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Review

Acute Retinal Necrosis: Pathophysiological Aspects, Diagnosis, and Treatment

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Abstract

Acute retinal necrosis (ARN) is a devastating viral infection commonly associated with varicella zoster virus (VZV) and herpes simplex virus types 1 and 2 (HSV-1, HSV-2). Typically, ARN affects individuals without immune status disorders between the ages of 50-70. In two-thirds of the cases, one-eye involvement is observed and the inflammation can be presented as panuveitis. The most characteristic clinical manifestations are vitreitis, occlusion of the retinal arterioles, and peripheral necrotizing retinitis. Retinitis presents with the appearance of deep, multifocal, yellowish-white foci, typically localized in the peripheral retina. Systemic antivirals are the first treatment of choice for ARN. The goal of the therapy is to stop the viral replication and disease progression in the affected eye, as well as to prevent involvement of the healthy eye. The other eye can be attacked in an interval of 5 days to 30 years. The visual prognosis after illness is poor. Early diagnosis and timely initiation of treatment play an important role in maintaining visual acuity and preventing the other eye from being affected.

Keywords

acute retinal necrosis, diagnostic criteria, infectious uveitis, retinitis, treatment

INTRODUCTION

Acute retinal necrosis (ARN) is a rare eye infection, which can potentially cause blindness. It is most commonly caused by varicella zoster virus (VZV) and less commonly by herpes simplex viruses (HSV-1 and HSV-2).[1-3] Cases related to cytomegalovirus (CMV) and Epstein-Barr virus (EBV) have also been reported in the literature.[4,5] It is not yet known why some individuals are more susceptible to developing the disease, as ARN is fortunately a relatively rare disease while herpes infection is common. The disease is typically seen in immunocompetent patients. The highest frequency is observed between the ages of 50 to 70, and in two-thirds of the cases, there is a one-eye involvement. Typical clinical manifestations are vitreitis, occlusion of the retinal arterioles, and peripheral necrotising retinitis.[6-8]

We review in this paper aspects of ARN that are related to pathophysiology, the disease's most important clinical features, and treatment that can help in making accurate diagnosis and improve the outcome of the disease.

Historical data

The disease was first described in 1971 by Urayama et al.[9] The authors documented similar changes in six patients with intraocular inflammation, retinal vasculitis, and large, white, confluent retinal infiltrates in one eye. The disease was called Kirisawa's uveitis, with some of the patients developing retinal detachment. There is no proven etiological cause and effective therapy.[9] Other publications (Brown and Mendis[10] and Cibis[11]) are also found in literature about patients with ARN-like clinical

features, in whom systemic herpes virus infection was the unifying factor.

Later in 1978, Young and Bird described four similar cases, but due to the involvement of both eyes, they termed the disease a bilateral acute retinal necrosis. In several of the eyes, the disease progressed to retinal detachment and phthisis, despite the antibiotic and corticosteroid therapy.[12]

In 1982, Culbertson et al. first detected a herpes virus infection with an electron microscope in all layers of the infected retina of enucleated eyes, and the disease was named acute retinal necrosis (ARN).[13]

A year later, Hayasaka et al. found many similarities in reports from the Japanese and English literature. They described the results of more than 10 years of observation of uveitis patients in whom only one eye was affected by the inflammatory process, and suggested the use of the term ARN.[14]

Epidemiological data

Although ARN mainly affects healthy individuals, it can also occur in immunocompromised individuals. The disease is not characteristic of childhood, and neither is there any racial predilection.[7] Varicella zoster virus and HSV-1 were isolated in older patients (>25 years) when immunity to VZV decreased, while HSV-2 is observed in younger patients (<25 years). According to some studies, both sexes are equally affected with slight predominance of men.[8] The clinical course and severity are determined by the spectrum of the virus, as well as the variability in the host immune response, with different viral agents leading to different severity of the disease. The most severe ARN is caused by VZV.[15] A concomitant systemic disease is often absent, although there is evidence in some cases of past or present viral infection. Other factors may also play a role in the pathogenesis of ARN. The seasons with a high incidence of ARN are winter and spring.[16] Genetic predisposition such as HLA-DQw7 has also been proved; HLA-Bw62, HLA-DR4 have been established for the Caucasian population, and HLA-Aw33, HLA-B44, and HLA-DRw6 - for the Japanese population.[17]

