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AN UNUSUAL FORM OF MEASLES MENINGOENCEPHALITIS

A REPORT OF TWO CASES (*)

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Summary. Two patients are reported with a chronic progressive illness characterized by dementia, ataxia and spasticity. There were no myoclonic jerks and both had normal electroencephalograms (EEG). Pathological findings in three brain biopsies were those of viral meningoencephalitis with perivenous demyelination. Serological data in both patients indicated the presence of a measles virus infection. Intracytoplasmic structures resembling measles virus nucleocapsids were found in the brain biopsy of one patient. Immunofluorescent staining showed antibody in the temporal lobe biopsy of both patients. It is suggested that these patients are examples of a chronic form of measles meningoencephalitis hitherto undescribed.

Key words: Measles meningoencephalitis – Multiple sclerosis – Subacute sclerosing panencephalitis – Viral antibodies.

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INTRODUCTION

Two of the best known neurological complications of measles virus are acute encephalomyelitis and subacute sclerosing panencephalitis (SSPE). Both can affect previously normal patients [14] or those with deficient [9] or suppressed [4] immune mechanisms. Although evidence for direct participation of measles virus in some cases of parainfectious (postmeasles) encephalomyelitis has been presented [2,28] the questions regarding the role of an immune mechanism in its pathogenesis has not yet been resolved [5].

We describe the clinical features of two patients with a nonremitting progressive syndrome of dementia, ataxia and spasticity. Immunological and pathological findings in these patients are described. Evidence suggested a direct pathogenetic role for measles virus. We are not aware of any previous report concerning such a syndrome caused by measles.

PATIENTS AND METHODS

case 1. A 25-year-old woman was admitted because of progressive weakness of the legs, which began 8 months earlier. She was in good health before, and had delivered her last child 2 months prior to the onset. She had become unable to walk in 2 months and lost bladder control. Soon after, she became ataxic in her upper limbs. There was no history of fever, diplopia or seizure. No remissions occurred before or during the long periods of observation in the hospital. There was no history of vaccination or known measles. Family history and the review of systems were unremarkable.

The abnormal physical findings were all neurological. The mental state as regards orientation, insight, memory and judgment was intact. Her speech was slurred and explosive. Bilateral horizontal nystagmus was present. The optic fundi and the function of other cranial nerves were normal. Spastic tetraparesis, more pronounced in the legs, was found with exaggeration of reflexes, including that of the jaw. The plantar reflexes were extensor. The muscular power in the arms was preserved. In the legs, she could only move the toes. There was severe cerebellar ataxia in the upper limbs. Atrophy and fasciculations were absent. Sensation, includng stereognosis, was intact. Neither scoliosis nor pes cavus were present. She was readmitted 8 months later; definite moderate decline in mental faculties, bilateral optic atrophy and reduction of her voice to an incoordinate whisper were the singnificant new findings. No myoclonic jerk was noted in 2 years of observation. She was last seen in April 1978.

The following tests gave normal or negative results: Repeated electroencephalograms (EEG) (5 EEGs in both admission over a 2 year

period) electrocardiogram, computed tomography (CT), hemogram, and complete evaluation of collagen diseases and syphilis. Serum immunoglobulin levels were normal for IgG and IgA (1580 mg/dl and 175 mg/dl) while the IgM level was elevated, 462 mg/dl (normal 53-375 mg/dl). The CSF total protein measured 100 mg/dl and the CSF VDRL was negative. The CSF IgG was elevated, 25.3 mg/dl (normal 1.1-10.2 mg/dl) while the albumin level was in the normal range, 27 mg/dl (normal 6.1-71.3 mg/dl). These last two values gave a CSF IgG/ albumin ratio that was considerably elevated, 0.94 (normal 0.038-0.322). Serum protein electrophoresis (SPE) demonstrated an increase of gamma globulins, 45.2% (normal 3-13%) and a single minor monoclonal band in the mid-gamma region. There was no evidence of increased capillary permeability to large molecular weight proteins by SPE or immunoelectrophoresis. Complement fixation test for antibodies against herpes simplex and vaccina viruses in the CSF did not show any significant titer (less than 1/2). Table 1 shows antimeasles antibody levels obtained on both admissions, as determined by previously described methods [12, 17, 20]. Immune complexes in the serum as measured by radioimmune assay [22] was 8.7% of the C_1q counts offered. Binding of 6% or more was considered as positive (> 2 S.D. from the control values).

