediate effect on funduscopic retinal appearance.

4.2 Clinical Findings

Photopsia and sudden visual field loss in one or both eyes typically in young, Caucasian (90 %), myopic women (f:m = 3:1) in their early thirties are characteristic clinical symptoms and findings in the initial phase of the disease.

4.2.1 Photopsia

The visual sensations in the early phase are described by almost 90 % of patients as multicoloured and associated with shimmering or amoeboid micro-movements in the area of visual field loss. They may be

exacerbated by bright light, stress, fatigue and exercise. These photopsias tend to persist.

4.2.2 Loss of Visual Field

Defects in the visual field are most commonly noted in the superior and temporal quadrants and are usually asymmetric (Fig. 4.1). However, any portion or almost the entire visual field may be involved. They almost always include the blind spot (90 %), which is often enlarged. The size of defects often increases within days or weeks before stabilizing. Visual field testing is probably the best parameter to monitor the disease and should be repeated regularly. In the long-term follow-up study of Gass reviewing 51 patients for a minimum of 3 years, visual field changes stabilized within 6 months in 78 % of patients, progressed in 4 %, and partially improved in 20 % [7]. Over time, the visual field defect can enlarge and can move peripherally or centrally.

Patterns of visual field loss caused by AZOOR in descending order of frequency are blind-spot enlargement, ring scotomas, hemianopic scotomas, 360-degree concentric contraction, arcuatelike scotomas, and multiple isolated scotomas [7].

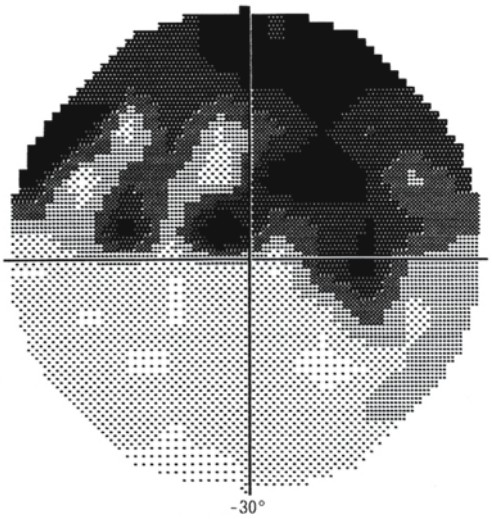

Fig. 4.1. Zonal visual field loss in the upper hemisphere including the blind spot (same eye as in all other figures)

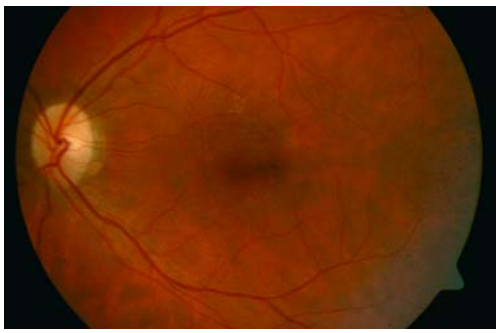

Fig. 4.2. Normal fundus appearance with subtle RPE changes in the macular area (same eye as in all other figures)

4.2.3 Fundus Changes

Early in the disease subtle pigment epithelial (RPE) changes may be noted on funduscopy (Fig. 4.2). However, in many patients no visible alterations are seen (hence the term "occult"), which may give rise to misdiagnoses and unnecessary neurologic and neuroradiologic work-up.

In later stages of the disease the visual field defects correspond to areas of visible pigmentary alterations. In areas of atrophy, retinal vessels may become narrowed. Migration of RPE can mimic the bone spicule appearance of retinitis pigmentosa (RP). Segmental perivenous sheathing may also occur.

In Gass's follow-up study about half of the affected eyes had normal fundi at final examination [7].

4.2.4 Laterality

In Gass's follow-up series AZOOR developed into a bilateral condition in about two-thirds of the patients [7]. At initial presentation, approximately 60 % of the patients had unilateral involvement. Delayed development of AZOOR occurred in 61 % of fellow eyes with a median delay of 31 months in Gass's follow-up study [7]. Only one-fourth of patients had unilateral involvement at final follow-up examination.

4.2.5 Fluorescein Angiographic Findings

Fluorescein angiographic findings in AZOOR patients at initial presentation are generally normal (Fig. 4.3). However, some patients may have leakage at the optic nerve head and from retinal vessels on fluorescein angiography. In a few patients choroidal neovascularization has been observed with concomitant severe impairment of visual acuity [8]. Cystoid macular oedema has also been reported.

4.2.6 Optical Coherence Tomography

Even in the presence of normal fundus appearance and normal fluorescein angiography findings, optical coherence tomography (OCT) can detect morphological changes in the retina of AZOOR patients. The retinal thickness has been reported to be reduced by 10–20 % in AZOOR compared to normal vertical extension [9].

4.2.7 Electroretinographic Findings

Abnormal ERG findings occur in the majority of patients and prove the retinal origin of the visual field defects. During the early phases, cone function may be more affected than rod function. However, with time both cone and rod function may be severely impaired. One study analysed ERG changes in 24 AZOOR patients and found that about one-third had a normal ERG in both eyes but showed abnormal interocular differences for some of the measured parameters [10]. Full-field ERG is usually sufficient for detecting the abnormality.

