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Classification criteria for acute retinal necrosis syndrome

The Standardization of Uveitis Nomenclature (SUN) Working Group[*,1,2,3]

Abstract

Purpose: To determine classification criteria for acute retinal necrosis (ARN).

Design: Machine learning of cases with ARN and 4 other infectious posterior/ panuveitides.

Methods: Cases of infectious posterior/panuveitides were collected in an informatics-designed preliminary database, and a final database was constructed of cases achieving supermajority agreement on diagnosis, using formal consensus techniques. Cases were split into a training set and a validation set. Machine learning using multinomial logistic regression was used on the training set to determine a parsimonious set of criteria that minimized the misclassification rate among the infectious posterior/panuveitides. The resulting criteria were evaluated on the validation set.

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Results: Eight hundred three cases of infectious posterior/panuveitides, including 186 cases of ARN, were evaluated by machine learning. Key criteria for ARN included: 1) peripheral necrotizing retinitis; and either 2) polymerase chain reaction assay of an intraocular fluid specimen positive for either herpes simplex virus or varicella zoster virus; or 3) a characteristic clinical appearance with circumferential or confluent retinitis, retinal vascular sheathing and/or occlusion, and more than minimal vitritis. Overall accuracy for infectious posterior/panuveitides was 92.1% in the training set and 93.3% (95% confidence interval 88.2, 96.3) in the validation set. The misclassification rates for ARN were 15% in the training set and 11.5% in the validation set.

Conclusions: The criteria for ARN had a reasonably low misclassification rate and appeared to perform sufficiently well for use in clinical and translational research.

PRECIS

Using a formalized approach to developing classification criteria, including informatics-based case collection, consensus-technique-based case selection, and machine learning, classification criteria for the acute retinal necrosis were developed. Key criteria included peripheral necrotizing retinitis and either PCR evidence of intraocular infection with herpes simplex or varicella zoster virus or characteristic clinical picture with circumferential or confluent retinitis, retinal vascular sheathing and/or occlusion, and vitritis. The resulting classification criteria had a reasonably low misclassification rate.

The first published use of the term acute retinal necrosis (ARN) was by Young and Bird in 1978,[1] to describe the clinical findings of four patients with the sudden onset of a bilateral, symmetrical, and rapidly progressive retinal necrosis. In the course of their disease all four patients also were described as having aqueous and vitreous inflammatory cells and retinal vascular occlusion. Young and Bird noted similarities between their four patients and patients with herpes simplex virus (HSV) and varicella zoster virus (VZV) retinitis, as well as with two prior cases of necrotizing retinitis and retinal vascular occlusion of unknown cause described by Willerson et al.[2] There also was a striking clinical similarity between the patients described by Young and Bird and six patients described in the Japanese literature by Urayama et al[3] and a single case report of a patient with herpes zoster ophthalmicus complicated by panuveitis and retinal arteritis described by Brown and Mendis.[4] Despite originally being described as a bilateral disease, it subsequently became evident that the majority of ARN cases were unilateral.[5]

Although herpesviruses were suspected causes of the ARN syndrome since its original descriptions,[6] the first immunolocalization of a herpesvirus antigen in the eyes of patients with the ARN syndrome was reported by Peyman et al in 1984.[7] In 1986 Culbertson et al[8] provided ultrastructural, immunohistochemical and viral culture evidence of VZV as a cause of the ARN syndrome. Numerous subsequent reports support HSV type 1 (HSV-1), HSV type 2 (HSV-2) and VZV as pathological causes of ARN.[9–13] Although some authors suggested that ocular infections with cytomegalovirus (CMV) and Epstein-Barr virus also may produce the characteristic findings of the ARN syndrome, the data to support these assertions have not been robust. Cases series have consistently reported that the viral cause of ARN segregates by age. HSV-2 is present in youngest group (mean age early third decade

of life); HSV-1 next youngest (mean age late third decade to early 4th decade); and VZV the oldest (mean age sixth decade of life).[9–16]

