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A New Look at Infectious Diseases

Enterovirus Infections

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The enteroviruses belong to the picorna group and comprise the following:—(a) Poliovirus types I, II, and III; (b) Coxsackie group A types 1-23; (c) Coxsackie group B types 1-6; (d) ECHO types 1-30.

Poliomyelitis was first recognized as a clinical entity by Heine in 1840 and transmission of the virus demonstrated by Landsteiner in 1908. Recognition of the other enteroviruses, however, awaited the advent of tissue culture in 1948 and over the subsequent years more and more types were identified and knowledge of the various diseases attributed to them has emerged. The name Coxsackie was derived from a village in New York State where the first of these viruses was isolated. ECHO stands for enteric cytopathogenic human orphan, as these viruses were not at first known to cause any disease in animals or man and, though we now know this is no longer the case, the name has persisted.

Normally the enteroviruses inhabit the intestinal tract of man, but they can invade the body and may show special affinities for some tissues and organs. They have no definite geographical preferences; in temperate climates illnesses caused by them are most often seen in the late summer and autumn months, whereas in the tropics they tend to occur throughout the year. Subclinical and inapparent infections far outnumber those manifesting as clinical illnesses. These viruses are highly infectious, transmission being predominantly by the faecal-oral route, and, though able to cause disease in any age group, most frequently affect children and young adults.

The polioviruses, Coxsackie group B, and ECHO viruses grow readily in a variety of tissue cultures but Coxsackie group A viruses (except A9) do not unless specially adapted after primary isolation in suckling mice. The enteroviruses can be isolated from throat swabs in the early stages of the illness and from the faeces for rather longer. With improved techniques they can now be isolated from the cerebrospinal fluid in an increasing proportion of cases presenting as virus meningitis and can then be assumed to be the cause of the

meningitis. In all other cases, however, the illness cannot be attributed to the virus isolated unless paired sera taken at 10-14 day intervals show a significant rise (four-fold or greater) of specific neutralizing or complement fixing antibody.

Clinical Manifestations

When they invade the body the polioviruses affect only the nervous system and are best considered separately. The ECHO and Coxsackie viruses, however, are responsible for a wide variety of clinical syndromes though many of these are due only to certain types. The incidence of the various enteroviruses varies from one year to the next—for example, in 1971 the strains most frequently isolated were Coxsackie A9, Coxsackie B1-5, and ECHO 4; whereas in 1972 they were Coxsackie A9, Coxsackie B4 and 5, and ECHO 4 and 11. The incubation period probably varies according to the type of clinical illness resulting and is difficult to define as the time of infection is rarely known. It is probable that in the majority of cases it falls within the range of 7-12 days.

POLIOVIRUSES

Although poliomyelitis is predominantly a disease of childhood, its age incidence depends on the standards of hygiene and ease of faecal transfer. Epidemics occurred in Great Britain from 1947 to 1956 mainly due to type I, and about one-third of the paralytic cases were over the age of 15 years. With the advent of poliomyelitis immunization (first with killed virus vaccine and then with oral attenuated virus) poliomyelitis has become an uncommon disease and in recent years virtually absent. In the underdeveloped countries, however, where immunization has barely begun, it remains an important disease. It has been variously estimated that the ratio of inapparent to paralytic infections is between 100 and 850 : 1, and it is now thought that the virus reaches the nervous system via the blood stream rather than via peripheral nerves from the pharynx or intestinal tract.

Abortive Cases

A small proportion of cases (24-5%) present as a

minor illness—with malaise, pyrexia, slight sore throat, and headache. This lasts less than 48 hours and is recognizable only if some member of the household develops the "major" illness—for example, virus meningitis or paralytic disease. In a few patients, especially children, the latter may be preceded by the "minor" illness, which may merge with the "major" illness or precede it by a day or so.

Non-paralytic Poliomyelitis (Aseptic Meningitis)

The onset of non-paralytic polio is abrupt, with headache, vomiting, pyrexia, and signs of meningitis. It is indistinguishable from other forms of virus meningitis; pyrexia and symptoms usually subside in less than a week, and recovery is uneventful.

Paralytic Poliomyelitis

Paralytic poliomyelitis usually starts with the meningitic phase (though this may be transient or inapparent) associated with stiffness of the back and neck and onset of paralysis within 24-48 hours. The lumbar and cervical enlargements of the spinal cord are most frequently involved, and the lower brain stem (bulbar paralysis) is affected in about 5-10% cases. The severity may vary from minor paresis of a limb to paralysis of all four limbs, intercostal and diaphragm paralysis, and inability to swallow due to bulbar paralysis. Severe damage to the pons-medulla may occasionally lead to involvement of vital centres and cause death. The full extent of paralysis is normally reached within 48-72 hours of onset, though some further spread may occur until the end of the febrile phase, which is usually less than a week.