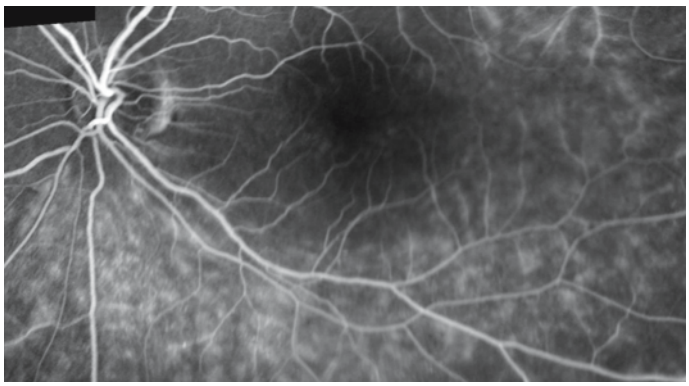

Fig. 4.3. Fluorescein angiography in AZOOR (same eye as in all other figures)

4.2.8 Vitreous Cells

About 50 % of patients have cells in the vitreous body in the first few months after onset [3]. The infiltration is generally mild. The degree of vitritis appears to be related to the degree of visual field loss and the development of fundus changes simulating RP corresponding with the zone(s) of visual field loss. If vitreous cells are absent it is highly likely that the patient will not develop RP-like changes in the future and will maintain a good visual acuity.

4.2.9 Relative Afferent Pupillary Defect

A relative afferent pupillary defect occurs in one-fourth of cases. However, optic atrophy has not yet been described even in eyes with large zones of severe visual field loss.

4.2.10 Associated Systemic Diseases

Gass reported associated systemic autoimmune disease in 28 % of all affected patients including Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, and relapsing transverse myelopathy [7]. About 20 % of patients had a history of antecedent viral-like infection.

4.3 Diagnosis

The diagnosis of AZOOR is based on clinical findings. The history of the acute onset of scotoma, particularly when it involves the superior and temporal visual field associated with photopsia, should alert the clinician. The presence of unexplained visual field loss often leads to an extensive medical and neurological work-up, which can delay the correct diagnosis.

4.4 Prognosis

The course of the disease is variable. Gass reported a final visual acuity of 20/40 in at least one eye in almost 90 % of cases on final follow-up examination [7]. However, 8 % were legally blind. Although most patients retain good vision, all have permanent visual field loss. Patients often have a period of activity (about 6 months) and then show stabilization or sometimes even improvement. There may be relapses (in the same or opposite eye) in about one-fourth of these patients.

4.5 Differential Diagnosis

Infectious aetiologies such as syphilis and Lyme disease should be ruled out serologically. Other causes of outer retinal dysfunction such as retinitis pigmentosa and cancer-associated retinopathy (CAR), melanoma-associated retinopathy (MAR), tapetoretinal degenerations, and cone dystrophies should be considered. The differential diagnosis of sudden visual field loss and visual field defects includes retrobulbar neuritis, pituitary gland tumours, and other intracranial lesions. The angiographic changes should be differentiated from other forms of retinal vasculitis like sarcoidosis and multiple sclerosis.

4.6 Treatment

It is unclear if corticosteroids alter the course of AZOOR. Systemic immunosuppressive treatment has been given as well as antiviral and antibiotic drugs. However, it seems that no type of therapy has had a significant effect on the clinical course.

4.7 AZOOR Complex

Some patients with AZOOR may have had or will develop other idiopathic retinal conditions. Because of overlapping clinical findings, Gass combined several clinical entities in a group that he called the AZOOR complex. These include MEWDS, MCP, AIBSE, AMN, and AZOOR. The frequency of acute visual field loss and photopsias in patients with these retinal conditions suggests that AZOOR may be an underlying or associated condition.

Interestingly, each of the AZOOR complex disorders shares the features of female predominance, development of one or more zones of visual field loss usually including the blind spot, photopsias, and reduced ERG amplitudes (Figs. 4.4, 4.5). These findings indicate that the photoreceptors are the main target cells in these diseases. In three of these disorders white spots at the level of the outer retina can be detected [MEWDS, *punctate inner choroidopathy* (PIC), and MCP].

