Atypical demyelinating disease


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SYNOPSIS A 17 year old girl died after an illness characterized by progressive mental deterioration and severe myoclonic jerks. Extensive pathological, virological, and immunological studies failed to support the diagnosis of subacute sclerosing panencephalitis but were compatible with disseminated demyelinating disease. The spinal fluid was positive for measles virus antibodies when examined by the fluorescent antibody technique, by complement fixation, and by haemagglutination inhibition tests, but the antibody titres were not high. The concentration of vaccinia antibody in the serum was consistent with that found in the general population and none was detected in the spinal fluid. Animal and tissue culture studies failed to disclose a viral agent, but pathological sections revealed perivascular cellular infiltration, demyelination, rare inclusion bodies, and multinucleated giant cells. Although these studies were not definitive, a record of procedures used and results obtained, both positive and negative, may be helpful to other investigators interested in defining more accurately the clinical features and the pathogenesis of these diseases.

This paper reports a case with clinical and pathological features indicative of a demyelinating disease of unusual type.

CASE REPORT

The patient was born on 1 March 1955 and died on 31 August 1972. Her history revealed that she suffered from mental deterioration beginning at the age of 16 years. She was studied at another hospital for headaches and dizziness and gave a history of having been struck on the head by a baseball bat, the exact time unknown. Spinal fluid revealed a protein of 68 mg/100 ml and an electroencephalogram (EEG) showed occipital slowing. Brain scan revealed an abnormal area over the corpus callosum. A pneumoencephalogram was within normal limits. At this time, it was learned that her father was confined in an institution in another state with a diagnosis of multiple sclerosis. The family was broken and further history on the patient was available only from foster parents who could provide very little detail of her history except as recorded. A report from the Los Angeles County Hospital regarding her father confirmed the diagnosis of multiple sclerosis by the Neurology Service.

She was admitted to Los Angeles County General Hospital on 3 September 1971 and discharged on 30 November 1971 to Rancho Los Amigos Hospital. Spinal fluid (CSF) on 7 September revealed a protein of 108 mg/100 ml with 25 white blood cells per mm³. A subsequent spinal fluid on 13 September revealed a protein of 99 mg/100 ml. At this time a diagnosis of Dawson's inclusion-body encephalitis was entertained and measles virus antibody studies were ordered. These were performed in the laboratory of J.M.A. on 27 September 1971. The haemagglutination-inhibition (HI) titre of the serum to measles virus was 1:8 and that in the spinal fluid was less than 1:2. Measles virus HI serum titres were repeated on 20 December 1971 and were recorded as 1:8. On 20 March 1972, her HI serum titre for measles virus was 1:64 and spinal fluid was 1:2. The results were the same on 15 May 1972.

Several samples of serum and spinal fluid were sent to the Viral and Rickettsial Disease Laboratory of the California State Department of Health and the results are summarized as follows: measles virus HI titre in the serum was 1:32 on 27 September and 1:16 on 20 December 1971 and the complement fixing antibody titre (CF) was 1:64 on these dates. Measles

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virus CF titre was 1:64 on 20 March, 15 May, and 14 July 1972. The HI titre to measles virus in the spinal fluid on these three dates was 1:2 and the titre by the CF test was 1:8.

By the indirect fluorescent antibody (FA) technique using fluorescein-tagged anti-IgG, the spinal fluid reacted at the dilution of 1:8 with both nuclear and cytoplasmic measles virus antigens present in measles virus infected tissue culture cells. FA tests were performed at the State Viral and Rickettsial Disease Laboratory. The titres observed were very low compared with the customary findings in subacute sclerosing panencephalitis.

On 12 November 1971 a brain biopsy was performed and showed mild perivascular infiltration but no inclusion bodies. A diagnosis of leucoencephalitis was made at the Los Angeles County General hospital. Cultures of brain tissue at passage 8 and cocultures with CV-1 at passage 6 established at the Viral and Rickettsial Disease Laboratory were negative for measles virus antigen when stained by the direct FA method. Frozen sections of the original brain tissue also showed no staining with the antimeasles virus conjugate nor with the other four antiviral conjugates listed in the Methods section.

On 2 December 1971 the patient was stuporous and lethargic with frequent generalized myoclonic jerks, five to 10 per minute. She responded poorly to verbal stimuli. Her pulse rate was 120/min, temperature 38.3°C, blood pressure 150/100 mmHg. The EEG showed bursts of spikes and slow activity. On 13 March 1972 the CSF protein was 50 mg/100 ml, colloidal gold curve 1111100000.

