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Viral syndromes

Erik Lycke

Only occasionally do virus infections display clinical features distinctive enough to provide a diagnosis of the aetiology of the infection. More often the generalized virus infections make the clinical picture less characteristic and therefore many different viruses induce infections with a similar symptomatology. A listing of viruses which are aetiologically important in association with a particular pattern of clinical symptoms, a syndrome, often leads to a reiteration of the same groups of viruses under different syndrome titles. In the case of some viral infections, the relative importance is insufficiently known and often detailed knowledge about prevailing local conditions is required before any evaluation can take place. The prevalence of an infection is influenced not only by climate and environment but also by many socioeconomic factors. Thus it is far from certain whether data from the international literature should be adopted without question to illustrate the specific national situation. The following account of viral syndromes and the medical importance of various virus infections has deliberately been kept to an outline. It is presented mainly in tables and so-called ‘cakes of etiology’ using the information on the virus family level. There are, however, observations demonstrating that a particular type of virus is more frequently isolated than others in association with a clinical syndrome. Only the most important of these observations will be described. The pathogenetic background has been commented on in Chapters 13 and 14.

Respiratory tract infections

The majority of all upper respiratory infections are caused by viruses (Figure 34.1). The impression that viral infections dominate is strengthened if, in addition, the abundance of subclinical virus infections is considered, in particular those in children.

The possibilities of estimating the relative medical importance of various respiratory viruses are complicated by the epidemic occurrence of the infections, like influenza, parainfluenza, RS- and adenovirus infections. Epidemiological factors, seasonal variation, etc. markedly influence the overall number of cases. A comparison like the one in Figure 34.1 between the medical importance of different virus infections will therefore, by necessity, be a rough approximation. Probably there are still a number of unknown viruses which play important roles in upper-respiratory-tract infections. The coronaviruses, a yet little recognized virus group, may turn out to be important inducers of respiratory tract infections in adults.
Acute *laryngotracheitis or croup* is associated primarily with infections of parainfluenza type 1. This type of virus is about 4 times more often isolated from children with croup as parainfluenza type 2 even though the latter in the earlier literature is designated as CA (croup-associated). Less common are RS-virus infections in cases of croup.

*Common colds* are probably most frequently caused by rhinoviruses but both enterovirus and coronavirus infections may cause a similar pattern of symptoms. By no means all of the common cold-associated viruses have been isolated. To use a well worn phrase we are only seeing the tip of the iceberg.

![Figure 34.1. The relative importance of viruses in upper-respiratory-tract infections](image)

A somewhat different distribution is discernible between bacteria and viruses as to their relative importance for upper and *lower-respiratory-tract infections* (*Figure 34.2*). Bacterial infections (infections with pneumococci and mycoplasmas) are responsible for many of the adult patients hospitalized with *pneumonia* while viruses (influenza-, parainfluenza-, RS- and adenoviruses) in adults are less often causes of the lower-respiratory-tract infections. However, pneumonia might commonly be a predominant symptom of a generalized virus infection or occur in infections complicated by immunosuppressive treatments. These cases are occasionally observed with entero-, EBV-, CMV- and HSV infections. It should also be kept in mind that measles, rubella and chickenpox all start as respiratory tract infections.

The most serious medical consequences of viral pneumonia are encountered in the old, the newborn or the patient with a circulatory or respiratory handicap. Influenza is a cause of increased mortality among the old whilst RS virus is the most important respiratory virus infection in small children. Particularly in individuals
Infections of the pharynx

with generally low nutritional and socioeconomic conditions, the RS-virus-induced bronchiolitis and pneumonitis are responsible for an increased mortality rate in infants.

Patients receiving treatment with immunosuppressive and cytostatic drugs, or who are otherwise immunologically handicapped, are, as mentioned, more susceptible to lower-respiratory-tract infections when infected with measles and adenoviruses, but pneumonia could also result from a reactivated CMV and HSV infection. The latter kind of infections, gradually becoming more common in medical clinics in industrialized countries, particularly in association with organ transplant surgery, are often referred to as opportunistic infections. These opportunistic infections, some of which are bacterial, viral or fungal, others of parasitic origin, are generally subclinical and latent but may become serious and life-threatening in the immunocompromised host.

