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Jakob-Creutzfeldt disease

Modification of clinical and electroencephalographic activity with methylphenidate and diazepam

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SYNOPSIS The electroencephalogram in three patients with Jakob-Creutzfeldt disease showed two separate abnormalities—namely, progressive background suppression and periodic generalized synchronous triphasic sharp wave complexes which evolve to a uniform morphology and periodicity. The abnormalities, when found in the EEG of a patient in middle-age with a dementing illness, should not be confused with other periodic electroencephalographic phenomena. Since the neuropathological abnormalities of Jakob-Creutzfeldt disease are non-specific, the electroencephalogram is essential for the recognition of this disorder, although serial recordings may be necessary to establish the diagnosis. Modification of the electroencephalographic abnormalities occurs with afferent stimuli and with methylphenidate or diazepam, suggesting that the phenomenon of background suppression is independent of the presence of the periodic complexes. Modification of clinical activity with methylphenidate suggests that some degree of reversibility of function exists in this inexorably fatal disorder. Further detailed studies of the electroencephalogram in cases of Jakob-Creutzfeldt disease are indicated.

Creutzfeldt (1920) and Jakob (1921, 1923) described a rare form of progressive dementia associated with a variable clinical picture of corticospinal and striatal abnormalities and with pathological findings of widespread neuronal loss and either focal or generalized astrocytic proliferation. Variations in these features have, in the past, resulted in diverse terminology for this condition which is now termed Jakob-Creutzfeldt disease. It is thought to be more prevalent than was originally supposed and may be at least as common as Pick's disease (Torvik, 1970; Barrett, 1972). Jakob-Creutzfeldt disease (including its variants) has generated widespread interest since clinicopathological correlates have been observed with certain endemic disorders of the central nervous system of New Guinea (Klatzo *et al.*, 1964; Neumann *et al.*, 1964) and of Guam (Hirano *et al.*, 1961; Hirano *et al.*, 1961; Hirano *et al.*, 1966), and especially since serial transmissibility of a similar disorder in primates after the instillation of brain homogenate from cases of Jakob-Creutzfeldt disease has been demonstrated (Gajdusek *et al.*, 1966; Gibbs *et al.*, 1968).

The electroencephalographic (EEG) abnormality of periodic sharp wave complexes, originally described by Jones and Nevin in 1954, has been observed in a high proportion of patients (Kirschbaum, 1968; Siedler and Malamud, 1963; May, 1968) but controversy still exists regarding the specificity of the EEG in this condition (Gubbay and Barwick, 1966; Kiloh *et al.*, 1972; Förster and Kugler, 1970). Similar EEG discharges may be seen with other subacute afflictions of cortical and subcortical grey matter (Gloor *et al.*, 1968) but the configuration, duration, and periodicity of the sharp wave complexes in the recordings in Jakob-Creutzfeldt disease appear, nevertheless, to constitute the most useful clues towards the diagnosis of this condition (Gloor *et al.*, 1968; Hauser-Dumur and Radvanyi, 1970; Goldhammer *et al.*, 1972), especially since the neuropathological 'spongiform' abnormalities are now thought by most authorities to be non-specific (Torvik, 1970;

