Viral Diseases of the Eye

Edited by
RICHARD W. DARRELL, M.D., Dr. Med. Sci.

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Preface

Fourteen families of viruses include species capable of causing disease of the eyelids, conjunctiva, cornea, uvea, retina, optic nerve, and central or peripheral nervous systems. Several species have also been implicated in the development of ocular tumors.

The most common viral disease of the eye is an acute infection of the epithelial surface of the conjunctiva and cornea, which is characterized clinically by acute follicular conjunctivitis, epithelial keratitis, and preauricular lymphadenopathy; the causative agent is most often an adenovirus. A new viral type, enterovirus 70, has recently been identified as the cause of an acute follicular conjunctivitis with subconjunctival hemorrhage (acute hemorrhagic conjunctivitis) that affects individuals living in coastal tropical regions in a new epidemiologic pattern.

Immunosuppressed individuals are particularly vulnerable to viral infections of the retina, as is the case in cytomegalovirus infection. While human t-lymphotrophic retrovirus (HTLV-III) does not directly infect the retina, it so severely weakens the immune defense system in acquired immune deficiency syndrome (AIDS) that cytomegalovirus infection of the retina can take place.

The optic nerve and central and peripheral nervous systems are also targets of viral disease, either by direct infection or through a secondary immune response, as in postinfectious encephalomeningitis. The peripheral sensory nerves are host to herpes simplex virus and varicella-zoster virus in their latent states. Multifocal leukoencephalopathy caused by polyomavirus, and subacute sclerosing panencephalitis caused by measles virus are chronic and progressive degenerative diseases of the central nervous system.

The contributors to this book have explored in depth the viral diseases of the eye, as well as the complex biologic problems of resistance to infection, virus latency, reactivation of disease, and the host immune response.

I would like to thank my colleagues, attendings and residents, at the Harkness Eye Institute of the Columbia Presbyterian Medical Center, for sharing with me so many challenging cases during the past 20 years.

New York, New York

Richard W. Darrell

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RESPONSE TO INFECTION

Introduction (Taxonomy of Viruses)

RICHARD W. DARRELL

Viruses are essentially molecules of nucleic acid capable of penetrating living cells and of redirecting the host's cellular machinery to create additional copies of both viral nucleic acid and protein. Within this framework, viruses are a very diverse group of infectious agents. They contain either DNA or RNA as their nucleic acid, vary greatly in size, from 22 nm (parvovirus) to 250 × 300 nm (poxvirus), are coded for different enzymes, and differ in the complexity and geometry of their electron micrographic appearance.[1,2] The nucleic acid of the virus is called the genome and is surrounded by a protective protein shell, or capsid; genome and capsid together comprise the nucleocapsid. Capsids are constructed of repeating subunits arranged in geometric or otherwise precise patterns, as, for example, the icosahedral symmetry of adenovirus or the helical symmetry of orthomyxoviruses and paramyxoviruses (Table 1).

Viruses also differ in their host ranges, both in the living animal and in tissue culture. The latter is important because several different types of tissue culture cells must be used to isolate an unknown virus that may grow well in one but not in other types of cells. Within the living host, different virus species also display a preference for different types of tissue. For example, herpes simplex virus infects sensory nerves and becomes latent in nerve ganglia, whereas adenovirus is usually limited to epithelial and adjacent subepithelial tissues.

The sequelae of virus infection of the eye and visual system can be divided clinically into four general patterns (1) acute conjunctivitis, keratitis, and blepharitis following infection of the ocular surface, (2) chorioretinitis and uveitis following infection of the retina and uvea, (3) optic neuritis, papillitis, papilledema, oculomotor paresis, and meningoencephalitis following infection of the central and peripheral nervous system, and (4) the induction of tumors (Table 2). That viruses could cause ocular tumors was a matter of conjecture until recently, but new evidence has implicated several viruses in the development of cancer (e.g., melanoma).

