Section of Neurology

President S Nevin MD

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Viral Diseases of the Nervous System

Dr J V T Gostling
(Public Health Laboratory, Portsmouth)

Herpetic Encephalitis

Causal Agent

Herpesvirus hominis, the virus of herpes simplex, is encountered very frequently in fresh or suitably preserved specimens received in a virus diagnostic laboratory, and a large proportion of the population become infected by this virus early in life. Andrews & Carmichael (1930) reported that some 75% of normal people had neutralizing antibody to the virus. McNair Scott (1957) stated that 64% of outpatients at the Children's Hospital of Philadelphia had antibody; from observations of the number of cases of herpetic stomatitis seen at the hospital he estimated that 90% of infections must be subclinical. In another series complement-fixing antibody was found in 63% of the 5–15 age group and in 86% of those over 15 (Holzel *et al.* 1953).

The virus is one of a family of morphologically similar members. Other human pathogens in the family are the viruses of chickenpox and cytomegalic inclusion disease; and an important simian member is B virus, which is highly pathogenic for the human central nervous system.

The virus has a central nucleoid 35 mμ in diameter, which can be digested by DNAase, surrounded by a protein capsid 100 mμ in diameter, the whole being enclosed in a lipoprotein envelope 150–200 mμ in diameter.

The presence of the virus is recognized in the diagnostic laboratory by the damage or cytopathic effect caused to cells in culture, to which virus-containing material has been added. A variety of human cells and some nonhuman mammalian and avian cells are susceptible to such damage. The cytopathic effect consists of rounding, and in human embryo tissue ballooning, of the cells. Before this stage is reached, infected monolayers, fixed and stained with hæmatoxylin and eosin, show homogeneous, amphophilic, intranuclear inclusions and margination of nuclear chromatin.

Clinical Findings

The commonest manifestation of infection with the virus is a stomatitis contracted in the second or third year of life. Children once infected in this way are liable to recurrent infection, not inside the mouth but around the lips – the frequently seen herpes febrilis. In infants under 1 year a generalized infection occasionally occurs involving the central nervous system and all other organs.

In the adult, herpetic infection of the nervous system is more commonly an encephalitis or meningoencephalitis than a simple meningitis. This contribution will be confined to an account of infections in which the brain substance is involved. The virus of herpes simplex is said to account for 5–7% of viral encephalitides. But herpetic encephalitis arouses great interest – at least 15 authors have thought it worth while to report single cases.

The literature contains many larger series of cases. Haymaker and his associates (1958) described many fatal cases having lesions characteristic of herpes though few of them were virologically established cases of herpes infection. Three cases of acute necrotizing encephalitis were reported by Bennet *et al.* (1962) and these authors also reviewed 59 similar cases, some of them from the Haymaker series, in which the patients were more than 1 year old and died within four weeks. Virus isolation from the brain was attempted in 20 of these cases and herpesvirus was found in 13. Rawls *et al.* (1966) reported 5 fatal cases, herpesvirus being isolated from the brains of all 5.

Series which included nonfatal cases have been described by Ross & Stevenson (1961), Drachman and Adams (1962), Leider *et al.* (1965) and Miller *et al.* (1966), the diagnosis in these series being made by histology, virus isolation or the detection of complement-fixing antibodies to herpesvirus in the serum. The outcome in the nonfatal cases in these reports ranged from complete recovery, through defects of memory and limited muscle paralyses to dementia requiring permanent care in a mental hospital.

Cases encountered in Wessex in 1966 are listed in Table 1 in which are shown the histology and virus laboratory findings – that is the evidence leading to the conclusion that the infecting agent was herpes simplex virus – and the outcome of the illness. In the first fatal case virus was isolated from brain removed at autopsy. There being no sera from this patient the possibility that the isolated virus might be a contaminant had to be considered: it was found only in the brain of this patient and not in her lung, spleen or colon; nor was it found in the brain or other organs of another encephalitic patient sent to us from the same post-mortem room that day. The finding of intranuclear inclusion bodies by Dr A D Dayan confirms that the isolated virus was truly infecting and not contaminant.