Table 1. Antimeasles antibody titers in serum and cerebrospinal fluid

Case	Sample	Date	Tests[a]		
			HI	CF	N
(1)	Serum	11.11.76	2048	512	1024
	Serum	10.06.77	2048	ND	ND
	CSF	27.10.76	16	16	16
	CSF	10.06.77	128	32	32
(2)	Serum	09.06.77	384	16	192
	Serum	30.06.77	256	16	192
	CSF	09.06.77	12	2	8
	CSF	30.06.77	12	1	12

[a] Reciprocal dilutions of measles hemagglutination inhibition (HI) [20], complement fixation (CF) [12], and neutralization (N) [17] titers

ND = not determined

1 = absence of antibody in undiluted CSF

Case 2. A 28-year-old shepherd was in good health until 18 months prior to admission. Since then he had noted gradully increasing trouble with his

balance. There had been no diplopia, seizure or sphincter dysfunction. His speech was slurred but he did not know for how long. No symptomatic remission had occurred in the past. Past medical and family histories were unremarkable. Abnormal findings were entirely neurological. He showed poor insight, defective judgment and diminished memory. Bilateral optic atrophy (visual acuity in both eyes was 20/40) and horizontal nystagmus was present. Other cranial nerves were normal. There was mild spastic tetraparesis, involving the legs more than the arms, with exaggerated tendon jerks. The plantar reflexes were extensor. Atrophy and fasciculations were absent. His performances were all ataxic. No myoclonic jerks were noted during 5 months of observation. All sensory modalities were intact. Vertebral column and feet were normal in appearance.

Normal or negative results were obtained in the same tests as in Case 1 with the exception of slight widening of the sulci demonstrated by CT scanning (more pronounced in the temporal lobes). The EEG was normal on 3 occasions; each was recorded 1 month apart.

Serum immunoglobulin levels were normal for IgG, IgA and IgM. CSF total protein (35 mg/dl) and VDRL were normal with IgG and albumin levels of 4.9 mg/dl and 6 mg/dl respectively. The CSF IgG/albumin ratio was, as in Case 1, markedly increased, 0.82. Complement fixation test for antibodies against herpes simplex and vaccina viruses in the CSF did not show any significant titer (less than 1/2). The antimeasles antibody levels are shown in Table 1. Immune complexes in this patient 6.2% of the C_1q counts offered (> 2 S.D. from the control values).

SEROLOGICAL DATA ON CONTROL PATIENTS

Antimeasles antibody levels (HI) were measured in the sera and CSF samples from 40 control patients. Paired samples were obtained on the same day. The group consisted of patients with the following diagnoses: cerebral infarction (10), disk disease (10), motor neuron disease (5), Parkinsonism (10), myopathies (5). Titers in the control sera ranged from nil to 1:2048. A low level of antibody (1:4) was detected in one of the control CSF samples. It belonged to a patient with active tuberculosis and myopathy of an unresolved type. The highest serum antibody level belonged to the same patient.

HISTOLOGICAL FINDINGS

Informed written permission was obtained for diagnostic biopsies from the legal guardians of each patient. The specimens, measuring 1 cm in each dimension, were obtained after appropriate craniotomy under general anesthesia. These were processed in a standard manner for histological staining. Part of the cerebellar specimen was also processed for electronmicroscopy (EM).

Cerebellum (Case 1, November 1976). Severe loss of Purkinje cells with moderate atrophy of the molecular layer was seen in sections stained with hematoxylin and eosin (HE). Some of the folia were entirely depopulated of Purkinje cells. In the others the cell loss was patchy and the remaining cells were small and misshapen. Diffuse proliferation of reactive astrocytes were seen in the white matter. No demyelination plaques were seen in the section stained for myelin. There was no proliferation of the Bergmann glia cells. A slight to moderate mononuclear and plasma cell infiltration was present in the leptomeninges and in the perivascular spaces in the white matter. Intracytoplasmic aggregates of tubular structures, resembling measles nucleocapsids, were found in the thin sections (Fig. 1).