The respiratory virus infections are diagnosed in the laboratory by the combined use of virus isolation methods, detection of viral antigens in cells of nasal and/or throat washings, and by serology.

Infections of the pharynx

Fever and a reddened sore throat are among the most common symptoms of infection and are seen in association with many virus infections. The predominant number of cases of pharyngitis in children and young adults are due to virus infections. Table 34.1 presents some virus infections which may produce more characteristic pictures of gingivostomatitis and tonsillitis. Enanthemas with eruptions on the mucous membrane of the pharynx may be caused by the herpesviruses. Vesicular gingivostomatitis may result from both primary and recurrent HSV infections. The primary HSV stomatitis may lead to bleeding and ulcers of necrotic tissue. Patients with zoster sometimes present a distinctive picture with involvement of the mucosa of half the tongue to the middle line.
In this context it may be appropriate to recall the varying engagements of the salivary glands in mumps virus infections. Most commonly, the parotid glands are affected on both sides but sometimes the submandibular and sublingual salivary glands are infected. Infection of the glands on one side only is less frequent than the infection of the salivary glands of both sides.

Infections with exanthemas

The appearance, texture and consistency of the pocks and their distribution over the body were the four important signs for distinguishing clinically between smallpox and other vesicular and pock-producing infections. In smallpox the efflorescences develop synchronously while in chickenpox all the stages from the early maculopapular changes to the crusts are demonstrable. The pocks are hard as buttons in smallpox but soft and vulnerable in vaccinia and varicella virus infections. In chickenpox the exanthema is mainly located on the trunk while in smallpox most of the pocks are found on the head and limbs.

Maculopapular and vesicular rashes are common features also in several enterovirus infections in addition to the pox- and herpesvirus infections.

Coxsackie A viruses, mainly types 5, 9 and 16, have been associated with vesicular efflorescences on the palms, soles and in the mouth, so-called hand-foot-and-mouth disease. As with the pox- and herpesviruses, infective coxsackie virus can be isolated from vesicular fluid during the acute phase of the infection.
The maculopapular skin eruptions of measles and rubella cannot be distinguished from rashes seen in association with many enterovirus infections. In fact much confusion, anxiety, and even legal abortions, have resulted from epidemic outbreaks of enteroviruses in the past when the rash is similar to that of rubella and appears in pregnant women. Confusion has resulted also from the characterization of the appearance of a rash as morbilliform or rubelliform, terms which have been misinterpreted as indicating the aetiology. While in measles and rubella the laboratory diagnosis almost exclusively is obtained by serology studies, the aetiological characterization of enterovirus infections with rash is mainly based on the isolation of the virus. Maculopapular exanthemas may be encountered also in other virus infections, for example the adenovirus infections, and mainly in small children with fever and pharyngitis.

Distinctly different are the changes in the skin caused by the bleeding associated with the haemorrhagic fevers. The extensive diapedesis observed in these diseases is not restricted to capillaries of the skin but is present also in inner organs.

**Hepatitis**

Hepatitis A, B and so-called 'non A- non B' virus infections have been described in Chapter 30. Other virus infections may also affect the liver however and under some conditions lead to severe infections. Hepatitis may be part of a generalized infection affecting several organs; the infections may be congenital or neonatal infections but also affect adults. Newborn children with symptoms of a rubella-, cytomegalo- or herpes simplex virus infection may demonstrate extensive inflammatory and necrotizing engagement of the liver. In yellow fever, hepatitis and nephritis are parts of the haemorrhagic fever syndrome. A hepatitis may also be seen in mononucleosis, and signs suggestive of a pathological liver function in patients with enterovirus infections may sometimes be discovered in the laboratory. In immunosuppressed patients hospitalized for organ transplantation surgery, opportunistic herpesvirus infection may include infection of the liver.

**Gastrointestinal infections**

In adults the majority of epidemic diarrhoeal infections are probably bacterial but in children it is undoubtedly the virus infections which are the most important. Table 34.2 presents the most important infections associated with symptoms of gastroenteritis. Common to these infections is the lack of cell culture systems for cultivation of the viruses. It has been claimed that only enterocytes are permissive of infections with gastroenteritis viruses. Even though other cell systems might be susceptible, there are at present no cell lines available for isolation and propagation of the different gastroenteritis viruses. They are routinely demonstrated by electron microscopy, demonstration of viral antigens, or serology.