The evidence for a herpetic ætiology is less good in the second fatal case. It is not surprising that virus was not isolated from the CSF; herpes is a labile virus and isolation from this source is unusual. Unfortunately, the patient spent the last weeks of his life, and died, in a mental hospital beyond the reach of our laboratory: no more serum was taken from him and, regrettably, his brain was put into formalin, so that isolation of virus could not be attempted. This second fatal case did not have a high titre of complement-fixing antibody against herpesvirus. But his titre was higher than that of the only one of the cases of Rawls *et al.* (1966) which was serologically examined; and higher than that of one of the cases of Ross & Stevenson (1961), one of those of Drachman & Adams (1962) and 3 of those of Leider *et al.* (1965). The first serum in this second Wessex case was taken two weeks after the onset of his illness and this probably precluded the finding of a significant rise in titre. The remaining 3 cases are serologically convincing – the first serum in Case 3 was taken twelve days after the onset of drowsiness – too late again to catch the rise in antibody titre. We were very fortunate in Case 4 to isolate virus from the CSF; as stated above, this is unusual in herpetic encephalitis. One example has been reported by Hunt & Comer (1955) and another by Brunell & Dodd (1964). There was none in any of the series cited above.

Table 2 is based on information collected for me by Dr P K Robinson. Most of the patients had fever, headache and drowsiness. The column headed 'Motor or reflex defects' includes any abnormalities observed during physical examination – these included motor dysphasia, visual field defect, increased tendon reflexes, purposeless repetitive movements, nystagmus, ataxia, facial weakness, palatal palsy and deafness; all the patients had some of these defects. The two women (Cases 1 and 4) had epileptic convulsions – Case 1 only on the day before death. The two fatal cases had neck stiffness, and Case 4 had herpes labialis, but it is not known if she had had previous attacks.

The CSF was not under increased pressure in any of the cases, nor was there other evidence of increased intracranial tension. The cells found were always lymphocytes and the

Table 1

Encephalitis due to herpesvirus hominis in Wessex 1966: histology and virus laboratory findings

Case No.	*Age*	*Sex*	*Inclusion bodies*	*Herpesvirus isolation*	*Complement-fixing antibody titre v. herpesvirus*	*Outcome*
1	62	F	++	+ (pooled temporal lobes) + (pons)	No serum taken	Death in four weeks
2	58	M	– (left parietal biopsy 2.5.66 and autopsy)	– (CSF) – (Throat swab) – (Fæces)	4.5.66 20 25.5.66 40	Death in four months (12.8.66)
3	58	M	– (right frontal lobe biopsy 30.3.66)	– (CSF) – (right frontal lobe)	23.3.66 320 31.3.66 640	Alive, confused, disorientated, cannot recognize wife, doubly incontinent
4	53	F	No material	+ (CSF) – (labial herpes)	12.11.66 20 25.11.66 320	Alive, still in general hospital, no paresis, no fits
5	38	M	No material	– (CSF) – (CSF) – (Throat swab)	24.8.66 20 3.9.66 40 12.9.66 80 19.9.66 160	Alive, able to walk, speech slurred but improving

Table 2
Encephalitis due to herpesvirus hominis in Wessex 1966: clinical findings

Case No.	Fever	Headache	Drowsiness	Convulsions	Neck stiffness	Lip lesion	Motor or reflex defects	CSF Lymphocytes per c.mm	CSF Protein (mg/100 ml)	Special tests
1	+	+	+	+	+	−	+	52	40	EEG, V, BS
2	+	−	+	−	+	−	+	23	95	V
3	+	+	+	−	−	−	+	164	115	Biopsy
4	+	+	+	+	−	+	+	50	105	US
5	+	+	−	−	−	−	+	1	120	V

BS, brain scan with a radioactive isotope; US, ultrasound; V, ventriculography; EEG, electroencephalography

counts were not high. Miller *et al.* (1966) and Bennet *et al.* (1962) both mention the presence of red blood cells in the CSF, and sometimes xanthochromia, as being common in herpetic but not other forms of encephalitis. The Wessex cases did not show this.