Temporal Lobes (Cases 1 and 2, June 1977). Pathological findings were similar in both patients. Meningoencephalitis was found, evidenced by mononuclear cells in the leptomeninges and in the perivascular spaces of the white matter (Figs. 2,3,4). The intensity varies from mild to moderate in different regions. Thickening of the leptomeninges was noted. The mononuclear inflammatory response was accentuated around the subarachnoid veins and their penetrating branches (Figs. 5, 6). Within the leptomeningeal inflammatory response a number of plasma cells were found. A definite loss of neurons was seen in the gray matter in patches of varying extent. The majority of the remaining neurons were small and ill-looking. Reactive astrocytes were scattered in the white matter. Small glial nodules were also present. No inclusion bodies were found. Sections stained for myelin showed small and large areas of subcortical demyelination with a shelving border. Widening of the perivascular spaces was seen, surrounded by round and clearly circumscribed areas of demyelination (Fig. 7). Indirect immunofluorescent (IF) staining of fresh tissue in both patients was done according to the standard method [7], using fluorescent antihuman IgG, IgA, IgM and IgG + IgA + IgM (whole) from a commerical source (Behringwerke, West Germany). The brain tissues stained for IgG, IgA and IgM with an intensity in that order (Figs. 8,9). Similar IF staining of biopsy material from three control patients gave negative results. Attempts to isolate measles by cocultivation of the biopsy material with fresh vero cells remained negative after 10 passages.

DISCUSSION

Histological findings in the brain biopsies from the two patients are consistent with that seen with viral meningoencephalitis [10]. A two and eightfold increase in the level of antimeasles antibodies (within 8 months) in the CSF and the EM findings of an intracytoplasmic tubular structure closely resembling measles virus nucleocapsid are sufficient evidence for a casual implication of that virus in Case 1.

In the second case, also, such evidence exists. It is in this case, however, that the results of antimeasles antibody ratios in the sera and CSF of our control patients are more pertinent. The serum/CSF ratios of HI antibody titers in Case 2, viz. 24, are much lower than the ratios in the control patients reported by others (more than 80), indicating intrathecal production of antimeasles antibodies in this patient [6,21,24]. It is also difficult to imagine the nonspecificity of the different antimeasles antibodies in the CSF of our patients [26]. It is therefore concluded that both patients were suffering from an unusual form of measles meningoencephalitis.

A review of the literature indicates that a chronic progressive illness after measles although rare, has not escaped the attention of previous observers. Miller et al. [19], in their review of postmeasles encephalomyelitis, mention a "unique" case of a progressive illness lasting 8 months (reference No. 14). Postmeasles encephalomyelitis is a monophasic disease resulting in early death, nonprogressive neuropsychological residua, or in complete recovery [19]. Further, it was pointed out that some of these patients "appear quite normal on discharge from hospital but their further development is retarded and their intelligence quotient may gradually fall during the ensuing years" [19]. It is conceivable that the mechanism for this decline of intelligence was the persistence of a smoldering encephalitis in these particular patients.

In our cases their age, the absence of myoclonic jerks and the normal EEGs, (on repeated examinations, and 2 years after the onset of illness) were the principal features which distinguished the condition from that of SSPE on clinical grounds. In SSPE the EEG is almost always abnormal, often with characteristic quasi-periodic high amplitude complexes, by 6 months after the onset of SSPE [15,25,27]. This correspodes to our observations. (We have investigated 33 cases of SSPE within a period of 3 years in Iran. EEG was abnormal in all of them by the time diagnosis was established. Myoclonic jerks were present in 30 patients. The remaining three patients had a rigid form of the disease.)

Clinically, the symptoms of our patients were similar to those cases with a disseminated progressive form of "possible" multiple sclerosis [13,16,18], with dementia as an additional part of the symptomatology in our cases. Their negative family histories, normal electrocardiograms and the CFS findings (raised IgG/ albumin ratios) [11] are consistent with the above statement. It was the absence of remissions which precluded the designation of "probable" multiple sclerosis (on clinical grounds).

The pathological findings in our cases are consistent with those of perivenous encephalitis [3,5,23] and SSPE [10], with perivenous and regional demyelination as additional pathological findings. The attention of workers investigating the pathogensis of multiple sclerosis is increasingly directed toward the presence of perivenous inflammatory responses as a common denominator between multiple sclerosis and perivenous encephalomyelitis [1,5,8].

