Ill defined neurological diseases of possible viral origin

R. N. P. SUTTON

M.A., D.M., D.Sc., M.R.C.Path., D.C.H.

Withington Hospital, Department of Virology, Manchester M20 8LR

Summary

Any approach towards elucidating the aetiology of an ill defined disease such as 'epidemic neuromyasthenia' has to be a comprehensive and wide-ranging one. Although viruses must be strong candidates, by reason of their ubiquity, this need not necessarily be the case and we have recently seen the onset of Legionnaires' disease as a new entity caused by a bacterium. We do not always recognize that a particular virus may affect the entire community and that the patient seen in hospital may represent only the tip of the submerged iceberg and that, in closed communities more of the iceberg will be seen. Silent viral epidemics are probably frequent and may only be recognized in retrospect. As an example the recent epidemic with adenovirus type 7 will be alluded to. Possible variations in virus and, to a lesser extent, in the host which could modify the course of an individual infection are discussed.

Introduction

William Harvey, in his preface to *De Motu Cordis* (Franklin, 1957) showed a fine sense of balance in regarding 'as credulous and empty those who accept and believe all at first glance and equally as dull and senseless those who do not see the things that are manifest to the sense'. In our own time, D. C. Gajdusek wrote concerning the slow virus disease kuru, 'to see whole groups of well nourished healthy young adults dancing about with athetoid tremors which look far more hysterical than organic is a real sight. And to see them, however, regularly progress to neurological degeneration in 3 to 6 months, usually 3, and to death is another matter and cannot be shrugged off' (Gajdusek, 1976).

Gajdusek's approach to the slow virus infections has been a wide-ranging one. The present problem, variously called benign myalgic encephalomyelitis, 'epidemic neuromyasthenia', etc., demands a similar type of approach. There is a strong likelihood that this condition may be due to a viral infection, but this does not, by any means, exclude the possibility that there could not be other aetiologies. A bacteriological possibility is still open, witness the recent description of the agent responsible for Legionnaires' disease.

Viruses in the community

With the exception of cosmic radiation, viral infection is probably the commonest insult experienced by man in his lifetime. About half-a-dozen or more respiratory virus infections are suffered each year and in childhood the number is much greater (Sutton, 1965). Study of antibody levels indicates, that with almost every virus, infection occurs early in life and almost all individuals become infected by early adulthood. In some cases, notably the Epstein-Barr virus, infections in early adult life are more severe than in childhood, possibly owing to an increased infecting dose, or possibly because of other factors.

The gossip in any general practitioner's waiting room at any time of the year will tell us that there is 'something going around'. Sometimes it is easy to detect the offending virus, for example during the occasional epidemic of influenza A. Less clear, and visible only from the laboratory, are epidemics which are due to any one of a range of other viruses.

Fig. 1. Respiratory viruses in a children's hospital - 1977.

In a children's hospital in South Manchester, during 1977, 561 viruses were recovered from 2834 specimens. In some cases, there were perhaps one or two recoveries of a particular virus during the whole year. In others, there were repeated recoveries. It is

FIG. 2. Enteroviruses and adenoviruses in a children's hospital - 1977.

reasonable to assume that the viruses found in children admitted to hospital mirror the prevalence of viruses in the community although occasionally cross infection may distort the mirror image. The

prevalence of some of the respiratory viruses in the children's hospital just described is given in Fig. 1. Respiratory syncytial virus (RSV) and influenza A were present in the early part of the year, together with para-influenza 3 later on. In the autumn, the annual epidemic of RSV began once more. Turning from respiratory viruses to those which are spread by the faecal-oral route, there was (Fig. 2) an increased prevalence of three types of echovirus, Coxsackie B5 virus and adenoviruses of types 7 and 31 at different times of the year. From these figures, which represent just the merest tip of the iceberg, one can well imagine that waves of virus infection were sweeping through the community: thus, in 1974 there was such an epidemic, that of echovirus type 19. At the clinical level, these epidemics may well not have been recognized and, at the same time, it is likely that there were other viral epidemics going on. One of these viral epidemics, for which we have some information was caused by adenovirus type 7 (Sutton *et al.*, 1976). Infections with this virus have been recognized since the 1950s but, in the years immediately before 1971, there were few recoveries. Between 1972 and 1974 or 1975, there was an epidemic apparently spreading from the North-East to the South-West at a rate of about a few miles per day. The clinical features in forty-two patients are given in Fig. 3. Upper respiratory tract infection was seen in almost all, headache, meningism, drowsiness, conjunctivitis and rash in a smaller number. This was