The disease can be observed in one or both eyes, but more often, it begins unilaterally. In almost one-third of the patients, the second eye is involved in the inflammatory process, usually within a period of three months, but the literature also describes cases of later manifestation - up to 20 years after the onset of the disease.[18-20] Inflammation and retinal necrosis are less severe in the later-affected eye, with less retinal detachment and a better visual outcome.[21]

The research by Vandercam et al.[22], who described seven cases of ARN following herpetic encephalitis in a retrospective investigation, is noteworthy. In five of the patients with normal immune status, the involvement was unilateral and the causative agent was HSV, while the other two, who were immunocompromised, had a bilateral involvement with the causative agent VZV. Herpetic encephalitis can be considered a risk factor for the development of ARN.[22] Transmission of the virus from the brain to the eye and reactivation of a latent virus from the frontotemporal lobe and the optic chiasm is a presumed possible mechanism.[23-25] A study done on experimental models shows that a reverse mechanism from eye to brain is also possible. In these cases, the virus spreads from the affected eye to the central nervous system along the parasympathetic nerve fibres of the oculomotorius and HSV encephalitis develops within a few days after ARN.[26]

Pathogenesis

The virus affects the neurons, pigment epithelium, and vascular endothelium in all layers of the retina and induces necrosis with cell cytolysis. It has been found that antibodies are produced mainly in the retina, which explains why B-Ly infiltration predominates there. The formed antigen-antibody complexes, together with the inflammation of the vascular walls of the arterioles, lead to vaso-occlusion with subsequent ischemia. The choroidal vessels are also affected by a similar inflammation. In the vitreous body, T-Ly cell infiltration is mainly found, which causes moderate to severe vitreitis. In the late stages, fibrous membranes are formed in the vitreous and on the surface of the thinned necrotic retina, during the contraction of which ruptures occur, most often on the border of the normal and damaged tissue.[8,27]

Clinical finding and diagnostic approach

In some cases, ARN begins with episcleritis or scleritis, periorbital pain, and anterior uveitis, which may be granulomatous or non-granulomatous. Intraocular pressure is often elevated. These symptoms are followed by decreased visual acuity due to the appearance of vitreous opacities and necrotising retinitis, and sometimes by the involvement of the optic nerve (optic neuritis) in the inflammatory process. The phase of active retinitis lasts for about 4-6 weeks. Retinitis is presented with the appearance of deep, multifocal, yellowish-white foci, typically localised in the peripheral retina. The foci tend to confluence and concentrically cover the retina, as well as to extend to the posterior eye pole, without following the architectonics of the retinal vessels.[8,28] The macula is usually spared from the process. Concomitant active vasculitis with perivascular haemorrhages and thrombosis of the arterioles is characteristic. Kyrieleis periarteriolar plaques can sometimes be visualised. The pigmentation of the peripheral lesions resembles a shell, starting from the posterior edge. The disease is often accompanied by retinal holes located on the border of normal and necrotic retina. Giant ruptures of the retinal pigment epithelium may also occur.[6]

In 1994, the American Uveitis Society (the Executive Committee of the American Uveitis Society) defined the mandatory criteria for the diagnosis of ARN, based on clinical findings **(Table 1)**.[17]

Table 1. American Uveitis Society diagnostic criteria (1994)

Obligatory criteria
One or more foci of retinal necrosis with discrete borders in the peripheral retina
Rapid progression in the absence of antiviral therapy
Peripheral, circular spread of inflammation
Occlusive vasculopathy with arterial involvement
Prominent inflammatory reaction in the vitreous and anterior chamber
Additional criteria (not required at diagnosis)
Pain, scleritis, optic nerve involvement

To assess the severity of inflammation and visual prognosis, Holland et al. divide the retina into three zones: zone 1 – with involvement of the retina up to 3000 μm from the fovea or 1500 μm from the papilla. It is believed that retinitis in zone 1 is an immediate threat to vision and treatment must be started immediately without waiting for a diagnostic confirmation of the infection. Zone 2 – the inflammation is located between zone 1 and the clinical equator, and zone 3 – peripherally from zone 2 to ora serrata.[29]

The diagnosis of ARN, according to these criteria, is based on the clinical picture. In recent years, with the advancement of technology, in case of diagnostic difficulty, samples from the anterior chamber or vitreous can be analysed in search of viral particles. The polymerase chain reaction is the method of preference in detecting a viral disease as it is highly accurate. It identifies viral DNA from a small amount of vitreous sample or anterior chamber fluid using enzymatic amplification of nucleic acids, DNA polymerase, and specific primers. In patients suspected of ARN, PCR is positive in 79%-100% of cases, and also allows for the type of viral causative agent to be determined. Studies show that the test is sometimes negative even for virus-positive serum antibodies.[30]