The immunological and pathological data provided support for the opinion that out patients had a chronic form of measles meningoencephalitis manifested by a syndrome which has not been clearly delineated in the past.

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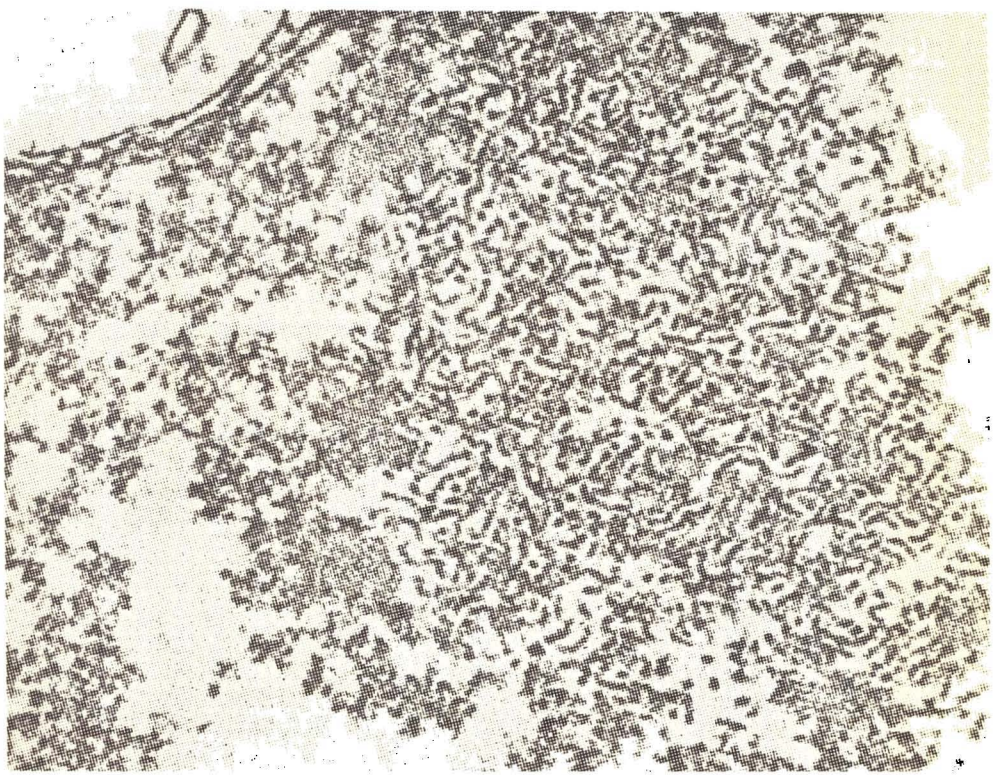

Fig. 1. Cerebellum, Case 1. Accumulation of tubular structures closely resembling measles nucleocapsids in cytoplasm of an identified cell. ×72,000