An electroencephalogram in Case 1 showed widespread diffuse slow activity suggestive of encephalitis. None of the 3 ventriculograms showed distortion of the ventricles. Nor did scanning or ultrasound reveal any local lesion or displacement, where tried. Both the fatal cases had, in fact, been suspected of having cerebral abscesses early in their illnesses.

In connexion with these tests for a space-occupying lesion it may be mentioned that Bennet *et al.* (1962), in reviewing the literature, found 16 of 59 cases of acute necrotizing encephalitis, and 2 of their own which presented as acute intracranial masses, ventriculography supporting such a diagnosis in 2 of them.

Frontal lobe biopsy from Case 3, examined by Dr Dayan, showed evidence of encephalitis, foci of necrosis in white and grey matter, neuronophagia and inflammatory cuffing of vessels, but no inclusion bodies. The finding of inclusion bodies at biopsy is exceptional; it has been reported in one case by Dodge & Cure (1956). Their patient had an antiherpes complement-fixing antibody titre of 64 on the fifteenth day of illness, which fell several months later to 16.

Discussion

There are various questions raised by these cases of encephalitis and those in the literature to which I have referred. First, how justifiable is it to attribute the disease to the virus of herpes simplex on the basis of antibody findings alone? This was done in all the surviving cases reported by Leider *et al.* (1965), Miller *et al.* (1966) and Ross & Stevenson (1961) as well as in the surviving Wessex cases except Case 4.

Dascomb and his colleagues (1955) examined sera from 55 patients suffering from other diseases and found none with antiherpes complement-fixing antibody titres early in disease greater than 32 and none showing a fourfold rise. Miller *et al.* (1966), reporting their 10 fatal and 10 nonfatal cases, considered this point: they examined 6 subjects with recurrent labial herpes and found that in their quiescent periods none had a titre higher than 32. It seems justifiable to accept a fourfold rise or a titre of 160 or more as evidence of active herpetic infection.

The next question is whether herpetic encephalitis is part of a primary invasion of the body, or whether it is something which those suffering from recurrent cutaneous herpes are liable to contract.

Miller *et al.* (1966), citing Ross & Stevenson (1961) in support, regard the disease as part of a primary infection on the grounds that gingivostomatitis is frequently present, whereas labial herpes, they say, rarely accompanies encephalitis, that many cases of encephalitis have very little antibody to start with and that the rise is slow in contrast with the prompt rise in cutaneous recurrences. Their own observations are at variance with these last two statements; their recurrent herpetics in quiescence had little antibody, and the one they observed in recurrence had a very small rise in titre. McNair Scott (1957) states that adults with cutaneous recurrence show little rise in titre. Rawls *et al.* (1966), reporting their 5 isolation-positive, fatal cases, think the encephalitis is a recurrence of a latent infection which would account for its frequently being localized and the early presence of antibody. Certainly the finding of Leider *et al.* (1965) – that 3 of their patients had a history of recurrent cutaneous herpes before their encephalitis – supports the latter view, and one of our Wessex cases had labial herpes as opposed to gingivostomatitis at the time of her encephalitis.

It seems possible that herpetic encephalitis can occur either as a primary or as a recurrent infection. I would think that, in adults at least, the recurrent type is more common.

The last matter deserving mention is the relationship between two rather similar diseases.

It seems to be tacitly agreed that 'herpes simplex encephalitis' and 'acute necrotizing encephalitis' are one and the same thing, and Haymaker *et al.* (1958) are agreed, with others, that 'subacute inclusion encephalitis' and 'subacute sclerosing leukoencephalitis' are the self-same disorder. These same authors admit to disagreement amongst themselves as to whether these two entities, the acute and the subacute, are variants of the same disease process. They point out that the subacute disease is mostly, but not entirely, confined to children and young adults whereas the acute disease affects all ages; and that virus has not been isolated from a subacute type of case. Recent electron-microscope studies in which virus-like, but not herpesvirus-like, particles have been seen in the brains of patients dying of the subacute disease, support the view that the latter is a distinct entity (Tellez-Nagel & Harter 1966; Dayan *et al.* 1967).