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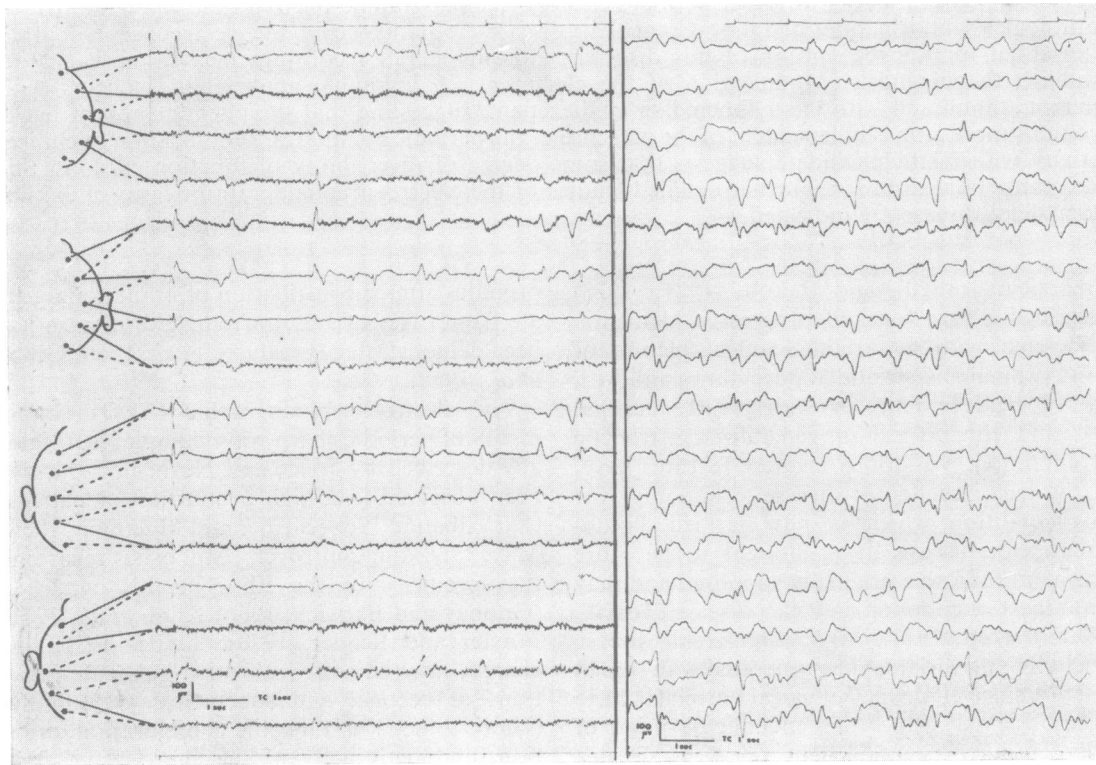
Robinson, 1969; *British Medical Journal*, 1972).

Jones and Nevin (1954) in their original paper described the characteristic morphology, periodicity, and waxing and waning quality of the periodic discharges seen in the electroencephalograms of their patients with subacute vascular encephalopathy, a condition which is now generally regarded as a variant of Jakob-Creutzfeldt disease. They also showed that the intravenous administration of short-acting barbiturate suppressed the spike or sharp wave component of the periodic complexes. Nelson and Leffman in 1963 also demonstrated the suppression by barbiturate of the EEG periodic complexes in a patient with the disease and, in addition, showed that the periodic complexes were enhanced by the intravenous administration of chlorpromazine or pentazol. Förster in 1970 used massive doses of intravenous diazepam in patients with the disease and reported only slight and short-lived suppression of the EEG sharp potentials. Recent publications (Goldhammer and Braham, 1969; Burger *et al.*, 1971) have stressed the need for further analysis of the EEG abnormalities of Jakob-Creutzfeldt disease and the present paper reviews such findings in three cases of this disorder studied during the past five years. The results of clinical and electro-



(a) (b)

FIG. 1. (a) *Case L.H. Patient in terminal quiescent state. EEG shows repetitive generalized synchronous spike and sharp wave triphasic complexes at a repetition rate of approximately one per second. Intervening background rhythms markedly suppressed.* (b) *Case R.M. EEG shows generalized synchronous triphasic periodic sharp wave complexes at repetition rate of 0·6 per second. Morphology of periodic complexes, which occur intermittently in short runs, is characteristic of the early stage of Jakob-Creutzfeldt disease.* (*Calibrations 100 μV; 1 s.*)