The introduction of new diagnostic techniques has led to the launch of several multicentre studies by the Japanese Ophthalmological Society to develop and validate new diagnostic criteria based on ocular findings, clinical course, and virological tests of intraocular fluids. For this purpose, the Japanese Acute Retinal Necrosis Study Group formed a commission of eight uveitis specialists and one statistician, in which the clinical experience of the participants played an important role. A total of 454 patients were studied, of whom 45 with ARN and 409 patients with uveitis, serving as a control group. Based on the results obtained, new diagnostic criteria were developed, published in 2015 and including 6 ocular findings in the early stages of the disease, 5 clinical courses, and virological tests of intraocular fluids **(Table 2)**.[31]

In virally confirmed ARN, the diagnosis is made in the presence of 1a or 1b ocular findings combined with an available clinical course criterion. In virally unconfirmed ARN, the diagnosis is accepted in the presence of four out of six ocular symptoms from an early stage, as 1a and 1b are necessarily present, as well as two of the five criteria for clinical course.[31]

Table 2. Japanese Ophthalmological Society new diagnostic criteria (2014)

1. Ocular findings in the early stage
a) anterior chamber cells or mutton-fat keratic precipitates
b) yellow-white lesion(s) in the peripheral retina
c) retinal arteritis
d) hyperemia of the optic disc
e) inflammatory vitreous opacities
f) elevated intraocular pressure
2. Clinical courses
a) rapid expansion of the retinal lesion(s)
b) development of retinal breaks or retinal detachment
c) retinal vascular occlusion
d) optic atrophy
e) response to antiviral treatment
3. Virologic testing of intraocular fluids consisted of analysis by PCR or the Goldmann-Witmer coefficient for HSV-1, HSV-2, or VZV.

*HSV-1: herpes simplex virus type 1; HSV-2: herpes simplex virus type 2; VZV: varicella zoster virus

There is insufficient data in the literature to compare anterior chamber and vitreous body samples, neither is there any information as to which are more sensitive. If ARN is suspected, treatment must be started immediately without waiting for results.

The laboratory tests aiding a diagnosis include serum or intraocular antibodies, viral cultures, retinal biopsy, cytochemical and immunohistochemical analysis. Routine use of these methods is limited due to low sensitivity and specificity, limited distribution of tests, cost, the need to prepare when taking ophthalmic material, and the risk to the patient.

Differential diagnosis

Because ARN often begins as anterior uveitis, the fundus examination should be performed after drug mydriasis. Differential diagnosis is made in a wide range of chorioretinal-involving diseases **(Table 3)**.

Progressive outer retinal necrosis (PRN/PORN) is a rare but devastating disease, in whose aetiology VZV plays a major role. The disease is characteristic of immunocom-

Table 3. Differential diagnosis of acute retinal necrosis

Progressive outer retinal necrosis syndrome
Cytomegalovirus retinitis
Toxoplasmosis
Acute multifocal hemorrhagic retinal vasculitis
Syphilis
Behçet disease
Sympathetic ophthalmia
Vogt-Koyanagi-Harada syndrome
Pars planitis
Intraocular lymphoma/leukemia
Exogenous bacterial endophthalmitis
Fungal endophthalmitis
Central/branch retinal vein occlusion
Ocular ischemic syndrome

promised patients and has an extremely rapid clinical course with the frequent involvement of both eyes. It can start with a sudden loss of vision without pain. The inflammatory process is localised in the outer layers of the retina in the form of multiple inflammatory foci with unclear borders, spreading from the centre to the periphery with early involvement of the macula and posterior eye pole. At the end of the disease, the inner layers are also damaged. Inflammatory infiltration into the anterior chamber and vitreous is minimal in contrast to ARN. Damage to the retinal vessels and the presence of intraretinal haemorrhages are not typical.[32]

CMV retinitis occurs mainly in immunocompromised patients, and in half of the cases both eyes are involved in the inflammatory process. The disease is localised in the posterior eye pole. Vitreitis is mild, but the visual acuity decreases in the initial stages, without pain, due to the early involvement of the macula in the inflammatory process. There is a pronounced haemorrhagic syndrome involving mainly the venous vessels of the retina and the presence of moist exudates, in contrast to ARN, which mainly affects the arterioles and the haemorrhages are significantly fewer. Compared to ARN, the clinical course is slower and the disease has a self-limiting pace.[7,32]

Toxoplasmosis can also manifest itself with a large, peripheral white chorioretinal lesion and pronounced vitreitis. Typical of the disease, an old chorioretinal scar is usually found near the active zone.