Clinical Features

The essential features of paralytic poliomyelitis are: (a) lower motor neurone paralysis with loss of reflexes preceding detectable paralysis; (b) paralysis, patchy and asymmetrical in its distribution; (c) absence of sensory loss, though some patients complain of subjective sensory disturbance in the early stage; (d) absence of involvement of long tracts.

Most of the muscle recovery will occur in a month and later improvement is largely due to hypertrophy of muscle fibres where the nerve supply is intact. Severe paralysis of limbs always leads to severe sequelae. Large muscle groups—for example, the shoulder girdle—fare badly compared with the small muscles of the hands, which are supplied by a larger number of anterior horn cells. The overall mortality is 7-10%, being highest (20%) in young adults, where the most severe cases are seen. Most of the deaths are due to brain stem involvement and complications arising from respiratory muscle and bulbar paralysis.

If the essential features of paralytic poliomyelitis are considered, the only important differential diagnosis is acute infective polyneuritis where sensory changes may be minimal or absent. In the latter the spinal fluid shows a raised protein level without an increase in the number of cells, whereas in poliomyelitis the protein is only slightly raised (less than 100 mg/100 ml) and there is an excess of cells, as in virus meningitis. In polyneuritis spread of paralysis may occur over a longer period (1-2 weeks) and prognosis for recovery is much better than in poliomyelitis and may be virtually complete.

Vaccine-associated Paralytic Disease

Rare cases of paralytic illness (1 in 4,000,000 doses) have been described, occurring within 28 days of the oral attenuated

poliovirus vaccine and compatible with having been caused by the vaccine. There is also evidence of a few cases having occurred among household contacts (chiefly adults); nevertheless, the incidence of serious disease caused by oral vaccines is so rare that no restrictions have been placed on their use.

ECHO AND COXSACKIE VIRUSES

Virus Meningitis

With the exception of mumps, the enteroviruses are the only common cause of virus meningitis, and today in Great Britain this means the Coxsackie and ECHO viruses. When poliomyelitis was prevalent, tissue culture was not available for routine diagnostic purposes and it is uncertain whether the cases of aseptic meningitis—about equal in number to the cases of paralytic illness—were predominantly due to polioviruses or not. It is known, however, that when a particular enterovirus is present in large numbers of the population the other enteroviruses tend to be excluded (interference phenomenon).

The illness, which most frequently affects children and young adults, is of sudden onset with headache, vomiting, and meningitic signs—which in some cases may be as marked as in bacterial pyogenic meningitis, though usually they are less so and may be minimal and transient. Not all Coxsackie and ECHO viruses are associated with meningitis but an increasing number of cases due to them have been reported in recent years.

In most cases the clinical findings give little indication as to the virus concerned. Rashes sometimes occur especially with certain ECHO viruses—for example, 4 and 9—and these are usually macular and maculopapular (rarely petechial), relatively sparse, and of varying distribution, though perhaps more commonly seen on the face and neck and rubelliform in type. Generalized muscle pains may occur and pleurodynia suggests a Coxsackie group B infection.

The cerebrospinal fluid shows a pleocytosis of 10-2,000 cells, with a varying proportion of polymorphs and lymphocytes; though the latter usually predominate, up to 85% polymorphs may be encountered in the early stages. The protein is only slightly raised (less than 100 mg/100 ml) and the sugar level is normal unless the blood sugar is reduced.

The diagnosis of virus meningitis presupposes no overt involvement of the nervous system, though differentiation from encephalitis is not always easy because in some patients non-specific drowsiness or confusion may be present. Follow-up has not shown neurological sequelae and though fatigue, irritability, and decreased ability to concentrate have been recorded in a few cases, these have been temporary. Evidently virus meningitis is more common than is generally realized and many mild cases are undoubtedly missed and probably greatly exceed those diagnosed.

Virus meningitis is an illness of acute onset and rapid recovery. In atypical cases it is very important to consider the possibility of partly treated bacterial pyogenic meningitis, neighbourhood reactions to a focus of infection near the meninges, and tuberculous meningitis. The last is now an uncommon disease in Great Britain but it should be remembered that the onset may be relatively acute. Suspicion should be aroused if the cerebrospinal fluid protein is over 100 mg/100 ml and the sugar and chloride levels reduced. Acid-fast bacilli can be found in nearly all cases on first examination if the entire spun deposit of at least 5 ml is examined by Ziehl-Neelsen's method.

Paralytic Illness

On rare occasions a paralytic illness indistinguishable from poliomyelitis may occur with certain ECHO and Coxsackie

viruses. The paralysis is of lower motor neurone type and usually mild and transient but more severe cases have been described, notably those due to Coxsackie A7. With the control of poliomyelitis there is no evidence to suggest an increased neutropism of the other enteroviruses.

