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Acute retinal necrosis caused by herpes simplex virus type 2 in children: reactivation of an undiagnosed latent neonatal herpes infection

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Abstract

Herpes simplex virus type 2 (HSV-2) is known to cause acute retinal necrosis (ARN). The availability of HSV-2 specific PCR tests for diagnostic analysis has greatly increased our ability to discriminate ARN caused by HSV-2 from ARN caused by either HSV-1 or VZV. Of great interest, HSV-2 appears to be the most common cause of viral ARN in children and adolescents. Although a few children with ARN are known to have had neonatally acquired herpes infection, most children lack a history of known herpes disease. Thus, the origin of the HSV-2 infection is a mystery. The hypothesis of this review is that HSV-2 ARN in children and adolescents may be the first sign of a previously undiagnosed and asymptomatic neonatal HSV-2 infection, which has reactivated several years later from latency in a cranial nerve and entered the retina. The review brings together 7 previously published ARN cases, plus one new case is added. Thus this review also expands the spectrum of complications from neonatal HSV-2 infection.

INTRODUCTION

Herpes simplex virus type 2 (HSV-2) is a frequent cause of acute retinal necrosis (ARN) in children¹. Often the children have had no known preceding HSV-2 infection. Therefore, the obvious question relates to the acquisition of the HSV-2 infection. In this chapter, we postulate that HSV-2 retinal disease is a delayed manifestation of an asymptomatic HSV-2 infection contracted perinatally. In other words, no signs of HSV-2 infection are recognized in the newborn period or infancy. However, during childhood, the virus reactivates in a cranial nerve, enters the retina and causes ARN.

This review was stimulated by a case seen at the Children's Hospital of the University of Iowa. The girl was 8 years ago when first seen for ARN. She had been voluntarily given up for adoption by her birth mother and was subsequently placed in a foster home at one week of age. The foster mother subsequently adopted the baby girl. The foster mother was unaware of any problems surrounding the delivery, and the newborn was not receiving any medications. At age 8, the girl developed ARN caused by HSV-2.

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NEONATAL HSV-2 INFECTION

To better understand the HSV-2 ARN hypothesis, a review of neonatal HSV-2 disease is outlined below². Neonatal HSV infections are well recognized in the United States. The estimated number is about 2500 cases per year. The risk of neonatal disease is much more common in women who have acquired their primary HSV-2 infection during their current pregnancy than in pregnant women who have a recurrence of a known past HSV-2 infection (approximately 40% versus 1 %, respectively). The clinical presentation of neonatal HSV-2 disease has been classified into three categories: (i) disseminated infection, (ii) encephalitis, and (iii) skin, eye, and mouth (SEM) infection. Disseminated disease usually presents in the second week of life and has the highest mortality. Encephalitis can occur by one of two routes. Encephalitis as part of a disseminated infection is a consequence of a viremia, which seeds the brain. In contrast, isolated HSV-2 encephalitis is most likely secondary to retrograde axonal transmission of virus into the brain.

The third category, called SEM, has the lowest morbidity and mortality. Although SEM is commonly recognized by the appearance of skin vesicles during the second week of life, the eye can be the sole site of infection. In fact, some newborns may present with HSV-2 conjunctivitis in the absence of other signs. Based on the hypothesis outlined in the Introduction, asymptomatic HSV-2 neonatal disease is likely related to the SEM category, e.g., associated with subclinical conjunctivitis. Asymptomatic HSV-2 entry could occur also at the site of a fetal scalp monitor. Yet another alternative site of asymptomatic infection in the neonate would be the olfactory nerve within the nose, a well-known site of entry for viruses³.

CASES OF HSV-2 ARN IN CHILDREN

ARN Case #1

As mentioned in the Introduction, this 8 year old girl was adopted at one week of age. There was virtually no birth history available to the adoptive mother. During early childhood, the mother recognized a developmental delay in the child, but otherwise the child had never had any serious infection. The child initially attended public school in the age-appropriate grade. Because of parental concerns about vision by the school, the child was seen by an ophthalmologist, who observed no retinal abnormalities. At age 8.5 years, the girl was assessed with the Beery-Buktenica Developmental Test of Visual Motor Integration. She received an age equivalent score of 5 years 11 months.

Just a few months after the above examination, redness developed in the right eye. She was again seen by the same ophthalmologist, who diagnosed acute retinitis based on the findings of semi-confluent small white retinal opacifications in the right eye from 4 o'clock to 7 o'clock. A biopsy was subsequently performed and submitted for PCR analysis for viral pathogens. PCR amplification was positive for HSV-2 but negative for HSV-1 and VZV DNA.