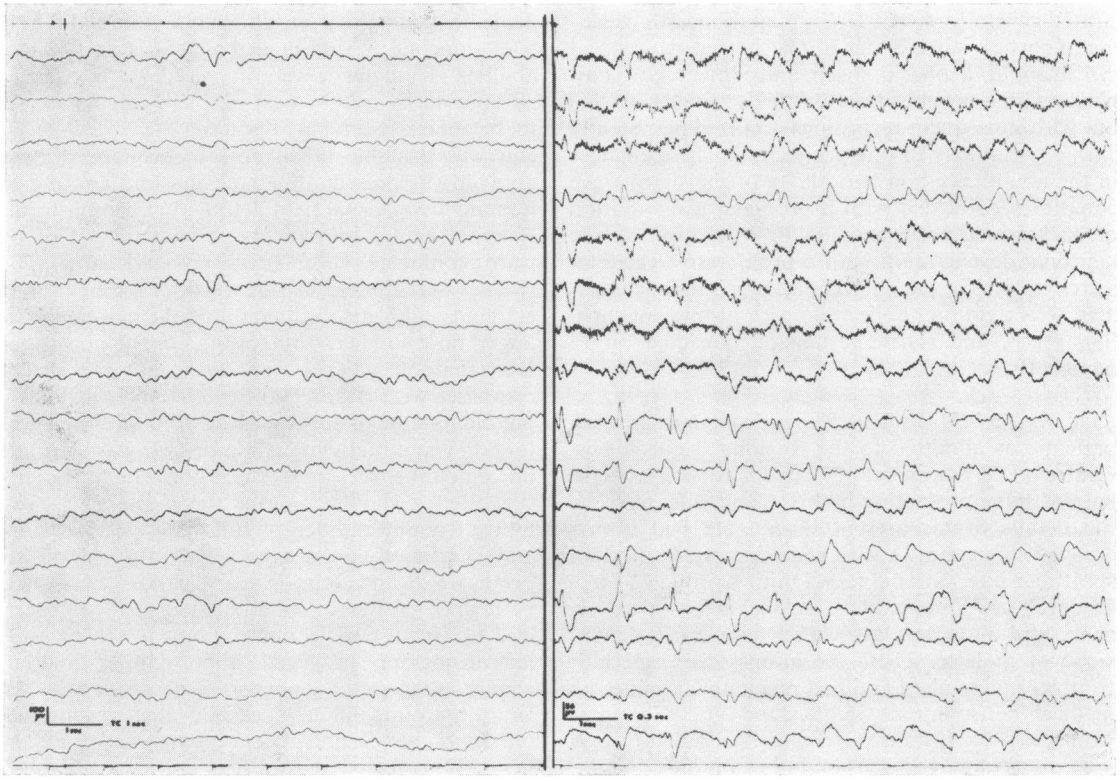
encephalographic monitoring during the administration of parenteral methylphenidate and diazepam in one patient (K.D.) are discussed in detail.

METHODS

Three patients with Jakob-Creutzfeldt disease were studied. EEGs were recorded on an Offner TC 16-channel or on a SLE 18-channel machine; in all cases bipolar montages (as in Fig. 1) were used with a sensitivity of 100 μV/cm and an amplifier time constant of 1 s, except Fig. 2b in which the calibration was 56 μV/cm and the time constant was 0·3 s.

CASE REPORTS

CASE L.H. (N28547) This 64 year old female patient was transferred from the Darlington Memorial Hospital to the Regional Neurological Centre on 28 June 1968 in a grossly demented state with intermittent myoclonic jerking of her extremities, a right spastic hemiplegia, right homonymous visual field defect, primitive facial reflexes, and truncal ataxia. Extensive investigations of blood, urine, and cerebrospinal fluid (CSF) showed no abnormality. Pneumoencephalography revealed generalized ventricular dilatation with widening of cortical sulci; EEG showed generalized periodic complexes, and brain biopsy revealed neuronal loss with spongiform astrocytic proliferation. Serial electroencephalograms indicated that the generalized synchronous periodic triphasic sharp wave discharges, which showed a repetition rate of about one per second, became per-



(a) (b)

FIG. 2. *Montages as in Fig. 1. Case K.D.* (a) *EEG performed on admission and while patient awake shows generalized slowing of background rhythms below 8 Hz. (Calibrations 100 μV; 1 s.)* (b) *Two weeks after admission. EEG shows intermittent periodic complexes at repetition rate of one per second which are generalized but more prominent over the left anterior head region. Background activity has become less abundant* (compare (a)). *(Calibrations 56 μV; 1 s.)*