The ARN syndrome is rare. In a prospective population-based surveillance study in the United Kingdom, 45 confirmed cases of ARN were reported in a 14-month study period, resulting in an estimated incidence of 0.63 cases per million population per year,[16] an estimate which was very similar to results previously published on the incidence of ARN in the United Kingdom five years earlier (0.50 cases per million population).[17]

Of note, eight patients captured in the United Kingdom 2012 surveillance study were recognized as having either a preceding or concurrent central nervous system herpetic disease.[14] Several case series and case reports similarly have reported an association between ARN and prior, subsequent and or concurrent viral meningitis or encephalitis, particularly among younger patients with HSV-1 or HSV-2 ARN.[10,18,19] Given the low incidence of ARN, the high prevalence of latent HSV and VZV infection, and the data the linking herpesvirus encephalitis or meningitis with selective defects in viral immunity,[20–22] it is possible that there may be genetic risk factors in the immune response for the ARN syndrome, although there are as yet limited data to support this inference.[23]

Because ARN is a rare disease, the data on treatment are of limited quality, largely coming from case series. Nevertheless, because of the viral etiology, rapid progression, and poor prognosis, there is a consensus that prompt treatment with antiviral agents is needed. In early reports patients were treated with intravenous acyclovir at a dose of 500 mg/m^2 every 8 hours (~850 mg every 8 hours in an average adult).[24] Subsequent studies have used oral valacyclovir, typically at a dose of 2 gm TID-QID,[25–,28] and one case series suggested similar results between oral valacyclovir plus intravitreal foscarnet and intravenous acyclovir.[26] Given that systemically-administered drugs need five half-lives to achieve steady state and the rapid progression of the disease, initial therapy with intravitreal antiviral agents (e.g. foscarnet) in order to achieve high intraocular drug levels appears appropriate.[25,28] Systemic therapy appears to decrease the risk of second eye involvement.[25] Although the optimal duration of oral therapy is uncertain, the high risk period for second eye involvement is the first 14 weeks after presentation,[25] and many experts suggest treating with lower dose maintenance therapy for at least 6 months. Retinal detachment is a frequent sequelae of ARN occurring in up to 85% of eyes.[5,23–28] Its frequency does not appear to be decreased by systemic antiviral therapy, perhaps due to the extensive amount of retinal necrosis at presentation, but one retrospective case series suggested that it may be decreased by the early use of adjunctive intravitreal foscarnet[5,26,28] Because of the poor visual outcomes in eyes with ARN (~50% 20/200 or worse at 6 months after presentation),[28] prevention of second eye involvement is an important goal of therapy.

The Standardization of Uveitis Nomenclature (SUN) Working Group is an international collaboration, which has developing classification criteria for 25 of the most common uveitides using a formal approach to development and classification. Among the diseases studied was ARN.[29–35]

Methods

The SUN Developing Classification Criteria for the Uveitides project proceeded in four phases as previously described: 1) informatics, 2) case collection, 3) case selection, and 4) machine learning.[30–34]

Informatics.

As previously described, the consensus-based informatics phase permitted the development of a standardized vocabulary and the development of a standardized, menu-driven hierarchical case collection instrument.[31]

Case collection and case selection.

De-identified information was entered into the SUN preliminary database by the 76 contributing investigators for each disease as previously described.[32,33] Cases in the preliminary database were reviewed by committees of 9 investigators for selection into the final database, using formal consensus techniques described in the accompanying article.[33,34] Because the goal was to develop classification criteria,[35] only cases with a supermajority agreement (>75%) that the case was the disease in question were retained in the final database (i.e. were "selected").[33,34]

Machine learning.