The Wessex cases do not help to settle this point.

The clinical course of our second case, running nearly four months from onset to death – suggested that he might have subacute encephalitis. However, the fairly abrupt onset of his illness, his age and, above all, the gross and microscopic appearance of his brain bring him into the acute group. The fact that Dr Dayan found no inclusions may be related to the very severe necrosis of this brain. Dodge & Cure (1956) remarked that they found no inclusions in the most severely necrosed areas in their case; they found them in less damaged regions. This second Wessex case had some antibody, after a month of disease. Regrettably we had no further sera from him.

In conclusion I would urge that serum be taken from all patients suspected of cerebral abscess or encephalitis as soon as they are seen. Whether a second or convalescent sample is taken may depend on the conclusions reached by the clinician during the illness of the patient. Without an early serum, the help the virus laboratory can give is markedly diminished.

REFERENCES

Andrewes C H & Carmichael E A (1930) *Lancet* i, 857
Bennet D R, Zu Rhein G M & Roberts T S (1962) *Arch. Neurol., Chicago* 6, 96
Brunell P A & Dodd K (1964) *J. Pediat.* 65, 53
Dascomb H E, Adair C V & Rogers N (1955) *J. Lab. clin. Med.* 46, 1
Dayan A D, Gostling J V T, Greaves J L, Stevens D W & Woodhouse M A (1967) *Lancet* i, 980
Dodge P R & Cure C W (1956) *New Engl. J. Med.* 255, 849
Drachman D A & Adams R D (1962) *Arch. Neurol., Chicago*, 7, 45
Haymaker W, Smith M G, van Bogaert L & de Chenar C (1958) In: Viral Encephalitis. Ed. W S Fields & R J Blattner. Springfield, Ill.; p 95
Holzel A, Feldman G V, Robin J O'H & Harper J (1953) *Acta pædiat., Uppsala* 42, 206
Hunt B P & Comer E O'B (1955) *Amer. J. Med.* 19, 814
Leider W, Magoffin R L, Lennette E H & Leonards L N R (1965) *New Engl. J. Med.* 273, 341
Miller J K, Hesser F & Tompkins V N (1966) *Ann. intern. Med.* 64, 92
Rawls W E, Dyck P J, Klass D W, Green H D & Herrmann E C (1966) *Ann. intern. Med.* 64, 104
Ross C A C & Stevenson J (1961) *Lancet* ii, 682
Scott T F McN (1957) *Amer. J. Ophthal.* 43, 134
Tellez-Nagel I & Harter D H (1966) *Science* 154, 899

Professor N R Grist
(Department of Infectious Diseases, University of Glasgow)

Acute Viral Infections of the Nervous System

In this paper I have attempted to deal briefly with those acute infections of the nervous system in which current virological tests are usually successful in establishing an ætiological diagnosis. Of these conditions, by far the commonest is aseptic meningitis.

Aseptic Meningitis

This accounts for 50% or more of infectious meningitis seen in hospital, with markedly higher prevalence in summer and autumn corresponding to the seasonal increase in the carriage of enteroviruses by the population. Cases nevertheless occur throughout the year, a substantial proportion being attributable to mumps. All ages are affected, particularly pre-school and school-age children, with male sex predominance. Head injury, presumably during viræmia, may precede the illness (Bell *et al.* 1965). Although most cases recover completely, minor temporary disabilities were reported to be common by Lepow *et al.* (1962). We have also encountered intracranial hæmorrhage in circumstances suggesting that it may occasionally result from viral meningitis (Bell *et al.* 1965). Permanent disability or death may follow the complications of encephalitis or paralysis.

The appropriate diagnostic techniques are attempted virus isolation from cerebrospinal fluid and fæces, and occasionally in early stages from throat or blood, together with tests for antibodies in paired sera. Typical findings are shown in Table 1: positive results were found in 77% of 353 cases examined in Glasgow in 1960 (Combined Scottish Study 1964). Predominant viruses were