On 20 March 1972 CSF protein was 60 mg/100 ml and colloidal gold curve was 1233321000. On 15 May 1972 the spinal fluid protein was 48 mg/100 ml, albumin 52%, globulin 48%. On 20 May 1972 a rash appeared which was diagnosed as typical herpes zoster. It cleared in three weeks. The patient slowly became more obtunded, developed more severe clonic jerks, sinking into almost complete unresponsiveness, and died from pneumonia 1½ years after the onset of the illness.

METHODS

Before the patient's death, serum and spinal fluid were collected at intervals and checked by haemagglutination inhibition (HI) and complement fixation (CF) tests for measles virus antibodies by standard techniques (Lennette and Schmidt, 1964). Post-mortem examination was carried out within two hours of death. Fresh brain was frozen and stored at −20°C. Brain tissues from grossly involved areas were frozen quickly in isopentane cooled with liquid nitrogen for fluorescent antibody (FA) studies, utilizing specific antiviral conjugates prepared against measles, vaccinia, varicella, parainfluenza 1, and herpes simplex viruses.

Animals (guinea-pigs, hamsters, and rabbits) were inoculated subcutaneously with the patient's brain material homogenized with an equal volume of Freund's complete adjuvant. Inoculations of 0.5 ml were made at two sites on two occasions one week apart. Normal brain material from a 7 month old child who died of congenital heart disease was similarly prepared and inoculated into animals. Three animals of each species were used for these inoculations. Positive controls consisted of hamsters inoculated subcutaneously with the Schwarz strain of measles virus vaccine in 1 ml amounts on two occasions one week apart. All animals were bled before inoculation and at a number of intervals thereafter.

Primary brain tissue cultures were prepared by mixing and trypsinizing material obtained from lesion areas according to standard procedures (Parker, 1961). Tissue culture media consisted of medium 100, fetal calf serum 20%, whole egg ultrafiltrate 10%, glucose 100 mg/100 ml, or Eagle's (Earle's) medium with added fetal calf serum 20%, glutamine 30 mg/100 ml, and antibiotics. Cocultures were established utilizing Hela, CV-1, and human embryo kidney cells. Haemadsorption tests with human or guinea-pig red blood cells were performed on cultures of the original brain tissue and on cultures fused with CV-1 cells. Cocultures with Hela cells were maintained for 20 passages. WI-38 diploid cells were fused with an equal number of brain cells which had been 10 weeks in tissue culture. This was achieved by treatment with 0.1 ml lysolecithin (6 μg/1 × 10⁶ cells) according to the procedure of Croce et al. (1971). African green monkey kidney (CV-1) cells (Hayflick, 1965) were fused with cultured brain cells (12 weeks) in the presence of lysolecithin (4 μg/1 × 10⁶ cells) as outlined previously.

RESULTS

ANIMAL EXPERIMENTS Guinea-pigs, hamsters, and rabbits inoculated with the patient's brain tissue plus adjuvant failed to develop measles virus antibody as measured by the HI test. The sera reacted non-specifically with measles virus antigens in both the CF and FA tests. Hamsters inoculated with the Schwarz strain of measles virus developed CF and HI titres of 1:32 against measles virus. This procedure has been successfully carried out in rabbits with brain material from a patient with neuromyelitis optica related to vaccinia virus (Adams et al., 1973). None of
the rabbits in the aforementioned report developed experimental encephalomyelitis. In this report no animal developed that condition. One guinea-pig did show a few scattered lymphocytes in the arachnoid mater.

Tissue Culture Studies. The haemadsorption reaction performed on 5-week brain cultures showed no evidence of parainfluenza viruses types 1, 2, and 3. After 3-5 months in tissue culture, no cytopathic effect was observed by light microscopy, but more than 25% of the cells were binucleate.

WI-38 diploid cell cultures fused with brain cells by treatment with lysolecithin showed no pathological changes. The mixture of CV-1 cells and brain cells treated with lysolecithin similarly showed no changes over the interval of 16 passages. Cultured brain cells fused with CV-1 cells by lysolecithin did not adsorb guinea-pig red blood cells when checked at the sixth passage.