The final database then was randomly separated into a training set (~85% of the cases) and a validation set (~15% of the cases) for each disease as described in the accompanying article.[34] Machine learning was used on the training set to determine criteria that minimized misclassification. The criteria then were tested on the validation set; for both the training set and the validation set, the misclassification rate was calculated for each disease. The misclassification rate was the proportion of cases classified incorrectly by the machine learning algorithm when compared to the consensus diagnosis. For infectious posterior and panuveitides, the diseases against which ARN was evaluated were: CMV retinitis, syphilitic uveitis, tubercular uveitis, and toxoplasmic retinitis.

The study adhered to the principles of the Declaration of Helsinki. Institutional Review Boards (IRBs) at each participating center reviewed and approved the study; the study typically was considered either minimal risk or exempt by the individual IRBs.

Results

Two hundred fifty-two cases of ARN were collected and 186 (74%) achieved supermajority agreement on the diagnosis during the "selection" phase and were used in the machine learning phase. These cases of ARN were compared to cases of infectious posterior/ panuveitides, including 211 cases of CMV retinitis, 174 cases of toxoplasmic retinitis, 35 cases of syphilitic posterior uveitis and 197 cases of tubercular uveitis. The details of the machine learning results for these diseases are outlined in the accompanying article.[32] The characteristics of cases with acute retinal necrosis are listed in Table 1, and the classification criteria developed after machine learning are listed in Table 2. In all of the cases the retinitis

involved the peripheral retina, though in 18% it had extended into the posterior pole. Key features of the criteria include a peripheral necrotizing retinitis and either confirmation of HSV or VZV infection on PCR of an intraocular fluid specimen or the characteristic clinical picture (Figure 1). The characteristic clinical picture includes: 1) either circumferential or confluent retinitis, and 2) retinal vascular inflammation (sheathing, leakage, and/or occlusion), and 3) greater than minimal vitritis, unless the patient is immune compromised. The overall accuracy for infectious posterior/panuveitides was 92.1% in the training set and 93.3% (95% confidence interval 88.2, 96.3%) in the validation set. The misclassification rate for acute retinal necrosis in the training set was 15% and, in the validation set, 11.5%. In both the training set and the validation set, the diseases with which it was most often confused were CMV retinitis and ocular toxoplasmosis.

Discussion

The ARN syndrome is a necrotizing retinitis that involves the peripheral retina. Necrotizing retinitides are characterized by full thickness retinal necrosis with or without inflammation, which, upon resolution, leave an atrophic and gliotic scar in the involved areas. Clinically, the initial presentation is white to yellow retinal edema and opacity with or without hemorrhage. Necrotizing retinitides may have relatively well demarcated borders, as in the case of ARN (Figure 1), or have satellites extending into adjacent retina, as is seen in CMV retinitis. The classification criteria developed by the SUN Working Group for ARN have a relatively low misclassification rate, indicating reasonable discriminatory performance against other infectious posterior and pan-uveitides. The SUN criteria require a peripheral necrotizing retinitis and either 1) confirmation of of intraocular infection with HSV or VZV (via PCR of an intraocular fluid) or 2) the classic clinical picture. The inclusion of both ways of classifying a case as ARN permits reporting of retrospective case series where intraocular fluid sampling may not have been performed in every (or even any) cases, and therefore will reduce potential bias if intraocular fluid sampling a a given center was reserved for those cases where the diagnosis was uncertain.

In 1994 the American Uveitis Society proposed standard diagnostic criteria for the ARN syndrome.[36] These criteria included: 1) well demarcated areas of retinal necrosis in the peripheral retina; 2) rapid circumferential progression of retinal necrosis; 3) occlusive vasculopathy; and 4) a prominent inflammatory reaction in the anterior chamber and vitreous. The guidelines further noted that the definition of ARN did not depend on the immunological status of the host or the isolation of any specific pathogen from ocular tissues. Furthermore, if a causal agent was identified, then the retinitis should be referred to as being caused by the agent, with the designation of ARN as a modifier.[36] The SUN classification criteria are similar in many respects to the proposed AUS criteria, except that rapid circumferential progression, which requires more than a single observation (and therefore cannot be used to diagnose ARN at the initial visit) was not included, and peripheral necrotizing retinitis with appropriate confirmation of the HSV or VZV viral etiology was included.