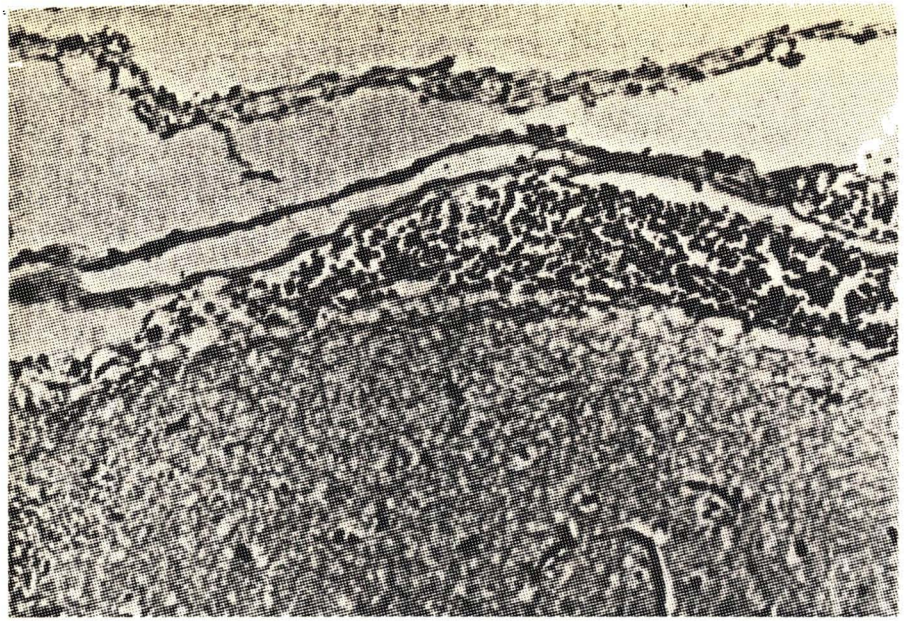

Fig. 2. Temporal lobe, Case 2. Leptomeningeal mononuclear infiltration. HE stain. Original magnification × 180

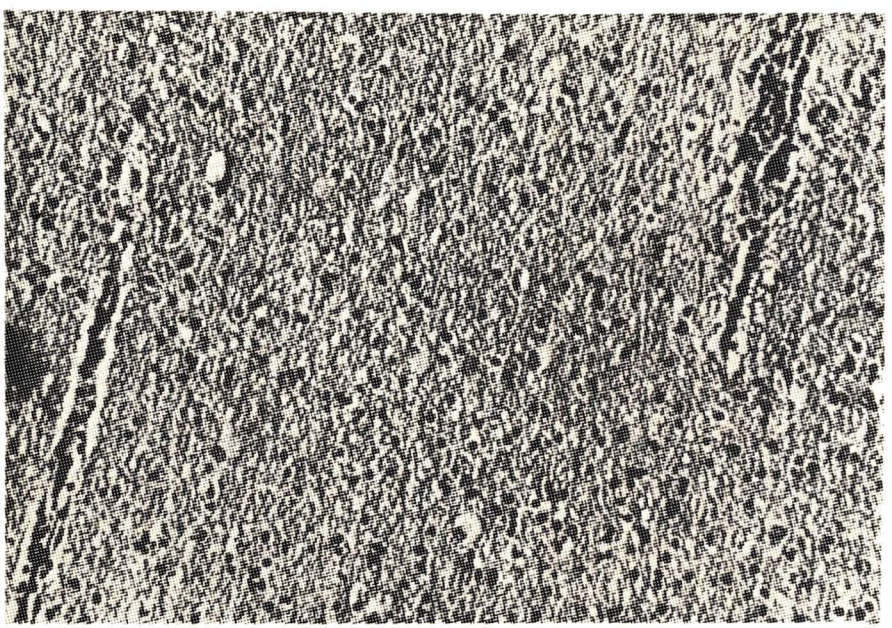

Fig. 3. Temporal lobe, Case 2. Perivascular mononuclear inflammatory response around two vessels within white matter and scattered reactive astrocytes. HE stain. Original magnification × 180

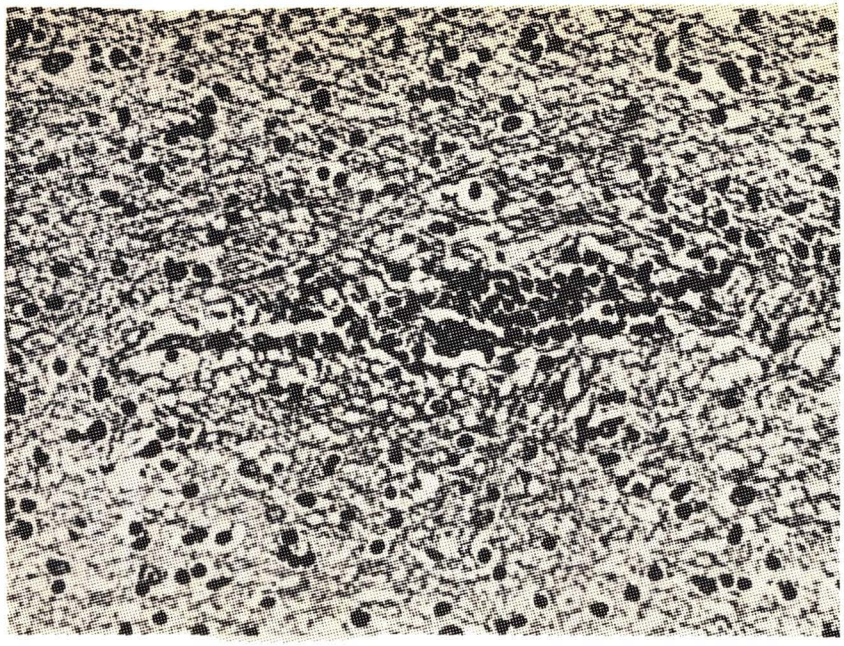

Fig. 4. Temporal lobe, Case 2. Higher magnification of section in Figure 3. Sponginess of perivascular white matter around central vessel can be seen. Original magnification × 288