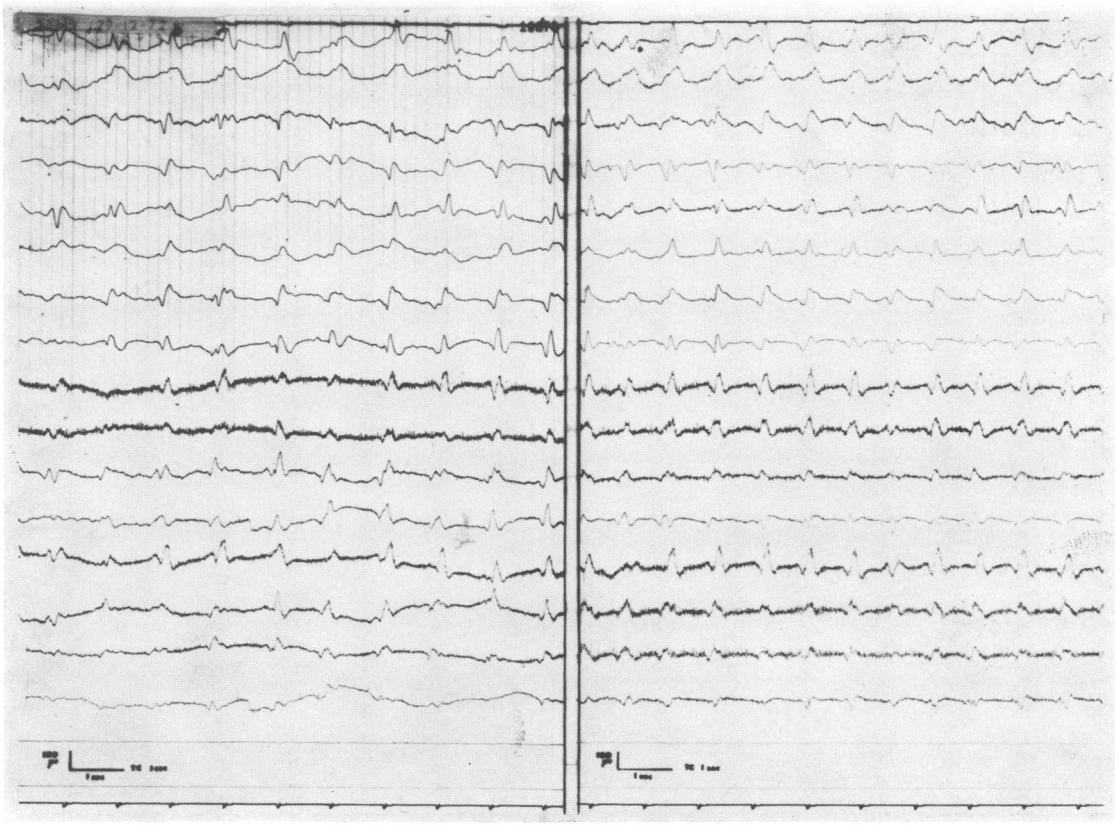
sistent and stereotyped in wave form as the patient's clinical condition deteriorated. This increase in the abundance of the electroencephalographic periodic discharges coincided with a progressive diminution of background rhythms in the intervals between the discharges so that by the time the patient reached a state of inanition the background activity showed almost complete suppression (Fig. 1a). The patient died on 19 November 1968.

CASE R.M. (N28719) This 56 year old female patient was admitted to the Regional Neurological Centre on 2 December 1970 with a four week history of forgetfulness and lethargy. After admission she developed progressive myoclonic jerking and rigidity of her limbs, hyper-reflexia, and extensor plantar responses, and she became unresponsive to verbal stimuli. Routine investigations of blood, urine, and cerebrospinal fluid and radiographs were within normal limits but pneumoencephalography demonstrated generalized ventricular dilatation with widening of cortical sulci. Serial EEGs showed generalized synchronous triphasic sharp and slow wave complexes with a periodicity of 0·6–0·7 seconds (Fig. 1b) but with subsequent recordings occurred persistently with a periodicity of one per second. These changes in the abundance and periodicity of the sharp wave complexes coincided with a progressive diminution of background EEG activity. Brain biopsy showed neuronal degeneration with a proliferative vacuolar astrocytosis. The patient's clinical condition deteriorated to a rigid immobile state with prominent sucking, grasp, and startle responses. She died on 13 March 1971.