Various hypotheses have been proposed to explain the pathophysiology of these diseases. Gass suggested that there may be an infectious cause [5]. Jampol and Becker on the other hand assumed that the patients share common non-disease-specific genes. Complex interactions between genetics, primary and secondary immune effector mechanisms, and environmental or other factors trigger the expression of disease seen clinically [11]. It may therefore be speculated that the AZOOR is mediated by these immune dysfunctional loci and that they would occur in association with the

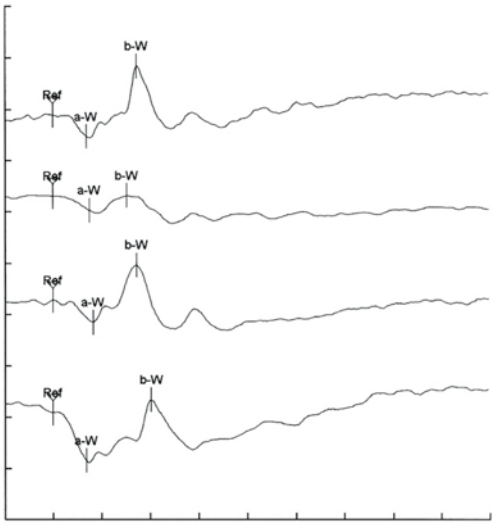

Fig. 4.4. Reduced amplitudes in photopic ERG in AZOOR (same eye as in all other figures)

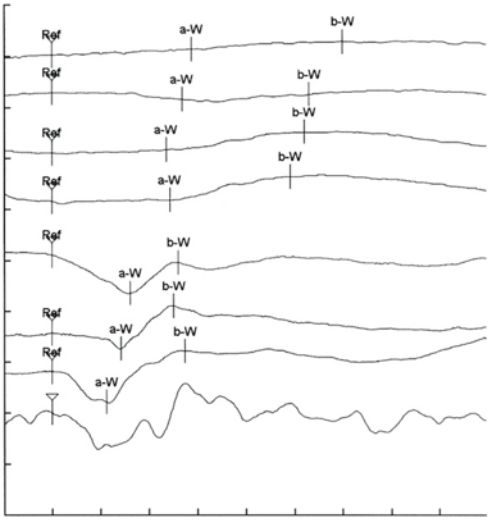

Fig. 4.5. Reduced amplitudes in scotopic ERG in AZOOR (same eye as in all other figures)

Table 4.1. Funduscopic and angiographic findings according to Gass [4]

Primary retinal receptor involvement (Type I)	Absence of fundus and angiographic changes corresponding to zone(s) of field loss (Type IA); occult retinal damage	AZOOR AZOOR, occult + multifocal chorioretinal lesions (MEWDS, PIC, MCP, AMN) AZOOR, occult annular type: white ring
	Fundus changes corresponding to zone(s) of of field loss (Type IB)	AZOOR, overt retinal type: white retina without angiographic changes corresponding to zone(s) of field loss
Combined retinal receptor and RPE involvement (Type II)	Presence of fundus and angiographic changes corresponding to zone(s) of field loss	AZOOR, overt combined retinal and RPE AZOOR, overt annular type: white or yellow orange ring

various immune diseases. It has been shown that these non-disease-specific genetic loci of autoimmune disease tend to cluster at certain sites in the genome (more than 20 sites have been identified) [11]. Familial hereditability studies of autoimmune diseases are currently in progress in white dot syndrome families to address this hypothesis further. At the genetic level, comparative genomic analysis of autoimmune and inflammatory disorders suggests shared genetic components for these clinically related diseases. The Genetic Association Database can be accessed online for further up-to-date information about collected, standardized and archived genetic study association study data (GAD; http://geneticassociationdb.nih.gov). This approach will allow the systematic analysis of complex human genetic diseases in the context of modern high-throughput assay systems and current annotated molecular nomenclature [1].

In the early phase these disorders can be subclassified on the basis of funduscopic and angiographic findings according to Gass [4] (see Table 4.1). *Acute annular outer retinopathy* has been described as a variant of AZOOR [6]. In these patients, the leading edge of dysfunctional retina exhibits an evanescent white intraretinal ring. This ring may be evidence of an intraretinal autoimmune reaction [2].

However, many features remain unexplained:

- The presence of many of these idiopathic inflammatory disorders in young healthy female patients (MEWDS, MFC, AZOOR) is similar to many other autoimmune diseases (e.g. systemic lupus erythematosus, scleroderma, rheumatoid arthritis, autoimmune thyroiditis)
- The occurrence of recurring episodes (*serpiginous choroiditis*, MFC, MEWDS, *acute posterior multifocal placoid pigment epitheliopathy*, APMPPE)
- The rare coincidence of two or more of these diseases in the same patient at different times (AMN, MEWDS, AZOOR, MFC [8])
- Some of the disorders seem to respond to immunosuppressive therapy (birdshot chorioretinopathy, MFC, serpiginous choroidopathy) while others do not (AZOOR, AMN). Yet another group has high spontaneous recovery rates with good visual prognosis (MEWDS, APMPPE)

Further research is needed for this fascinating disease spectrum to elucidate the underlying molecular mechanisms and to develop efficacious modes of therapeutic intervention.

Summary for the Clinician

- ***Acute zonal occult retinopathy*** **(AZOOR) should be suspected in typically young healthy female patients with:**
- **Rapid loss of visual function in one or both eyes with photopsias in the area of visual field**
- **Visual loss in one or more retinal regions with or without concomitant blind spot enlargement**
- **Minimal initial ophthalmoscopic changes or absence of funduscopically visible alterations in the retinal area corresponding with the visual field loss**
- **Abnormal responses on electroretinographic (ERG) testing. Cones tend to be more affected than rods**

References

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