Rotavirus is recognized by its characteristic double-layered capsid with cubical symmetry and by its size, 70 nm in diameter. There are rotaviruses of many different animal species and some have antigenic and biological properties in common with the three human serotypes.

Rotavirus is transmitted by the faecal-oral route; it replicates in the intestine villi which are destroyed by the infections. The first infection appears as early as the...
neonatal period. In the absence of resources for rehydration and restoration of electrolyte balance, the diarrhoea may be life-threatening. Rotavirus infections therefore create medical problems particularly in developing countries. Presence of IgA and IgG antibodies in the intestines and the transfer of secretory IgA with the milk from mother to child have been considered essential for recovery and immunity against the rotavirus infections. The importance of passive local immunization via breast-feeding may be an essential argument against artificial feeding in developing countries. Rotavirus is, as mentioned, diagnosed by electron microscopy of faecal specimens or by detection of viral antigens. In serology the antigenic relatedness between animal and human rotaviruses are sometimes utilized. In contrast to human rotavirus, the calf rotaviruses may be grown in cell cultures. Also hybrids between human and calf rotaviruses have been used for, among other reasons, the production of antigens to be used in diagnostic work for detecting rotaviruses.

**TABLE 34.2. Gastroenteritis viruses**

| Virus        | Family               |
|--------------|----------------------|
| Rotavirus    | Reovirus             |
| Norwalk virus| Parovirus-like*      |
| Astrovirus   | Picornavirus-like    |
| Calicivirus  | Picornavirus-like    |
| Hawaii virus | Picornavirus-like    |
| Adenovirus   | Adenovirus**         |

* Although not classified, Norwalk virus displays several features in common with the paroviruses.
** Adenoviruses associated with symptoms of gastroenteritis are genetically distinguishable from adenoviruses causing respiratory infections. They cannot as yet be cultivated in vitro

Also, other gastroenteritis viruses have been demonstrated by electron microscopy (Norwalk agent, Hawaii agent, astrovirus, calicivirus, etc; Table 34.2). Knowledge about these viruses and their association with acute gastroenteritis is as yet incomplete. Norwalk agent, as yet unclassified but perhaps a parovirus, has been observed in patients suffering from so-called *winter vomiting disease* and for some of the ‘non-cultivatable’ or enteric adenoviruses there are strong associations between infection and epidemic diarrhoeal disease. Myxovirus infections (influenza in small children and measles in undernourished children) may induce symptoms of gastroenteritis. Sometimes diarrhoeal disease has been associated with enterovirus infections. However, the causal relationship between enteroviruses found in faecal specimens and gastroenteritis is doubtful.

**Urogenital infections**

In many virus infections virus is excreted with the urine but this finding does not signal an impaired kidney function. Histopathological findings in some infections with CMV and HSV suggest that the kidneys sometimes may be involved. Several arboviruses responsible for haemorrhagic fevers are associated with nephrosis or
nephritis. A *nephropathia epidemica* has been reported from northern parts of Scandinavia, Finland and the Soviet Union. The virus, which seems to be a bunyavirus, is immunologically related to the Korean haemorrhagic fever virus. A similar virus is responsible for a syndrome of nephritis described in Japan. Virus reservoirs have been traced to wild small rodents.

*Glomerulonephritis* as a symptom of the hepatitis B virus syndrome has been attributed to deposits of antigen-antibody complexes in glomeruli and arterioli.

An acute *haemorrhagic cystitis* with blood in the urine and dysuria has been observed in association with the adenovirus types 2, 11 and 21 infections. Symptoms of cystitis are often recorded in cases of genital HSV infections particularly in women.