Infection of the epithelial surface of the cornea, conjunctiva, and eyelids is the most commonly encountered virus disease in clinical practice. The hallmarks are follicular conjunctivitis, variable epithelial keratitis, and enlargement of the preauricular lymph nodes. Herpes simplex virus and adenovirus infections are the usual causes, although in tropical regions, coxsackievirus A24 and enterovirus

Table 1. Characteristics of Virus Families Causing Diseases of the Eye

Family	Nucleic Acid	Morphology	Diameter of Naked Nucleocapsid (nm)
Herpesviridae	DNA	Enveloped icosahedral nucleocapsid	100
Poxviridae	DNA	Complex	225 × 300
Adenoviridae	DNA	Naked icosahedral nucleocapsid	75
Papovaviridae	DNA	Naked icosahedral nucleocapsid	45–55
Picornaviridae	RNA	Naked icosahedral nucleocapsid	25–30
Togaviridae	RNA	Enveloped icosahedral nucleocapsid	40–70
Bunyaviridae	RNA	Enveloped coiled circular nucleocapsids	100
Reoviridae	RNA	Naked double-shelled icosahedral nucleocapsid	75
Orthomyxoviridae	RNA	Enveloped helical nucleocapsid	80–120
Paramyxoviridae	RNA	Enveloped helical nucleocapsid	150
Rhabdoviridae	RNA	Enveloped helical nucleocapsid	75 × 180
Retroviridae	RNA	Enveloped coiled nucleocapsid	150
Arenaviridae	RNA	Enveloped coiled nucleocapsid	80–130
Coronaviridae	RNA	Enveloped helical nucleocapsid	100

70 cause acute hemorrhagic conjunctivitis. Vesicle formation on the lids or conjunctiva suggests infection by herpes simplex or varicella-zoster virus. Such vesicles are also seen in variola and varicella virus infections, but these diseases have been eliminated almost completely by vaccination. Similarly, the eradication of smallpox has reduced the need for vaccinia virus as a source of vaccination against the disease; therefore, the extreme blepharitis and conjunctivitis seen in vaccinia virus ocular infection is also observed rarely today.

Most virus families contain species capable of causing external ocular disease, for example, herpes simplex virus type 1 and 2, varicella-zoster virus, and Epstein-Barr virus among the herpesviridae; smallpox, chickenpox, vaccinia, and molluscum contagiosum viruses among the poxviridae; numerous adenovirus types among the adenoviridae; the virus that causes papilloma among the papovaviridae; coxsackievirus, enterovirus, and human rhinovirus among the picornaviridae; rubella virus among the togaviridae; influenza, parainfluenza, Newcastle disease, mumps, measles, and respiratory syncytial viruses among the orthomyxoviridae and paramyxoviridae families; and the coronaviruses among the coronaviridae. All of these can produce variable signs of virus infection of the ocular surfaces.

Virus infection of the retina and uvea causes chorioretinitis and uveitis with variable inflammation of the optic nerve and retinal vessels. All members of the herpesviridae family are capable of producing this clinical pattern, particularly in individuals whose immune system has been suppressed. Rubella virus infection (togaviridae) also affects the choroid and retina, and a retinitis is seen in the rarer bunyaviridae infections (Rift Valley fever). human T-lymphotrophic retroviruses (HTLV-III) have been isolated from patients with AIDS (acquired immune deficiency syndrome).[3–6] While these viruses do not directly infect the eye, they can so weaken the T-cell immune system that secondary infections can colonize the retina and choroid.

Virus infection of the central and peripheral nervous system is manifested clinically by optic neuritis, papillitis, papilledema, oculomotor paresis, and meningoencephalitis. Most members of the togaviridae, bunyaviridae, and reoviridae families cause encephalitis and are transferred by insects. Many members of the herpesviridae family can cause meningitis and encephalitis, particularly in immu-