CASE D.K. (N44714) This 53 year old German male patient was admitted to the Regional Neurological Centre on 28 November 1972 and was able, with the help of some prompting by his young wife, to relate the details of his present illness. He had always enjoyed robust health with wide interests in outdoor sport and international travel until April 1972 when he developed an irritable 'tingling' across his back, neck, and shoulders associated with an ill-defined sense of malaise. These sensations were especially troublesome at night and had precipitated numerous medical consultations in England and Germany. Multiple prescriptions of medications failed to provide significant relief from his symptoms but his condition did not seem severe enough to prevent his marriage in September 1972. During his honeymoon, his wife related, he experienced two 'spells' each characterized by the adoption of a blank facial expression, a strange look in his eyes, and verbal unresponsiveness. During one such episode he was involved in a minor automobile accident while driving on the autobahn in Germany, an incident throughout which he remained unperturbed even though his passengers were alarmed and distressed. For three weeks before his admission to hospital he had become forgetful, apathetic, and at times irrationally suspicious so that he was already a source of concern and embarrassment both at home and at work. His past history revealed that he had entered England involuntarily as a prisoner of war in 1944 but had remained in this country after his first marriage in 1948 and had developed a responsible position as an industrial equipment export executive.

General physical examination of D.K. on admission was unremarkable except for self-inflicted superficial excoriations over the extensor surfaces of both upper extremities. He was disorientated in time and recent memory was impaired. Throughout the examination he exhibited constant psychomotor restlessness as indicated by distractability and intermittent twitchings of his face, arms, and legs. He denied hallucinatory sensations but admitted that he felt 'someone is out to get me'. Abstraction and abilities of judgment were impaired but intelligence as assessed by arithmetical problem solving seemed to be intact. Nominal dysphasia was present. His gait was unstable in an apraxic fashion; dressing apraxia was present. Bilateral anosmia and a right homonymous visual field defect were demonstrated. External ocular movements showed paresis of upward conjugate gaze. Brisk jaw jerk and snout reflexes were present. A slight drift of the right upper extremity with incoordination of the extremities on finger–nose and heel–shin testing were demonstrated. Deep tendon reflexes were brisk but the plantar responses were flexor. No obvious abnormalities of muscle tone or of superficial or deep sensation were found. The initial clinical impression was of a midline parietal space-occupying lesion: the time course suggested a glioblastoma as the most likely possibility. Routine radiography of skull, cervical spine, and chest were unremarkable, as were blood and urine counts and serum chemistry. An EEG (33031) performed on the day of admission showed generalized slowing a background rhythms to 6 Hz without lateralizing or projected abnormalities and the changes suggested a diagnosis of dementia (Fig. 2a). Brain scan and bilateral carotid angiography were unremarkable. A pneumoencephalogram (6 December 1972) revealed generalized ventricular dilatation and widening of cortical sulci compatible with a diagnosis of cerebral atrophy with compensatory hydrocephalus. Examination of CSF showed normal values for pressure, cells, protein, and sugar. By 12 December 1972, two weeks after his admission, the patient had deteriorated to the point where he did not speak and responded only to simple commands

such as 'open your mouth'. He had developed a generalized increase of muscle tone and held his fists clenched and his upper extremities flexed in decorticate posture. Occasional myoclonic jerking of all limbs was noted. On 12 December 1972 a repeat EEG (33091, Fig. 2b) revealed generalized intermittent triphasic sharp wave complexes of 400 ms duration and with a periodicity of about one per second. At this stage, a clinical diagnosis of Jakob-Creutzfeldt disease was made. Brain biopsy was performed on 18 December 1972 and revealed neuronal loss with astrocytic proliferation of the 'spongiform' variety. By this time the patient had become mute and unresponsive to painful stimuli; he showed marked rigidity of the head, trunk and limbs, and bilateral extensor plantar responses. By 29 December 1972 spontaneous myoclonic movements had ceased: when approached, he responded by abducting his arms briskly and opening his eyes and mouth widely, the response being somewhat like the Moro reflex in children. At this time EEG (33143, Fig. 3a) showed generalized periodic triphasic sharp wave complexes but with modulation of amplitude in a waxing and waning fashion. No clinical accompaniments to the periodic discharges were observed. The amplitude and amount of the background rhythms between the complexes was reduced in comparison with the previous recordings. On 10 January 1973, paraplegia