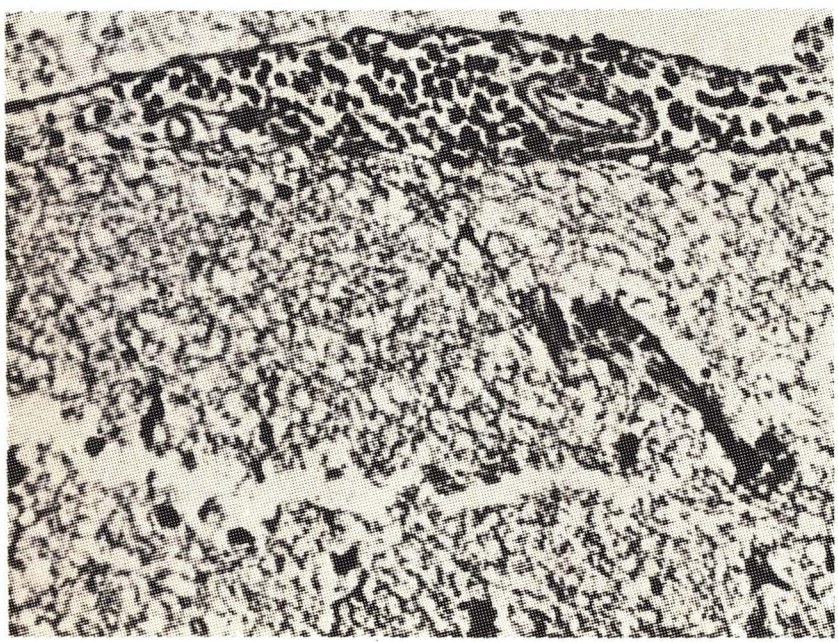

Fig.5. Temporal lobe, Case 1. Mononuclear infiltration around subpial vessels. HE stain. Original magnification ×180