Table 2. Virus Species Causing Disease of the Eye

Family	Subfamily or Genus	Species	Clinical Disease
Herpesviridae	Alphaherpesvirinae	Herpes simplex virus type 1	Herpetic ocular disease
		Herpes simplex virus type 2	Genital herpes with ocular infection in newborn and adults
		Varicella zoster virus	Chickenpox ocular disease in nonimmune, herpes zoster ocular disease in immune individuals
		B virus	Encephalitis
	Betaherpesvirinae	Human cytomegalovirus	Retinitis
	Gammaherpesvirinae	Epstein-Barr virus	Infectious mononucleosis
Poxviridae	Orthopoxvirus	Variola major	Smallpox
		Variola minor	Chickenpox
		Vaccinia	Vaccinia
	Parapoxvirus	Orf virus	Contagious pustular dermatitis
	Ungrouped	Molluscum contagiosum	Molluscum of lids
Adenoviridae	Mastadenovirus	Human adenovirus	Follicular conjunctivitis, keratitis
Papovaviridae	Papillomavirus	Human papillomavirus	Papillomas on lid or conjunctiva
	Polyomavirus	DAR Virus	Progressive multifocal leukoencephalopathy
		JC virus	
Picornaviridae	Enterovirus	Poliovirus 1–3; Coxsackievirus A,B; Echovirus; Enterovirus	Meningitis; acute hemorrhagic conjunctivitis in coxsackievirus A24 and enterovirus 70 infection
	Rhinovirus	Human rhinovirus	Common cold
Togaviridae	Alphavirus; Flavivirus	Insect-borne viruses named for geography of disease	Encephalitis
	Rubrivirus	Rubella virus	Rubella ocular disease
Bunyaviridae	Bunyavirus	Insect-borne viruses named for geography of disease	Encephalitis; retinitis in Rift Valley fever
Reoviridae	Orbivirus	Colorado tick fever virus	Encephalitis
Orthomyxoviridae	Influenzavirus	Influenza virus A,B,C	Conjunctivitis
Paramyxoviridae	Paramyxovirus	Parainfluenza virus 1–4	Conjunctivitis (type 1); respiratory infections (type 2–4)
		Newcastle disease virus	Conjunctivitis
		Mumps virus	Dacryoadenitis
	Morbillivirus	Measles virus	Conjunctivitis; keratitis

Table 2. Virus Species Causing Disease of the Eye *Continued*

Family	Subfamily or Genus	Species	Clinical Disease
		Subacute sclerosing panencephalitis	Chronic degeneration of the central nervous system
	Pneumovirus	Respiratory syncytial virus	Common cold
Rhabdoviridae	Lyssavirus	Rabies virus	Encephalitis; in rare cases, transmission is by donor corneal transplant
Retroviridae	Oncovirinae	RNA tumor viruses	Benign tumors and leukemia
		HTLV-III	Acquired Immune Deficiency Syndrome
Arenaviridae	Arenavirus	Lymphocytic choriomeningitis virus	Meningitis
Coronaviridae	Coronavirus	Human coronavirus	Upper respiratory disease
Unclassified viruses and virus-like agents	CHINA agents (chronic infectious neuropathic agents)	Agents of Kuru and Creutzfeldt-Jakob disease	Degenerative disorder of the central nervous system

nocompromised individuals. Poliovirus, coxsackievirus, echovirus, and enterovirus (picornaviridae) are all capable of causing meningitis, as are rabies and lymphocytic choriomeningitis viruses (rhabdoviridae and arenaviridae).

Progressive multifocal leukoencephalopathy, a slowly progressive degenerative disease of the central nervous system, is associated with DAR and JC viruses (papovaviridae). Subacute sclerosing panencephalitis, also a progressive degenerative infection of the central nervous system, has been linked to the measles virus (paramyxoviridae). Creutzfeldt-Jakob disease and rabies have both been transferred to a healthy individual by a corneal graft taken from a donor not known at the time to have these diseases.[7–10]

Viruses continue to present surprises to us in their relationship to cancer as well as to acute infectious disease. Occasionally, a new virus will appear in the context of a new epidemic disease, as is the case with enterovirus 70 in acute hemorrhagic conjunctivitis, and human T-lymphotrophic retroviruses (HTLV-III) in acquired immune deficiency syndrome (AIDS). Whereas most viruses cause an acute disease from which the patient recovers, other viruses remain latent with the body. Still other viruses do not become latent but continue a relentless course of destruction, as is evident in progressive multifocal leukoencephalopathy, subacute sclerosing panencephalitis, and Creutzfeldt-Jakob disease. A few virus species are instrumental in altering the normal growth controls within cells, thus causing cancerous growth. The broad spectrum of virus diseases of the eye will be discussed in detail in the following chapters.

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