In 2015, the Japanese ARN Study Group proposed criteria for ARN with 2 levels of certainty: virus-confirmed and virus-unconfirmed. Both virus-confirmed and virus

unconfirmed required anterior segment inflammation, yellow-white peripheral retinal lesions, and continued observation to determine course.[37] Virus-confirmed required any one of the following: rapid circumferential expansion, development of retinal breaks or detachment, retinal vascular occlusion, development of optic atrophy, or response to antiviral therapy. Virus-unconfirmed required any two of the above plus any two additional clinical features, including: retinal arteritis, disc hyperemia, vitritis, elevated intraocular pressure.[37] Like the AUS criteria, the Japanese criteria require observation at more than a single visit, and therefore cannot be used to diagnose ARN at the initial visit, whereas the SUN Criteria can be used at an initial visit.

Although originally described in patients without evident immune compromise, it subsequently was recognized that a morphologically similar syndrome occurs in immune compromised patients, although vitritis may not be present in these patients.[38,39] As such, the AUS criteria allowed for patients without and with evident immune compromise (e.g. AIDS, cancer, transplant, chemotherapy) to be diagnosed as having ARN.[36] The SUN Classification Criteria for ARN also allowed for patients with evident immune compromise to be diagnosed as having ARN, and indeed 15% of the cases in the database were immunocompromised.

The ARN syndrome is a morphologic syndrome, and there are other variants of herpetic retinitis, such as the progressive outer retinal necrosis syndrome.[40–43] In contrast to the ARN syndrome, it is seen exclusively in immune compromised hosts, often with profound immune compromise, has early posterior pole involvement, and an initial appearance of inner retinal sparing. It tends to progress even more rapidly than ARN and responds poorly to single agent antiviral therapy with intravenous acyclovir.[39] Successful management of HIV infection with modern antiretroviral therapy has substantially decreased the population at risk for progressive outer retinal necrosis, so that it now is seen rarely,[43] and too few cases were collected for formal analysis in the SUN project. In addition, cases of a non-necrotizing herpetic retinitis, papillitis, or retinal vasculitis have been reported.[44,45] These cases tend to present as corticosteroid-resistant posterior uveitis and have either HSV or VZV identified on PCR analysis of an intraocular fluid specimen. Given the absence of a peripheral necrotizing retinitis, these cases similarly would not be classified as the ARN syndrome. The term necrotizing herpetic retinopathy has been used by some experts to refer collectively to the group of infectious retinitides caused by herpes family viruses. Acute retinal necrosis is one of these diseases, and the SUN criteria address the individual diseases, not the entire group. The criteria for cytomegalovirus retinitis are presented in an accompanying article.[46]

Classification criteria are employed to diagnose individual diseases for research purposes.[35] Classification criteria differ from clinical diagnostic criteria, in that although both seek to minimize misclassification, when a trade-off is needed, diagnostic criteria typically emphasize sensitivity, whereas classification criteria emphasize specificity,[35] in order to define a homogeneous group of patients for inclusion in research studies and limit the inclusion of patients without the disease in question that might confound the data. The machine learning process employed did not explicitly use sensitivity and specificity; instead it minimized the misclassification rate. Because we were developing classification criteria

and because the typical agreement between two uveitis experts on diagnosis is moderate at best,[33] the selection of cases for the final database ("case selection") included only cases which achieved supermajority agreement on the diagnosis. As such, some cases which clinicians would diagnose with ARN may not be so classified by classification criteria.