Postmortem Findings. The body was extremely emaciated and organs, such as the heart and liver, reflected this change by marked atrophy. An extensive bronchopneumonia was present. The brain weighed 1,150 g. The leptomeninges were thin and transparent. The cortical anatomy appeared normal but congested. Coronal sections showed yellow-tan necrosis of both white and grey tissue in the vicinity of the superior and middle frontal gyri bilaterally. Similar degenerative change was seen in the anterior basal ganglia. Plaque-like changes were not found in the white matter. The brain-stem, cerebellum, and spinal cord revealed no lesions.

Microscopically, the necrotic change seen in
the frontal lobes showed marked perivascular infiltration by reactive cells. The exudate consisted predominantly of lymphocytes, but plasma cells and macrophages were also present. Endothelial cells in relation to small capillaries were swollen and more numerous than normal; moreover, there was a slight loss of neuropil adjacent to these small vessels. In adjacent tissue, there was a more diffuse leucocytic reaction with lymphocytes and plasma cells scattered among myriads of large pink staining reactive astrocytes. The astrocytes sometimes had several nuclei. Cavitation was seen in white matter that was largely made up of reactive astrocytes. Luxol blue stains were seen as in the cerebrum. The pontine nuclei, ascending and descending tracts appeared normal save for the occasional presence of perivascular lymphocytic cuffing (Fig. 4).

After intensive electron microscopic study we failed to find tubular structures similar to those found in patients with subacute sclerosing panencephalitis (Raine et al., 1969, 1972), or in cells infected with measles virus (Kallman et al., 1959; Tawara, 1965).

DISCUSSION

Although the patient’s history and clinical findings strongly suggested a diagnosis of subacute sclerosing panencephalitis, the critical laboratory data, positive and negative, failed to support the clinical impression of that disease. Brain biopsy tissues before death were negative when stained by the direct FA technique using measles virus antibody tagged with fluorescein. The pathological findings on biopsy material were also negative for any evidence of measles virus infection. However, the postmortem pathological findings revealed demyelination with perivascular cellular changes and rare inclusion bodies in cytoplasm and nucleus which were evident after considerable search. Inclusion bodies are readily seen in patients with subacute sclerosing panencephalitis.

The fact that her cerebrospinal fluid contained antibody to measles virus supports a possible diagnosis of multiple sclerosis. The antibody titres were not as high as those recorded in most patients with subacute sclerosing panencephalitis (Adams and Imagawa, 1962; Legg, 1967; Panelius et al., 1971; Pettay et al., 1971; Sever et al., 1971; Donner et al., 1972; McAlpine et al., 1972; Cendrowski et al., 1973; Panelius et al., 1973).

Recent reports from Finland and Sweden by Panelius et al. (1971) and Link et al. (1973) clearly support an immunological relationship between multiple sclerosis and subacute sclerosing panencephalitis. Panelius et al. (1972) reported that the gel precipitation (GP) test may ‘demonstrate not only antibodies to proteins in the measles virus, but also antibodies to virus-specific nonstructural proteins induced in host cells during the measles infection . . . moreover, almost complete identity could be demonstrated

![Fig. 4. Perivascular mononuclear cell infiltration with astrocytic proliferation in a demyelinated zone of frontal lobe. H and E, × 500.](http://jnnp.bmj.com/ on October 30, 2017 - Published by group.bmj.com)
between the GP lines produced by the serum from an SSPE patient and from an MS patient, both giving 5 measles-specific precipitation lines’. Link et al. (1973) presented further immunological observations on immunoglobulins and measles antibodies in subacute sclerosing panencephalitis. They demonstrated by electrophoresis a gamma band (in CSF but not in serum) containing an excess of IgG molecules of type K and with HI, CF, and antiribonucleoprotein (RNP) antibodies against measles virus. They concluded that synthesis in the central nervous system is more pronounced for antibodies against RNP component of the measles virus than for antibodies against measles virus envelope components.

Several specimens of serum and cerebrospinal fluid were kindly analysed in Dr C. H. Kempe’s laboratory (University of Colorado Medical Center, Denver, Colorado) for vaccinia virus antibodies. None was found in her spinal fluid specimens and serum levels were considered to be normal.

The careful and thorough study of the findings in this patient would suggest to the authors that her diagnosis must rest somewhere between atypical subacute sclerosing panencephalitis and multiple sclerosis. The tentative conclusions, if any may be drawn, are that these two diseases on occasion may overlap, and the final diagnosis from an aetiological point of view is demyelinating disease possibly associated with the measles virus.

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