Lues should be ruled out in any uveitis. Clinically, it can also manifest itself in the form of retinitis in two varieties: yellow-white retinal foci outside the vascular arches or grey-white annular, as well as map-shaped foci in the posterior pole. Occlusive vasculitis is characterised by the involvement of the arterioles, as well as the presence of vitreitis.[6]

Behcet's disease may manifest itself with the characteristics of retinal necrosis, but here the vasculitis of small arterial and venous vessels of the retina is very pronounced and typical. The diagnosis is also supported by the obligatory accompanying systemic manifestations.

Acute multifocal haemorrhagic retinal vasculitis is a rare disease of unclear origin in healthy adults. It begins with a sudden loss of vision, combined with vitreitis and retinal mostly venous vasculitis, unlike ARN. Non-confluent infiltrates and haemorrhages are observed in the posterior eye pole. The papilla may also be involved in the inflammatory process.[33]

Pars planitis is accompanied by a mild to moderate inflammatory reaction in the anterior chamber and massive infiltration into the vitreous, but the onset of the disease is gradual, and there is no ischemia and necrosis of the retina.

Treatment

Systemic antivirals are the first treatment of choice for ARN. The goal of the therapy is to stop the viral replication and disease progression in the affected eye, as well as to prevent involvement of the healthy eye. Great variability is observed regarding the duration of treatment according to various literature sources – between 5 days and 6 months. In immunosuppressed patients, the course of treatment should be extended. Systemic antiviral therapy stabilises the retina by reducing the duration of active disease and reducing the risk of affecting the other eye.[34] Palay et al. followed 54 patients/eyes with ARN, of whom only 31 received acyclovir. Out of these 31, in 27 patients the other eye was not affected by an inflammatory process within 12 months. In the group not treated with acyclovir, in 70% of the cases, ARN was also observed in the other eye.[35] The highest risk of involvement of the healthy eye in the inflammatory process is observed during the first 14 weeks after the onset of the disease. According to most authors, patients should receive systemic antiviral therapy during this period.[35,36] Acyclovir is highly specific for herpes infected cells and non-toxic to uninfected cells.[37] Play et al. report that the use of acyclovir reduces the risk of contralateral eye involvement from 75.3% to 35.1% over a 2-year period.[36]

The initial dose of acyclovir is 10-15 mg/kg every 8 hours when administered intravenously for 5-10 days, followed by 800 mg five times daily orally for a period of 6 weeks to 3 months. Acyclovir is an effective remedy against all viruses, but the dose that suppresses replication is different for the different causing agents. It is lowest for HSV1, while higher plasma concentrations are required for VZV and EBV. CMV is the least sensitive to the medicine. When taken orally, acyclovir demonstrates low absorption from the gastrointestinal tract, its plasma bioavailability ranging from 15% to 30%.[38] The peak plasma concentration is observed from 1.5 to 2.5 hours after administration, and its plasma half-life lasts for about 3 hours, which requires five applications daily. Higher plasma concentrations can be achieved by intravenous administration.[39] A small portion of acyclovir is metabolised by the liver. The major route of elimination is through the kidneys, which should be taken into consideration in patients with renal insufficiency.[40,41]

Valaciclovir (Valtrex) is L-valyl ester of acyclovir. It is rapidly and almost completely metabolised in the small intestine and liver to acyclovir and the essential amino acid L-valine. Accelerated absorption and rapid hydrolysis of valaciclovir to acyclovir results in significantly higher systemic drug levels. Studies indicate that the plasma bioavailability of valaciclovir after oral administration is 3 to 5 times higher than with orally administered acyclovir.[42,43] Following administration of 1 g of valaciclovir, the plasma bioavailability of healthy volunteers reaches 54.2%, which is comparable to intravenous acyclovir.[44] The dosage for valaciclovir is 1000-2000 mg every 8 hours orally.[42,43]

The viral resistance to acyclovir is low (0-0.6%) despite its wide use over the past three decades.[39] In resistant cases, the agent of choice is famciclovir at a dose of 500 mg every 8 hours orally, whose activity is similar to acyclovir. Ganciclovir and its derivative valganciclovir are used less common in treating ARN. They are the first choice in case of suspected CMV retinitis.[6]