(a) (b)

FIG. 3. *Montages as in Fig. 1. Case D.K.* (a) *Four weeks after admission. EEG shows that periodic triphasic sharp wave complexes of 400 ms duration and with a repetition rate of 1·05 per second have become persistent and stereotyped. Interval background activity is markedly suppressed.* (b) *Six weeks after admission. EEG shows persistent generalized and stereotyped periodic discharges at repetition rate of 1·28 per second with marked suppression of intervening background rhythms. (Calibrations 100 μV; 1 s.)*

in-flexion with marked truncal and limb rigidity was found. A sucking reflex was now present and tapping the lips, which elicited the snout reflex, also precipitated myoclonic jerks of the patient's limbs. His eyes and head periodically deviated to the right side with myoclonic jerking of his eyes that suggested an adversive seizure. A grasping reaction of the feet was found on stimulation of the plantar areas but tonic neck reflexes could not be demonstrated, indicating that decortication was present without decerebration. On 11 January 1973 EEG was performed with monitoring of the electrocardiograph (ECG) (73/0060). The periodic complexes were uniform with diminished modulation of amplitude as compared with the previous recordings, while background rhythms showed further suppression (Fig. 3b). Negligible alteration of the periodic complexes occurred during an adversive seizure. Needle stimulation of the left ulnar nerve, however, was followed by partial suppression of the complexes (Fig. 4a). Slow intravenous injection of methylphenidate (40 mg) was followed almost immediately by flattening of the periodic discharges (Fig. 5) but little alteration of the background rhythms occurred. The ECG showed an increased heart rate but did not otherwise change significantly. The patient, who had been unresponsive for the previous month, directed his gaze in the direction of the intravenous needle, tried to get off the examination table, attempted to remove the intravenous needle, successfully pulled out his nasogastric