FIG. 3. Clinical features in adenovirus type 7 infections 1971-1974. (Sutton *et al.*, 1976. By permission of the editor of the *Lancet*.)

a minor illness which resulted in only a few admissions to hospital. However, meningitis was initially suspected in nine and encephalitis in four of the forty-two patients in this survey. In two children, their condition gave rise to serious concern. The first was a 6-year-old boy who was admitted with a history of sore throat and fever which settled rapidly and he was sent home. Ten days later he was re-admitted with acute cerebellar ataxia with neurological signs and an abnormal EEG with an increase in slow wave activity, suggesting an encephalitic process. His ataxia resolved following treatment but 18 months later his cerebellar signs were still present although less marked. At that time an EMI scan revealed cerebellar atrophy. The second case, a boy 6 years of age was admitted to hospital and on the following day developed dramatic neck stiffness, opisthotonos, lethargy, vomiting and headache with abnormal plantar reflexes. He improved but one year later he was again under paediatric care; psychological tests at that time revealed that he was dyslexic. In these two cases, especially when we consider the incidence of neurological signs in the forty-two and also when we consider that during this epidemic at least one strain of adenovirus type 7 was recovered from the brain tissue in circumstances suggesting that a latent infection had been established (Lord, Sutton and Corsellis, 1975), serious sequelae clearly may occur in some patients whilst the majority suffer from relatively minor illness.

It is not suggested that adenovirus type 7 is responsible for 'epidemic neuromyasthenia'. Indeed, it may be possible that 'epidemic neuromyasthenia' is caused by a completely new and unidentifiable virus or other agent; such a supposition is incapable of proof or disproof. However, from the firm data which we have, it is quite clear that infections with a whole range of viruses are occurring throughout the community all the time. Most are either asymptomatic or result in trivial disease but occasionally there may be serious sequelae. It is not possible to explore the reasons (probably genetic) why one person has a serious sequel to an infection with a banal virus and another does not. The fact has been known for a long time and it is well known that a small proportion of people suffering from the exanthemata go on to develop serious neurological sequelae (Miller, Stanton and Gibbons, 1956). This is true for measles, mumps and chickenpox; it may well also be true for the ill defined diseases associated with infection by other viruses. 'Epidemic neuromyasthenia' in its chronic form may be such an unusual sequel.

Modifications in viral infections

It is worth-while to look at some of the potential

mechanisms by which viral infection may be modified. In the case of rare complications, it is reasonable to assume that host variation must play a part. This is probably a variation in genetic control and, in mice, strains may be susceptible or resistant to infection in a variety of ways, depending upon route of infection, the particular virus involved and the site of multiplication in the host. In one instance, a linkage has been shown through the H2 locus, possibly related to the immune response gene, and another manifestation of genetically induced variation may be produced through an increased production of defective interfering virus particles. Following infection, a virus may be dealt with promptly by the immunological mechanisms of the host, resulting in early recovery and complete elimination of the virus. It may also become persistent, possibly due to immunological abnormalities. A further possibility is that infection may result in secondary auto-immune phenomena. One example in man is the production of smooth muscle antibodies (Fig. 4) in infectious mononucleosis (Sutton *et al.*, 1974). This type of phenomenon may muddy the diagnostic waters; for example (Table 1) there are instances where proved infections with particular viruses are associated with positive tests for infectious mononucleosis. Some years ago, the author was concerned with another doctor's patient who presented with a history of fever, slight headache, incoherence and sensory dysphasia. Significant clinical features included 30 leucocytes/mm³ in her CSF and an abnormal electroencephalogram, leading to a diagnosis of an acute encephalitis. The presence of high (equal or greater than 512) levels of measles antibody in her serum together with the presence of measles antibody in her CSF suggested that this was the cause of her troubles. However, she also had a positive Paul-Bunnell reaction together with a polymorphonuclear leucocytosis ($11.0 \times 10^9/l$ of which $5.6 \times 10^9/l$ were atypical mononuclear cells) which suggested that infectious mononucleosis also played a part. Needless to say, the absence of lymphadenopathy, rash or palatal petechiae did not help at arriving at a firm diagnosis.