In conclusion, the criteria for ARN outlined in Table 2 appear to perform sufficiently well for use as classification criteria in clinical research.[35]

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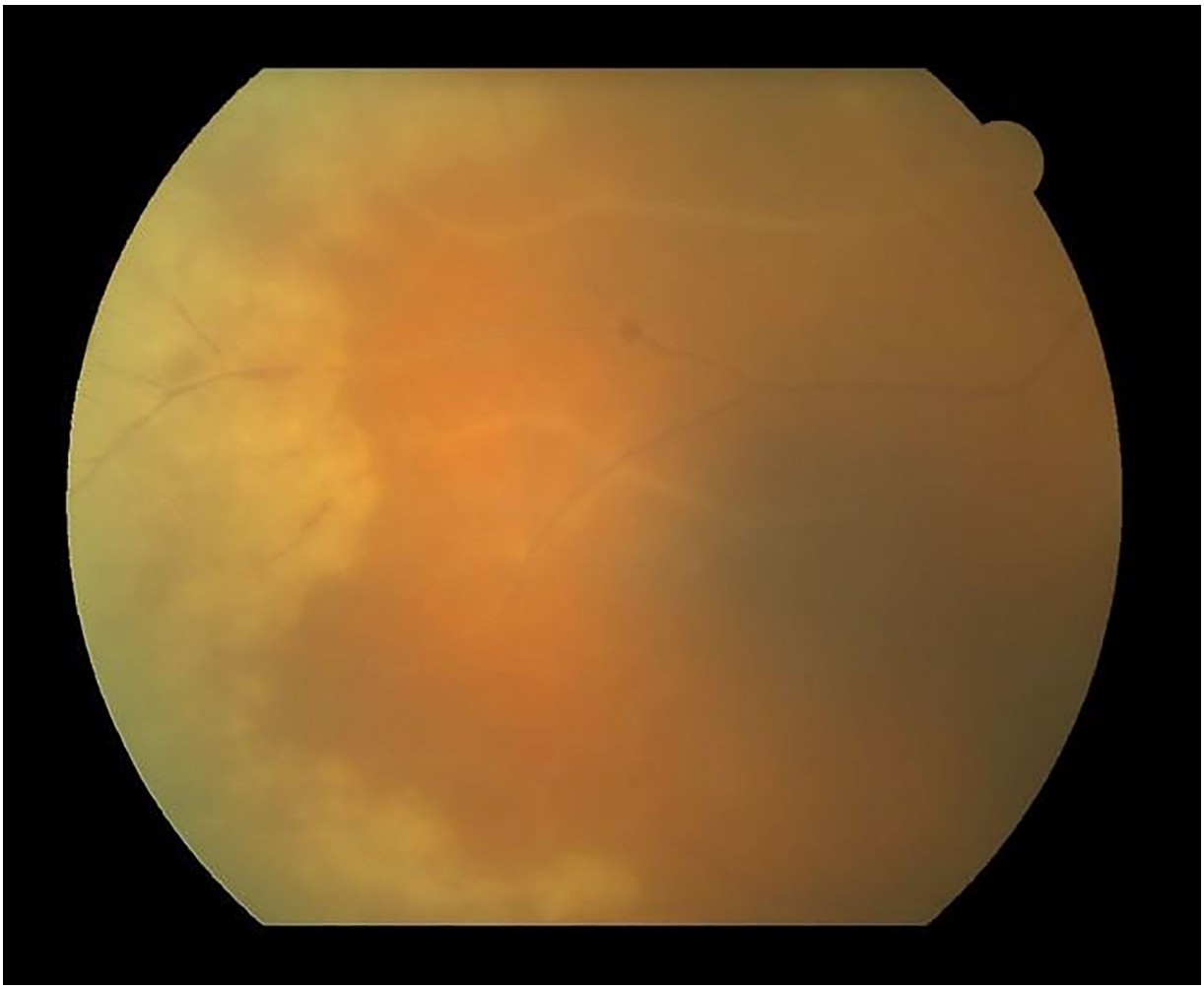

Figure 1.
Fundus photograph of a case of acute retinal necrosis with confluent, circumferential peripheral retinitis and vascular sheathing.

Table 1.