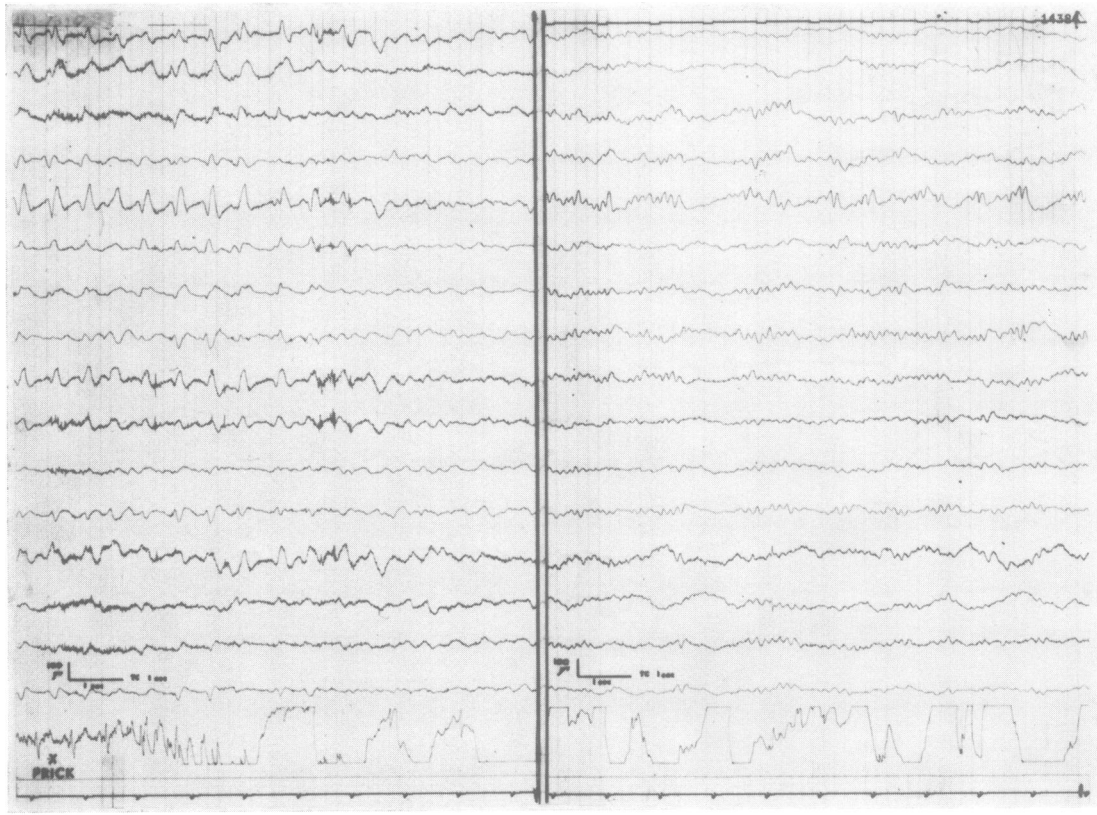
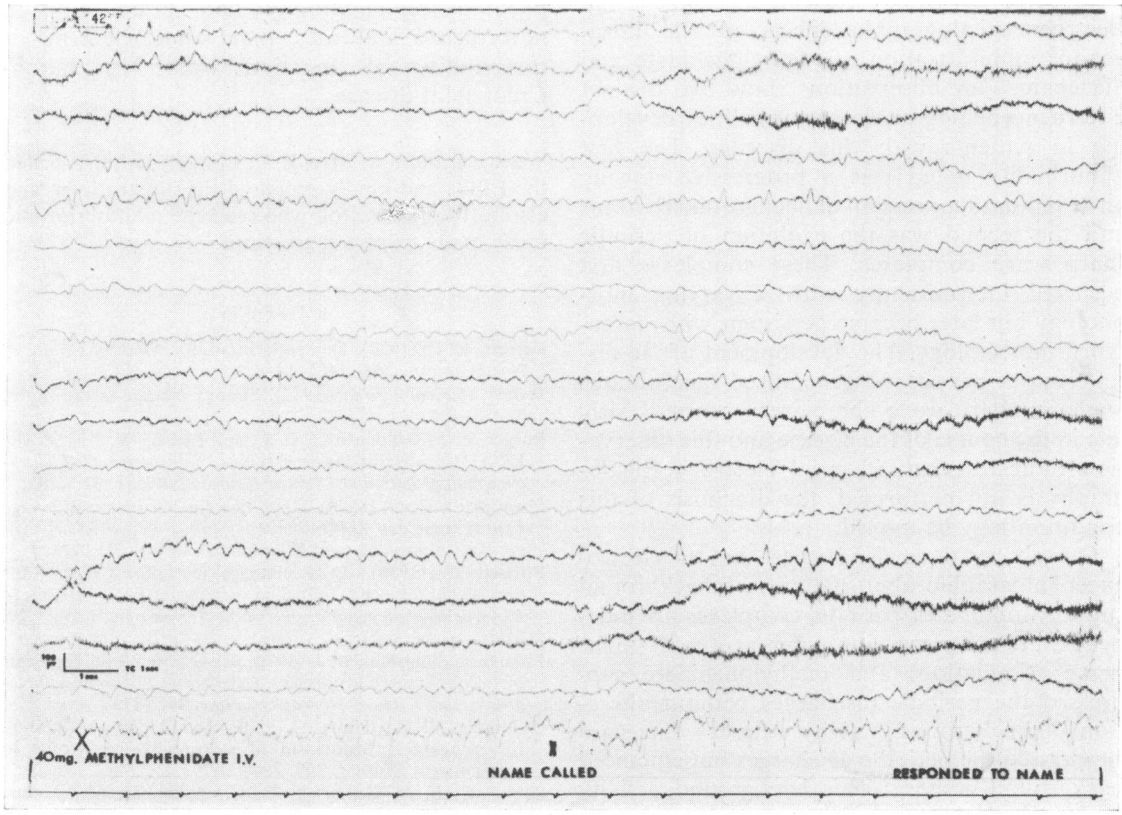