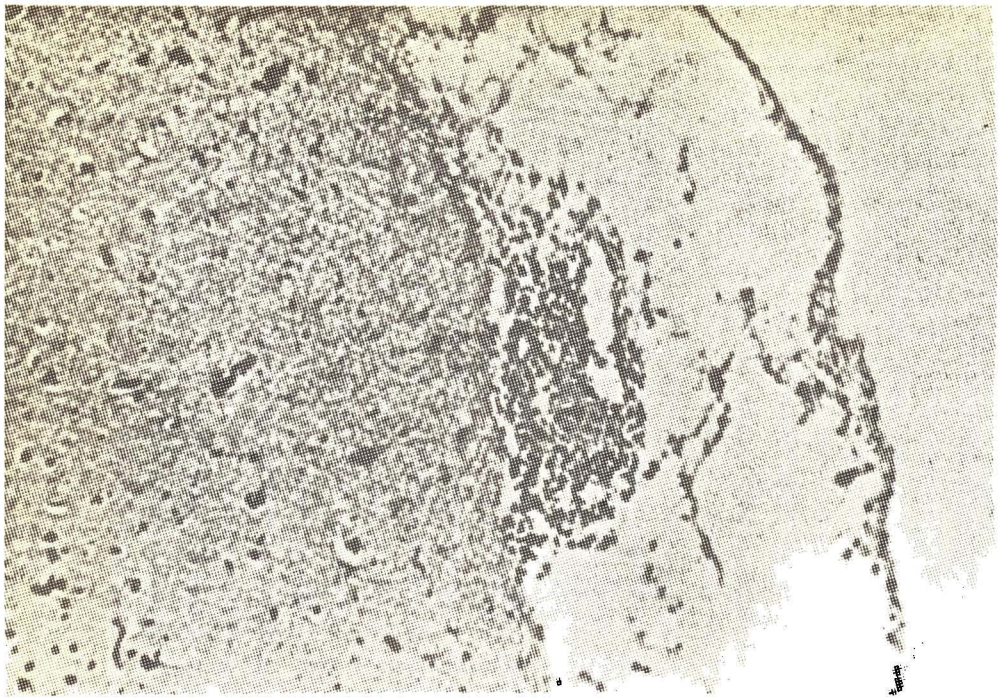

Fig.6. Details as in Figure 5. Original magnification × 120

Fig.7. Temporal lobe, Case 1. Enlargement of perivascular spaces and perivenous demyelination neighboring larger zone of demyelination with shelving edge. Outline of two vessels can be discerned with closer scrutiny. Myelin stain. Original magnification × 45

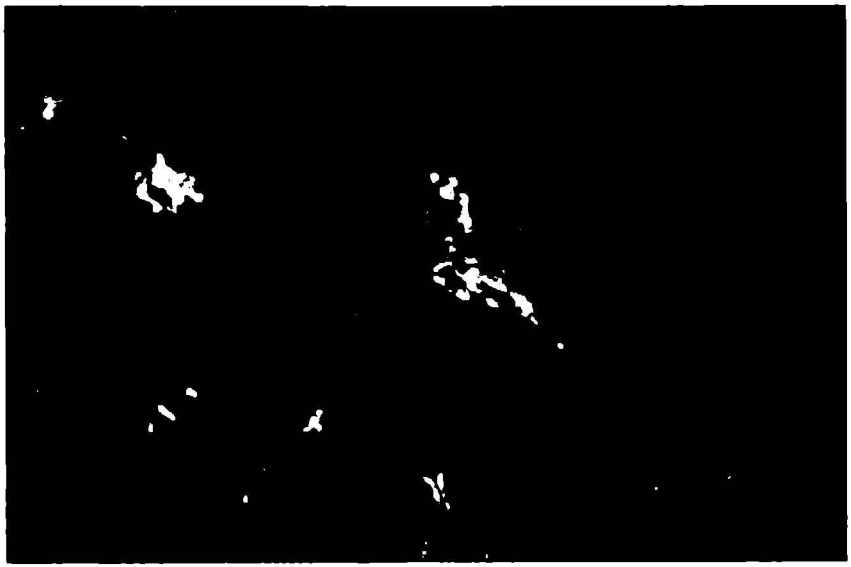

Fig. 9. Temporal lobe, Case 2. IgG staining, ×400

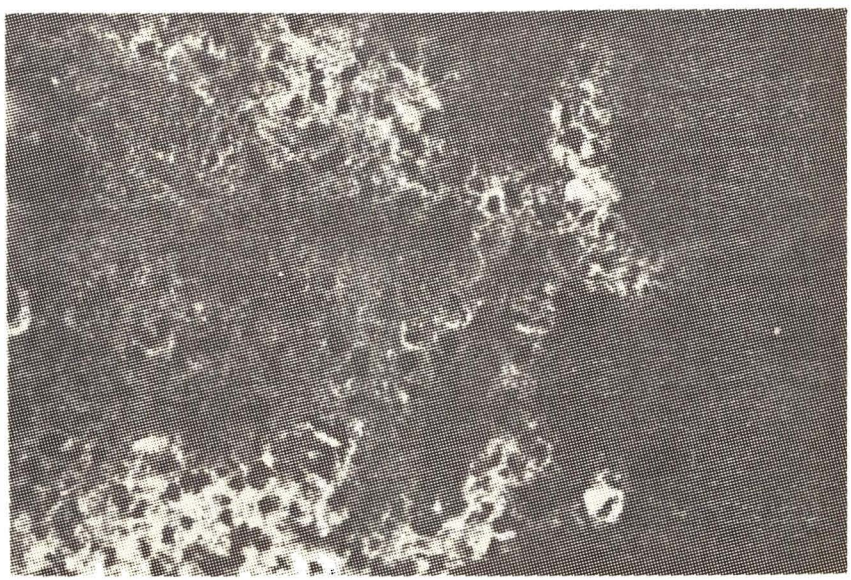

Fig.8. Temporal lobe, Case 1. IgG staining, × 400

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