Characteristics of Cases with Acute Retinal Necrosis

Characteristic	**Result**
Number cases	186
Demographics	
Age, median, years (25^{th} 75^{th} percentile)	50 (33, 63)
Gender (%)	
Men	55
Women	45
Race/ethnicity (%)	
White, non-Hispanic	61
Black, non-Hispanic	10
Hispanic	2
Asian, Pacific Islander	15
Other	5
Missing	7
Uveitis History	
Uveitis course (%)	
Acute, monophasic	67
Acute, recurrent	4
Chronic	18
Indeterminate	11
Laterality (%)	
Unilateral	87
Unilateral, alternating	0
Bilateral	13
Ophthalmic examination	
Keratic precipitates (%)	
None	19
Fine	27
Round	18
Stellate	6
Mutton Fat	29
Other	1
Anterior chamber cells (%)	
Grade 0	6
1/2+	9
1+	23
2+	27
3+	22

Characteristic	**Result**
4+	12
Anterior chamber flare (%)	
Grade 0	29
1+	32
2+	29
3+	9
4+	2
Iris (%)	
Normal	91
Posterior synechiae	6
Iris nodules	3
Iris atrophy (sectoral, patchy, or diffuse)	0
Heterochromia	0
Intraocular pressure (IOP), involved eyes	
Median, mm Hg (25^{th}, 75^{th} percentile)	15 (12, 19)
Proportion patients with IOP>24 mm Hg either eye (%)	6
Vitreous cells (%)	
Grade 0	7
1/2+	4
1+	31
2+	30
3+	21
4+	7
Vitreous haze (%)	
Grade 0	20
1/2+	11
1+	19
2+	31
3+	16
4+	4
Retinitis characteristics	
Number lesions (%)	
Unifocal (1)	37
Paucifocal (2 to 4)	25
Multifocal (≥5)	36
Lesion shape (%)	
Round or ovoid	13
Placoid	24
Wedge-shaped	20

Characteristic	Result
Ameboid	14
Not determined	28
Lesion character (%)	
Circumferential	30
Confluent	49
Granular	4
Lesion location (%)	
Posterior pole and periphery involved	18
Mid-periphery and/or periphery only	82
Lesion size (%)	
<250 μm	8
250–500 μm	15
>500 μm	77
Other features (%)	
Retinal vascular sheathing or leakage or occlusion	54
Hemorrhage	38
Systemic disease	
Immunocompromised patients (%)	15
Human immunodeficiency virus infection	3
Organ transplant	0
Chemotherapy or other immunosuppression	12
Laboratory data (%)	
Aqueous or vitreous specimen PCR * positive for HSV	29
Aqueous or vitreous specimen PCR * positive for VZV	53

* PCR = polymerase chain reaction. HSV = herpes simplex virus; 54 of 153 tested (35%) were positive. VZV = varicella zoster virus; 101 of 153 tested (66%) were positive. Two cases were positive for both viruses.

Table 2.

Classification Criteria for Acute Retinal Necrosis

Criteria
1. Necrotizing retinitis involving the peripheral retina
AND (either #2 OR #3)
2. Evidence of infection with either herpes simplex virus (HSV) or Varicella zoster virus (VZV)
a. Positive PCR * for either HSV or VZV from either an aqueous or vitreous specimen
OR
3. Characteristic clinical picture
a. Circumferential or confluent retinitis AND
b. Retinal vascular sheathing and/or occlusion AND
c. More than minimal vitritis †
Exclusions
1. Positive serology for syphilis using a treponemal test
2. Intraocular specimen PCR-positive for cytomegalovirus or Toxoplasma gondii (unless there is immune compromise, morphologic evidence for >1 infection, the characteristic clinical picture of acute retinal necrosis, and the intraocular fluid specimen has a positive PCR for either HSV or VZV)

* PCR = polymerase chain reaction. HSV = herpes simplex virus. VZV = varicella zoster virus.

† Vitritis criterion not required in immunocompromised patients.