Among the genital virus infections, the HSV type 2 and the genital wart virus infections are the most common clinically of the *sexually transmitted virus infections*. In patients attending outpatient clinics for venereal diseases, HSV-2 infections with symptoms of disease are recorded in about 3 per cent. However, there is a trend for an increasing medical implication of genital HSV-2 infections throughout the world. Also *condylomatosi*, the anogenital papillomas due to a wart virus infection (cf. Chapter 18), is a disease which has spread considerably among prostitutes and promiscuous individuals. CMV as well as the hepatitis B virus can both be transmitted sexually although clinical signs of genital infection are lacking. Moreover the immunosuppressive action of CMV infections may be important in the development of *Kaposi’s sarcoma* among male homosexuals. Kaposi’s sarcoma is usually associated with the *acquired immune deficiency syndrome* (AIDS). Although the aetiology of the underlying immune deficiencies is unknown, several different infections are involved; among those are many virus infections (CMV, HSV, hepatitis B etc.) but also pneumocystis carinii, syphilis and other bacterial and protozoal infections. Most of these are well recognized opportunistic infections. In addition to in male homosexuals AIDS occasionally may be encountered in heterosexual women. On the other hand, promiscuous sexual life seems to be a common denominator. By 1983 more than 600 cases of AIDS had been reported from US and 40 to 50 cases from Europe.

Finally the spread of mumps virus to the testes should be recalled. The *orchitis* which complicates about every fifth case of mumps may, if it appears in boys after adolescence, cause a reduced fertility.

**Infections of the nervous system**

Chapters 13 and 14 described how virus infections occasionally might reach the nervous system by haematogenous or neuronal pathways. The different modes by which the infection is carried to and propagated in the CNS undoubtedly influences the course of an CNS infection. Haematogenously spread virus may initially cause a *meningitis* and induce a *meningoencephalitis* when further transmitted to the brain.

Axonal spread of virus may induce *encephalitis* without the virus passing the blood-brain barrier and symptoms of meningitis may be sparse or absent.

Most of the epidemic enterovirus infections may result in meningitis. Usually, in outbreaks of poliomyelitis, a number of cases are registered as meningitis; non-paralytic polio was a diagnosis previously much used. As a rule there are more cases of meningitis than of paresis. Meningitis as a part of a syndrome consisting alternately also of herpangina, hand-foot-and-mouth disease, myalgia or an undifferentiated febrile condition with or without rash, is seen in coxsackie- and
echovirus infections. In outbreaks of coxsackie B virus infections, cases of meningitis coupled with myalgia, pleurisy and/or pericarditis are the characteristic symptoms. Meningitis is a common symptom also in other virus infections. As a complication of mumps, a meningitis may appear before, simultaneously with or, as a rule, after symptoms from the parotid glands. Mumps is often accompanied by meningeal irritation, in most cases subclinically.

Polio- and some other enteroviruses (coxsackie A7, coxsackie B, echo 2 and 4, entero 71) may affect motor neurons and cause paralytic disease (Table 34.3). Paralysis may in addition be a part of the syndrome of encephalitis. Many of the

| Syndrome                                      | Virus                                                                 |
|----------------------------------------------|----------------------------------------------------------------------|
| **Symptoms of the central nervous system**   |                                                                      |
| Poliomyelitis                                 | Poliovirus 1–3                                                       |
| Poliomyelitis-like                            | Coxsackie virus A7, enterovirus 71, occasionally also coxsackie B- and some echoviruses |
| Encephalitis                                  | Arboviruses, HSV, rabies virus, enterovirus 71, mumps- and measles virus |
| Postinfectious encephalitis                   | Measles-, mumps-, influenza-, rubella-, vaccinia- and varicella-zoster virus |
| Encephalopathy, Reye’s syndrome               | Influenza- and varicella-zoster virus                                |
| Subacute sclerosing panencephalitis (SSPE)    | Measles virus                                                        |
| Progressive rubella panencephalitis (PRP)     | Rubellavirus                                                         |
| Progressive multifocal leucoencephalopathy (PML) | Papovavirus                                                        |
| Jakob–Creutzfeld disease, Kuru                | Unclassified agents (see Chapter 17)                                  |
| **Symptoms of the peripheral nervous system** |                                                                      |
| Guillain–Barré syndrome                       | All the herpes-, measles- and influenza viruses                      |
| Transverse myelitis                           | Varicella-zoster virus, Epstein–Barr virus                           |
| Bell’s palsy                                  | Herpes simplex virus, varicella-zoster virus, Epstein–Barr virus     |