In recent years, the combination of systemic and intravitreal administration of antiviral drugs has been considered a more successful method of dealing with ARN. For intravitreal administration, foscarnet and ganciclovir are suitable, providing a direct and immediate therapy in the area of active infection. Flaxel et al. monitored and treated 29 eyes in 24 patients with PCR-proven ARN. Twelve patients were on combined antiviral therapy – systemic and intravitreal, and the other half were only on systemic treatment. The patients on combined therapy exhibited visual acuity two lines higher, as well as a lower rate of retinal detachment. When it comes to foudroyant ARN, the authors recommend an early vitrectomy and laser enclosure of the affected necrotic retina in order to prevent secondary retinal detachment. According to them, the combined intravitreal and systemic treatment reduces the risk of retinal detachment.[15] Other authors have not found a statistically significant difference between systemic treatment and that combined with intravitreal treatment.[45,46]

The use of corticosteroids is controversial. Systemic corticosteroids may be added only after treatment with an antiviral agent and never alone in the acute retinitis stage. They reduce the strength of the host's immune response; they are contraindicated in concomitant HIV infection. Included too early in the treatment plan, they potentiate viral replication and lead to rapid disease progression. On the other hand, they reduce the risk of complications, especially when the optic nerve is involved. Topical corticosteroids and cycloplegics affect anterior segment inflammation.[6,36]

The benefit of anticoagulants in the prevention of ischemic retinal and optic nerve damage is also unclear.[6]

The issue of prophylactic laser therapy is controversial. It is thought that it cannot prevent retinal detachment in 58% of laser-treated eyes. Laser coagulates are placed centrally in the area of atrophy, since a laser in the necrotic retina can cause iatrogenic ruptures. It is difficult to apply in cases of pronounced vitreitis, posterior synechiae, and cataracts.[6,47,48]

There is no consensus on the benefits of prophylactic vitrectomy. According to Hillenkamp et al., early vitrectomy does not improve the end result. This prevents retinal detachment, but not retinal ischemia and optic nerve atrophy, which are important for visual prognosis.[3]

Complications and prognosis

According to literature, about 50%-75% of the patients who have suffered from ARN develop tractional retinal detachment, and the presence of optic neuropathy increases the risk.[7] In cases of optic nerve involvement, necrosis spreads from the peripheral retina to the posterior eye pole, suggesting a longer duration of the disease before the symptoms are established. Severe retinal damage also increases the risk of retinal detachment. This is most often seen three months after the onset of the disease, so patients must be closely monitored. Other possible complications are vitreous haemorrhage, proliferative vitreoretinopathy, rhegmatogenous detachment, epiretinal membrane, retinal ischemia, cataracts, glaucoma, encephalitis, etc.

The visual prognosis for patients with ARN is poor, and in a great percentage of the cases, the final visual acuity is lower than 0.1. What matters is the visual acuity at the time of diagnosis, the time of initiation of antiviral therapy, and whether there is any concomitant retinal detachment or opticopathy. Early diagnosis and timely initiation of treatment play an important role in maintaining visual acuity and preventing the other eye from being affected.

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Острый некроз сетчатки: патофизиологические аспекты, диагностика и лечение

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Резюме

Острый некроз сетчатки (ОНС) представляет собой разрушительную вирусную инфекцию, обычно ассоциированную с вирусом ветряной оспы (ВВО) и вирусом простого герпеса 1 и 2 типа (HSV-1, HSV-2). Как правило, ОНС поражает лиц без нарушений иммунного статуса в возрасте 50-70 лет. В двух третях случаев наблюдается поражение одного глаза, а воспаление может проявляться панувеитом. Наиболее характерными клиническими проявлениями являются витреит, окклюзия артериол сетчатки и периферический некротизирующий ретинит. Ретинит проявляется появлением глубоких многоочаговых желтовато-белых очагов, обычно локализующихся на периферии сетчатки. Системные противовирусные препараты являются препаратами первого выбора при ОНС. Цель терапии – остановить репликацию вируса и прогрессирование заболевания в поражённом глазу, а также предотвратить поражение здорового глаза. Другой глаз может находиться под угрозой поражения в период от 5 дней до 30 лет. Зрительный прогноз после болезни неблагоприятный. Ранняя диагностика и своевременное начало лечения играют важную роль в поддержании остроты зрения и предотвращении поражения другого глаза.

Ключевые слова

острый некроз сетчатки, критерии диагностики, инфекционный увеит, ретинит, лечение