The patient was initially treated with valacyclovir 1000 mg BID for 2 months, then switched to oral acyclovir at a dosage of 800 mg TID for one year. At a 2 year followup visit, there had been no recurrence of ARN. After review of this case, we presumed that the birth mother had had an unrecognized HSV-2 genital infection and that the newborn infant was infected asymptomatically.

ARN Cases #2–4

The most complete description of the viral causes of ARN was published in 2000¹. In this retrospective report, the investigators from San Francisco reported 28 patients with ARN, all

with samples submitted for PCR analysis. They discovered VZV DNA in 13 patients (15 eyes), HSV-1 DNA in 7 patients (7 eyes), and HSV-2 DNA in 6 patients (6 eyes). In general, ARN caused by either VZV or HSV-1 occurred in older adults while ARN caused by HSV-2 occurred in children and young adults. Three of the 6 HSV-2 patients were ages 7, 9, and 16 years respectively. No birth history was given for the 7 year old (case #2). The 9 year old had had a history of a blister on the head positive for HSV (not typed) at birth (case #3). The 16 year old had previously had ARN in the other eye a few years earlier (case #4).

ARN Case #5

Another report of acute HSV-2 retinal necrosis occurred in a 9 year old girl from Rochester, NY⁴. She had a 2-week history of redness in the left eye. The retinal examination showed scattered multifocal patches of whitening between 12 o'clock and 6 o'clock. After a sample of aqueous humor was obtained by anterior chamber paracentesis, PCR testing was performed. The test detected HSV-2 DNA.

When the child's birth history was reviewed, the investigators discovered that the mother was known to have had genital herpes infections. However, the newborn had no evidence of perinatal herpes infection. Therefore, the presumption in retrospect was that the newborn had acquired an asymptomatic HSV-2 infection. This case is similar to case #1.

ARN Case #6

Another case report of acute HSV-2 retinal necrosis was diagnosed in a 3 year old boy from the Nagoya region of Japan⁵. At his first clinic visit, the boy had a 2-day history of hyperemia of the conjunctiva in his left eye. A retinal examination revealed white necrotic areas in the peripheral left retina. A subsequent PCR analysis of the aqueous humor detected HSV DNA. A serology test detected HSV-2 specific antibody but no HSV-1 specific antibody.

When a serology test was performed on the mother, she had a high titer of HSV-2 specific antibody. This result was unexpected because the seroprevalence of HSV-2 antibody in Japanese women is less than 7%. Again, the presumption in this case was that the newborn contracted an asymptomatic HSV-2 infection at childbirth. This case resembles both cases #1 and 5.

ARN Cases #7, 8

A larger retrospective analysis of acute HSV-2 retinal necrosis was published in 2004 by the ophthalmology service at a major medical center in Paris, France⁶. Their report included 11 patients, ranging in age from 10 years to 57 years. There is little information given about the 10 year old patient or his birth history.

In contrast, the clinical history of one of the other 11 patients relates directly to the hypothesis proposed in this review. A 32 year old patient with HSV-2 ARN had a past history of neonatal herpes simplex infection with subsequent blindness in the right eye in infancy. Beginning at age 22, he had his first episode of HSV-2 retinal necrosis in the left eye. In the next 9 years, he had three more episodes of retinal necrosis in the left eye. The latter case with multiple ARN episodes resembles cases #3 and 4.

PATHOGENESIS OF RETINAL DISEASE

The pathogenesis of HSV-2 ARN in children without a known history of neonatal HSV-2 has not been clearly defined. The hypothesis of this review is that these children contracted a subclinical HSV-2 infection at delivery from a mother with genital herpes (Figure 1). The

virus could have entered via sensory nerves located in the conjunctivae or nasal epithelium. Virus can also enter at a site where the skin has been penetrated by a fetal scalp monitor. These sites are innervated by either the trigeminal nerve (ophthalmic and maxillary branches) or the olfactory nerve. The virus would be transported retrograde into the ganglia, from which the virus could reactivate later in childhood and travel anterograde to the eye. There are several reports of different viruses entering the olfactory nerve, after which they are transported into the central nervous system (CNS)³.