TABLE 34.3. Virus infections of the nervous system

Arbovirus infections are accompanied by symptoms of meningoencephalitis and are, together with rabies, the most common encephalitogenic virus infections of the tropical and subtropical climate zones. In Europe, USA and Canada, herpes simplex virus type 1 is the virus most frequently isolated from cases of encephalitis. An incidence in these countries of one case yearly per million inhabitants is probably an underestimation. While the HSV type 2 infections are responsible for most of the meningoencephalitides observed in neonatally infected children and measles encephalitis is the feared complication of measles in children of school age, HSV type 1 is the most important cause of encephalitis in the adult population.

Occasionally the so-called postinfectious encephalomyelitides may be associated with symptoms of paralysis. Part of the pathogenesis of these diseases are myelin damages, probably immunologically elicited. Infective virus is not isolated. The
postinfectious encephalomyelitides develop after the acute phase of measles, mumps, rubella, influenza, varicella or vaccinia infection. Clinically it may be difficult to differentiate between postinfectious encephalomyelitis and forms of acute encephalitis.

Reye's syndrome is one of the sometimes fatal encephalopathies demonstrating degenerative changes in several parenchymatous organs and considered to be immunologically elicited. Reye's syndrome has been observed in association with varicella and influenza virus infections. Chronic degenerative encephalitis may follow as a sequela to measles (SSPE) and rubella (PRP). Belonging to the group of encephalopathies, but with a different pathogenesis, is the progressive multifocal leucoencephalopathy from which papovaviruses have been isolated. Although the infections are seen in the immunocompromised patients and the viruses may be referred to as opportunistic agents, they are believed to be aetiologically important for the disease. The progressive spongiform encephalopathies (Jakob–Creutzfeld disease and kuru) have been described in Chapter 17.

The Guillain–Barré syndrome is an acute febrile polyneuritis, and has been observed after infections with herpesviruses, measles, influenza and after vaccination against influenza. In rare cases, a myelitis with the symptomatology of a transverse lesion is observed in patients with varicella and EBV infections. Herpesvirus infections (HSV, EBV, and particularly VZV) have been discussed as a possible aetiology to Bell's palsy, a paresis of the facial nerve.

Apparently, virus infections may be responsible, both directly and indirectly, for acute as well as chronic diseases of the nervous system. Both the central and peripheral nervous systems may be affected. Even if the diseases are uncommon, they are of considerable medical importance due to their invalidating and life-threatening consequences.

Infections of the sensory organs

Virus infections of the CNS may occasionally result in symptoms from the optic nerve. Acute optic neuritis has been described in context with epidemic viral meningitis and acute mumps infection. A retinitis may be part of the syndrome of measles and SSPE. Haemorrhages and exudate over the retina may be demonstrable in the necrotizing neonatal HSV infection.

Impairment of vision as a consequence of infections which have reached the eye from without, however, is more frequent. Conjunctivitis may be encountered in adeno-, entero- and herpesvirus infections. If the infection affects the cornea as well the result may be a serious complication, a keratoconjunctivitis. Outbreaks of epidemic keratoconjunctivitis caused by adenovirus type 8 have only rarely caused persistent impairment of vision. A worldwide epidemic with severe acute haemorrhagic conjunctivitis was associated with enterovirus 70 but coxsackie A 24 has also been incriminated with haemorrhagic conjunctivitis. Necrotic changes of the cornea with scarring or ulcers may follow eye infections with herpes simplex virus. If untreated this infection may lead to perforation and an iridocyclitis with blindness. A similarly serious course may result from a zoster ophthalmicus affecting sclerae and cornea. Furthermore, one of the herpesviruses, CMV, may induce congenital eye infections as well as an acquired haemorrhagic retinitis later in life. CMV and rubella virus constitute the medically most important aetiology to
virus-induced eye malformations. The symptomatology of congenital rubella eye infection includes in addition cataract, retinitis and strabismus. Hearing defects following congenital rubella and CMV infections may be due to central as well as inner ear defects. Sensory-neural hearing damage is the most common symptom of the rubella syndrome and is demonstrable in 50 per cent of the children. Neurological defects combined with impairment of hearing have been observed also after mumps infections. Common in both children and adults are the infections which reach the middle ear from the nasopharynx via the auditory tube and cause an otitis. The aetiological importance of virus infections of the upper respiratory tract for induction of infections of the middle ear has still not been evaluated satisfactorily. It is possible however that many cases of bacterial otitis develop secondarily to upper-respiratory-virus infections, the latter having reduced the defence barrier of the ciliated epithelium.