In situations such as those found in the various outbreaks of 'epidemic neuromyasthenia', the possibility exists of variations in the infecting virus. The author assumes that spread of the infecting agent has been facilitated by the close proximity of patients, for example in nurse's homes, and also that the epidemic has become apparent by the increased numbers of patients presenting themselves to a single attending doctor. There are four possible variations in an infecting virus which could be relevant. These are, temperature sensitive (TS) mutants, defective interfering (DI) particles, antigenic drift and dual

FIG. 4. Antibodies to smooth muscle in infectious mononucleosis. (Sutton *et al.*, 1974. By permission of the editor of *Clinical and Experimental Immunology*.)

TABLE 1. Positive tests for infectious mononucleosis associated with confirmed infections with other viruses

	Monospot	
	+	-
Measles*	1	20
Herpes simplex*	1	15
Cytomegalovirus*	0	7
Mumps*	1	0
Totals: 3/45 (7%)		
*Virologically confirmed		

infections. Almost every virus has its TS mutants: very often this mutation results in a reduction of virulence for the natural or experimental host and it seems possible that TS mutants might induce unexpected adverse effects in man. In particular, it may be that viruses of low pathogenicity might be more readily incorporated, in the form of complementary DNA, into the host cell DNA to produce chronic infections. There are experimental hints in this direction, for example, when Newcastle disease virus persistently infects cells *in vitro*, there is a progressive selection of temperature sensitive conditional lethal mutants (Preble and Younger, 1975).

Defective interfering particles (Huang, 1973) are deletion mutants which replicate along with the virus but interfere with the production of complete infectious viral genome. They are potential means whereby chronic infection could develop. Many instances occur in the laboratory and in animal experimental situations; there do not seem to be any proved instances in man, probably owing to the difficulties of detecting non-infectious virus *in vivo*, especially when the virus may be an unknown one. Antigenic change is well recognized in influenza but for it to ensure the preservation of a virus *in vivo* in the presence of antibodies has only recently been recognized. Equine infectious anaemia is associated

with a continued excretion of virus in the presence of high titres of antibody and it has been shown that the antibodies which the horses develop are to the strain of virus present at the time of initial infection and the virus recovered at later times is antigenically quite distinct, so there has been a demonstrable *in vivo* antigenic drift (Kono, Kobayashi and Fukunaga, 1973).

The possibility of a dual infection has also to be considered and experimental work, particularly in acute sclerosing panencephalitis (SSPE), shows that the SSPE virus genome differs from classical measles virus in that there is an extra 10% or so of genetic information available (Hall and ter Meulen, 1976), possibly resulting from a second infection and a papovavirus has been seen under the electron microscope on several occasions. This double infection or recombination could account for the rarity of SSPE.

Some possible future approaches

In this article, it has not been possible to contribute any firm answer to the problem of 'epidemic neuromyasthenia'. Nevertheless, the most secure place in which to hide a tree is in a forest and it is reasonable to assume that we must look for the causative agent or (much more likely) agents amongst the mass of viruses which surround us in the community. Individual outbreaks will need to be investigated to the best of our ability and any strains of virus which are recovered should be carefully studied. It is pertinent to add that, in the outbreak of adenovirus type 7 which has been described, strains were recovered which differ from the standard type strain (Dr G. Wadell, personal communication); these differences may be relevant to the apparent neuropathogenicity. It is more likely that the answer to this aetiological riddle lies already at hand than that an, as yet, unidentifiable virus is responsible.

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