A nasal CNS invasion route has been described for meningococcal bacteria, which may also be relevant for viruses⁷. In a mouse model, investigators demonstrated that after nasal instillation, bacteria traveled along olfactory nerves into the subarachnoid space and meninges. Similarly, it may be possible for HSV-2 instilled into the nares of an infant during childbirth to spread from the subarachnoid space surrounding the olfactory nerve to the subarachnoid space surrounding the optic nerve, since the spaces are contiguous where the cistern of the lateral fissure joins the basal cistern. Thus the initial route of entry into the CNS would not be neuronal, although the virus would eventually enter the optic tract and establish latency. Earlier studies in mice have documented spread of herpes to the eye after inoculation of the murine snout⁸.

TREATMENT OF HSV-2 ARN

Immediately after diagnosis, the traditional treatment of HSV-2 ARN in children is usually intravenous acyclovir at a daily dosage of 30 mg per kg⁹. After the retinal inflammation has subsided, the patient is switched to oral acyclovir for a period of months to a year. The dosage of oral acyclovir in children for treatment of herpes infections is 60 mg per kg per day, usually divided three times daily. Acyclovir tablets are formulated at 400 mg and 800 mg. Some physicians also add oral prednisone (1 mg per kg per day) to the ARN treatment regimen during the acute stage of retinal inflammation.

A recent clinical study has investigated the penetration of the second generation acyclovir compound called valacyclovir¹⁰. Valacyclovir is now available as a generic drug; previously the drug was called Valtrex. Valacyclovir is known to be much better absorbed orally than acyclovir. In the study, 10 volunteers were given an oral dosage regimen of 1 gram three times daily prior to elective pars plana vitrectomy. The levels of the anti-viral drug in the vitreous were within therapeutic range for all 10 volunteers. This result suggests that oral valacyclovir may be an acceptable alternative to intravenous acyclovir for treatment during the acute phase of HSV-2 ARN. Note that the child described in the first case report was treated initially with oral valacyclovir.

There is also one report in which a child with ARN was treated with a single injection of intravitreal foscarnet⁴. However, the new data with oral valacyclovir are very promising and suggest that intravitreal injections may not be necessary.

In most published cases, the children with HSV-2 ARN were continued on prophylaxis with oral acyclovir after the retinal inflammation had subsided. There is no consensus on the length of prophylaxis, which ranged from months to a year. In 2010, valacyclovir became a generic medication. Because valacyclovir is much better absorbed than acyclovir, valacyclovir may be a better choice for prophylaxis in the future. There are as yet no standardized valacyclovir recommendations for children. Dosages for treatment used in individual reports have been around 60 mg per kg per day (divided every 8 hours), up to a maximum of 3 grams per day. Dosages for prophylaxis have not been established, but a 50% reduction in the treatment dosage is a suggestion. The only concern about administration of oral valacyclovir is to check once that the child has normal renal function (serum creatinine level within normal range for age).

SUMMARY

In summary, the preceding case reports provide compelling clinical evidence that HSV-2 infection can occur in children who lack a history of neonatal herpes infection. Nevertheless, at childbirth, HSV-2 must have entered a neuronal circuit involving a cranial nerve, where the virus remains latent for the early childhood years (Figure 1). Subsequently, the virus reactivates from latency during later childhood to cause acute HSV-2 ARN.

In some of the case reports cited in this review, the mother was known to have genital herpes infection, but no transmission of infection was recognized in the newborn. Finally, in a few cases, infection of the newborn was documented, but the ARN event did not occur until 9 to 22 years after birth. The hypothesis suggests that all these scenarios represent a continuum of neonatal HSV-2 infection.

Among infants with perinatally acquired HSV-2 infection, ARN can be part of the presentation during the first month of life¹¹. Also, ARN can be a component of congenital herpes infection¹², a relatively rare fetal manifestation of maternal herpes infection. However, these cases were not included as individual case reports in this review because the connection between neonatal or congenital HSV-2 infection and subsequent ARN is generally obvious. The goal of this review is to extend the above observation to include infants with HSV-2 ARN in childhood, but without a documented history of neonatally acquired HSV-2 infection.

It is possible that HSV-2 ARN in older adults could also be due to a reactivation of a perinatally acquired asymptomatic HSV-2 infection. However, an obvious confounding factor is that HSV-2 could have been contracted sexually by these same individuals during early adolescence. For example, some reports of HSV-2 ARN in young adults are associated with HSV-2 meningitis, which is a known complication following acquisition of a primary HSV-2 infection in adolescence⁶.

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Figure 1.

Pathogenesis of ARN caused by HSV-2 infection. Possible entry sites for HSV-2 during delivery of infant to an HSV-2 seropositive pregnant woman are listed on the left side. On the right side, note possible cranial nerves that may be involved in transport of HSV-2 from the face and, later in childhood, reactivation with subsequent transmission to the eye.