Patients with viral infections of the nasopharynx may find that their smell and taste sensations have disappeared. Usually the anosmia is present during or shortly after the infection. If the effects of the local inflammatory reaction are responsible normal sensations will return when the infection is over. Infections destroying the structure of the mucous membrane, including the basilar membrane, olfactory glands and nerve terminals, may however result in a longlasting functional impairment with absence of the sense of smell and taste.

**Neonatal infections**

Infections in a child acquired after the rupture of the fetal membranes when it is passing the birth canal or infections occurring during the earliest period of life are usually referred to as neonatal infections. The clinical picture is characterized by the greater susceptibility of the newborn to infections but is otherwise not principally different from the course of infections met later in life. Since the organogenesis is completed none of the malformations or organic defects which constitute the congenital infections are encountered (see Chapter 15). It is possible that a neonatal infection of the still immature CNS may have a particular negative influence, however.

The neonatally infected child first excretes virus several days after birth. Children infected with CMV shed virus 3–4 weeks postinfection and children becoming hepatitis B virus carriers first shed virus at 3–6 months after birth (see Chapter 30).

*Table 34.4* gives an account of the most important and frequent neonatal infections. The majority of the infections are subclinical. When clinical symptoms are manifested they may range from short periods of nutrition difficulty to life-threatening infections. The generalized infections particularly are dangerous. Often these children are handicapped in other ways too, being born prematurely or being immunologically defective, etc.

Herpes simplex type 2 infections are in most cases transmitted to the child in association with birth and they become most serious in children born to mothers with a primary genital HSV infection. If the mother has a recurrence of her infection the disease of the child usually becomes restricted, perhaps because of passively transferred maternal antibodies. A caesarean section before rupture of the fetal membranes reduces the risk of neonatal infection as may also a prophylactic transfusion with anti-HSV immune globulin, although very limited experience is yet available. Subclinical infections are common also among neonatal
CMV infections. Only occasionally does neonatal CMV infection lead to clinical symptoms and sequelae seem rare although they might not be excluded. *Failure to thrive, pneumonitis and hepatosplenomegaly* are the most regularly observed symptoms of the clinically overt infection.

RS virus often produces serious symptoms of *bronchiolitis* with asphyxia in newborns. These symptoms also affect children of mothers immune to the infection. Reactions between maternally transferred antibodies and RS virus antigens of cells of the infected child have been considered as pathogenetically essential although this seems doubtful since it has been shown that children born to sero-negative mothers may be affected.

**TABLE 34.4. The most common neonatal infections**

| Virus            | Clinical symptoms                                      |
|------------------|--------------------------------------------------------|
| HSV              | Restricted or generalized necrotizing infection        |
| CMV              | Thriving problems, pneumonitis, hepatitis               |
| VZV              | Neonatal varicella, pneumonitis                        |
| Measles virus    | Pneumonia, measles                                     |
| RS virus         | Bronchiolitis, pneumonitis, undifferentiated fever      |
| Poliovirus       | Meningoencephalitis, paralytic poliomyelitis           |
| Enterovirus 71   | Meningoencephalitis                                    |
| Hepatitis B virus| Generalized infection                                  |
| Rotavirus        | Gastroenteritis                                        |

Poliovirus infections occasionally appear as *neonatal paralytic infections*. The disease is present in children of non-immune mothers. Of the neonatal enterovirus infections, the coxsackie B virus is responsible for the most important infections. *Nosocomial coxsackie B virus infections* in nurseries and paediatric wards are particularly feared as the infections which affect heart, brain and liver are associated with high mortality rates. Often the disease is introduced to the wards by a subclinically infected patient, staff member or visitor.

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