FIG. 4. *Montages as in Fig. 1. Case D.K. Electrocardiographic (lead 1) monitor on channel 17.* (a) *EEG shows partial suppression of periodic complexes following mechanical stimulation of the left ulnar nerve with a needle.* (b) *EEG shows suppression of periodic complexes and enhancement of background rhythms after intravenous injection of diazepam (10 mg). The changes lasted for several minutes (compare Fig. 3b). (Calibrations 100 Vμ; 1 s.)*

tube, called out repeatedly 'No, no, no' and responded to simple commands. Within 20 minutes of the injection he settled back into his previously unresponsive state and the EEG resumed its periodic activity, at first in a modulating fashion similar to that noted with the earlier recordings. At this time, diazepam (10 mg) was administered intravenously, which caused no alteration in the patient's quiescent clinical state but which suppressed the periodic EEG activity and, in addition, showed an enhancement of the EEG background rhythms to such a degree that abundant medium amplitude alpha activity, which had been virtually absent at the onset of the recording, appeared over the posterior head regions (Fig. 4b). This alteration of the EEG towards an almost normal state persisted for a further 10 minutes of recording and the procedure was then terminated. The patient died on 4 February 1973.

Brain biopsy was performed and reported (Professor B. E. Tomlinson) as follows: Histological examination shows a cortical and, to a lesser extent, white matter abnormality. In the cortex there is almost certainly a considerable loss of neurones affecting particularly the deep layers. This is not accompanied by gross evidence of spongiosis but occasional neurones in the more superficial cortex are associated with a clear-cut small vacuole adjacent to the perikaryon which does not appear to be artefact. The most prominent change, however, is an increase of astrocytes and also probably of oligodendrocytes in the deep white matter, the latter forming numerous clusters in places, often in the vicinity of



(a) (b)

FIG. 5. *Montages as in Fig. 1. Case D.K. Electrocardiographic (lead 1) monitor on channel 17. EEG shows suppression of periodic complexes (compare Fig. 3b) after intravenous administration of methylphenidate (40 mg). At this time the patient responded verbally to his name and also responded appropriately to simple commands. (Calibrations 100 μV; 1 s.)*

neurones and creating the appearance of neuronophagia. This latter phenomenon is very difficult to assess because of its variability in different parts of the cerebral cortex with increasing age, but it does appear to be considerably in excess of normal in this case. Astrocytic increase is probably also present in the white matter, but no gross gliosis, no demyelination and no vascular lesions.

The appearances are consistent with Jakob-Creutzfeldt disease.

Postmortem examination was performed and the histological features were in agreement with those found in the brain biopsy.

DISCUSSION

We have studied three cases of Jakob-Creutzfeldt disease with serial electroencephalography and have observed, in one patient, the clinical and electroencephalographic effects of the intravenous administration of methylphenidate and diazepam. Our observations show two distinct electroencephalographic abnormalities developing in patients with this disorder. The first abnormality noted was a progressive slowing and eventual suppression of background rhythms and the second was the evolution of periodic sharp wave complexes. These complexes first occurred intermittently with a varying morphology but later became persistent with stereotyped morphology. The development of the distinctive one per second generalized synchronous triphasic sharp wave complexes occurred fairly late in the course of the disease and this observation indicates that, if serial electroencephalography is not performed, the diagnosis of this condition may be missed.

Our observations also suggest that the electroencephalographic abnormalities of background suppression and of periodic complexes are independent phenomena, since afferent stimuli (ulnar nerve stimulation) and methylphenidate suppressed the periodic discharges without alteration of background activity whereas diazepam suppressed the periodic discharges but enhanced background activity. This background activity might simply be slow 'fast activity' due to the diazepam since it was seen in channel 5 as clearly as in many of the posterior derivations and it was appreciably asymmetrical. Similar changes may be seen in the EEGs of severely brain damaged children sedated with trimeprazine. Methylphenidate was also observed to create a transient alerting phenomenon in the clinical response of one patient. Thus, this patient, who was mute and immobile for several weeks, was able to speak and show appropriate motor responses to simple commands after intravenous injection of methylphenidate.

We do not propose to speculate upon the involvement of neuronal pathways in Jakob-Creutzfeldt diseases which results in the development of electroencephalographic abnormalities, nor can we explain how such abnormalities can be modified by afferent stimulation or by various drugs. The alteration of clinical and electroencephalographic activity, albeit transient, which occurs in the presence of cerebral atrophy and neuronal degeneration (as demonstrated by pneumoencephalography and brain biopsy), nevertheless indicates that some element of reversibility of function exists in Jakob-Creutzfeldt disease.

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