Epidemic Myalgia (Bornholm disease)

All six types of Coxsackie group B viruses may cause epidemic myalgia, which was first described as a disease entity by Sylvest in 1933 long before the aetiology was known. Children and young adults are most frequently affected. The onset is sudden with pain most often over the lower part of the chest or abdomen on one side and the myalgia may also involve other muscles in the back, neck, or limbs. The severity of the pain, which is aggravated by movement, varies from mild discomfort to disabling pain which may last up to three weeks though usually only 2-4 days. There is tenderness at the site of the pain, often abdominal pain (especially in children), headache, and pyrexia. Rarely orchitis may occur as a complication and sometimes also the other manifestations of enteroviral infections—for example, virus meningitis and pericarditis.

Acute Febrile Illness

This may affect infants, children and young adults, but cannot be readily recognized clinically when it occurs as sporadic cases but may be seen in the same household as more readily recognized manifestations of enteroviral infection. It is often accompanied by a rash which, as in virus meningitis, may be macular or maculopapular but occasionally petechial and rarely with a vesicular element. In most cases, the distribution does not follow any constant pattern and the rash lasts only a few days in a patient who is not seriously ill. Lymphadenopathy may occur, and when this is predominantly occipital and cervical the infection may closely simulate rubella. This relatively benign condition has been described with several enteroviruses but especially ECHO 4, 9, and 16, and Coxsackie A9 and 16.

Hand, Foot, and Mouth Disease

This was described for the first time in 1957 and most cases are due to Coxsackie A16 (occasionally A5 and 10). The disease may affect adults, though it occurs predominantly in young children, and tends to occur in small outbreaks, especially in nurseries. There is little constitutional upset, though children may be unwell for a few days. The lesions in the mouth are scanty (1-8) but painful and usually appear as small ulcers, especially on the mucous membranes of the lips and anterior part of the tongue. On the hands and feet the lesions, also scanty, may take the form of maculopapules, vesicles, or thin-walled bullae. A maculopapular rash may also occur on the buttocks in infants. There is little constitutional upset, though children may be unwell for a few days, and the mouth lesions and rashes clear up within 5-10 days. Virus may be isolated from the mouth ulcers, skin lesions, and faeces.

Herpangina

This is seen especially in infants and children and is due to several strains of Coxsackie group A viruses. The onset is

abrupt with pyrexia, and sore throat; vomiting, abdominal pain, and headache may also occur. The fauces and pharynx appear red with scanty papules and ulcers on the anterior pillars, palate, and uvula but the rest of the mouth is spared. This condition is not common but lymphonodular pharyngitis without ulceration probably occurs more frequently (mainly Coxsackie A10) although difficult to recognize unless routine virological examination is carried out. In most cases the sore throat lasts only a few days.

Neonatal Generalized Infection

This fortunately uncommon condition is due to Coxsackie group B viruses and in most cases the infection is acquired after birth. The presentation may be that of heart failure and the electrocardiograph confirms evidence of myocarditis. Other cases may present as a meningoencephalitis with convulsions and coma and, though not manifest during life, evidence of myocarditis is found post mortem. In these fatal cases Coxsackie group B viruses may be found in a large variety of organs. Undoubtedly milder cases occur without recognizable syndromes.

Pericarditis and Myocarditis

Most cases are due to Coxsackie group B viruses and unlike most enteroviral infections the illness (in some cases), may last several weeks. Though complete recovery is to be expected, sudden death may sometimes occur. The illness may occur in both adults and children, usually at the time that cases of virus meningitis are occurring in the community, and presents with pyrexia and precordial pain with characteristic electrocardiographic changes. It is difficult to estimate the relative importance of the Coxsackie viruses in the overall aetiology of myocarditis and pericarditis.

Entero-respiratory Infection

Most of the ECHO and Coxsackie serotypes, especially the former, have been shown to be able to produce mild acute febrile or afebrile upper respiratory or non-respiratory illnesses which are indistinguishable from those caused by many other agents. Lower respiratory tract infections due to these viruses are, however, rare. Similarly, ECHO viruses have been isolated in some outbreaks of diarrhoea and vomiting in infancy and early childhood, and these may also be associated with respiratory tract symptoms. There is no evidence to suggest, however, that enteroviruses are an important cause of gastroenteritis in infancy and early childhood. Most cases in infancy nowadays are of unknown aetiology; presumed viral and *Escherichia coli* serotypes play a less important part.

Conclusion

Enteroviruses can cause a wide variety of clinical illness and the full spectrum has not yet been fully elucidated, especially in neonates, where rarely the infection may result in serious and fatal illness. With the exception of the polioviruses, however, in the other age groups the amount of serious disease due to enteroviruses is relatively small, and virus meningitis remains perhaps their most important manifestation. More detailed follow-up of a large number of cases of virus meningitis should be carried out to clarify whether its reputation as a benign disease is fully justified.