Non-fatal subacute sclerosing leucoencephalitis

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Subacute sclerosing leucoencephalitis (S.S.L.E.), by which is meant not only the type of disease described by van Bogaert (1945) but also the inclusion body type earlier described by Dawson (1933), usually runs a progressive and ultimately fatal course of a few months. Osetowska's (1961) 50 cases from van Bogaert's laboratory included 48 with durations of 1-5-18 months and a mean duration of 6.5 months. However, there were also two patients in this series who survived for four and five years respectively, and a number of such cases are reported in the literature, sometimes with long periods of apparent arrest of the disease followed by further progression to a fatal end.

The cases which we intend to describe are certainly very rare, in that after a long period of slowly progressive illness each patient recovered his former capacities to some degree; it is this fact of recovery which encourages us to think that we are not concerned with remissions which will ultimately be followed by relapse and death. On the other hand, the necessary lack of full pathological confirmation of the diagnosis in these cases contrasts with most previous reports; indeed, such a paper as that of Osetowska, from the viewpoint of a pathologist, could not have been written had the outcome in each case not been fatal. Nevertheless, we think that the evidence in our cases is sufficiently strong to make the diagnosis almost certain. Brief reports on both patients have already been made (Cobb, 1966).

CASE REPORTS

CASE 1 (No. 72532). D.F., a 21-year-old chemistry student, was admitted to the National Hospital under the care of Dr. Macdonald Critchley in August 1957, with a five-month history of episodes of altered consciousness. Initially the attacks consisted in momentary blank spells, which were sufficient to interrupt conversation or produce slight hesitancy of gait. Subsequently, however, he began to fall in the attacks and, during the weeks before his admission, the patient sustained numerous minor lacerations of the face and limbs. The seizures occurred up to 20 times each day and their frequency was unaffected by treatment with Epanutin and phenobarbitone. Between attacks the patient felt quite well but had noticed some recent difficulty with concentration, which he attributed to the anti-convulsant therapy.

On admission he was found to be mentally slow but showed no definite evidence of intellectual deterioration. Apart from brisk deep limb reflexes neurological examination was entirely normal. The results of examination of the cerebrospinal fluid on 29 August 1957 were as follows: pressure 160 mm; 4 lymphocytes/cmm; protein, 40 mg/100 ml.; Pandy, weakly positive; Lange, no change. W.R., negative in the blood and cerebrospinal fluid. Radiographs of the skull and chest were normal. Serial E.E.G.s consistently showed a left occipito-temporal recurring monophasic or diphasic slow wave, for which reason left carotid arteriography and lumbar air encephalography were performed; both were normal.

During the patient's stay in hospital the attacks continued to occur two or three times a day; in one which was witnessed conversation ceased abruptly, the head turned to the right and the right arm abducted at the shoulder and flexed at the elbow. This was followed by jerking movements of the right forearm, which persisted for several seconds. After a period of post-ictal confusion the patient regained his senses but was unable to recall the conversation which immediately preceded the seizure. The cerebrospinal fluid was re-examined on 12 October 1957: pressure, 135 mm; 1 lymphocyte/cmm; protein, 50 mg/100 ml.; Lange colloidal gold curve, 5432100000.

He was treated with Epanutin, Mysoline, and Diamox and finally discharged in October 1957 with a provisional diagnosis of 'intractable epilepsy'.

The patient was re-admitted in April 1958 because of intellectual deterioration. The seizures had ceased in February of that year but since then he had noticed gradual impairment of both memory and concentration and in recent weeks had found difficulty with reading, writing, and performing simple calculations. In addition, he had noticed difficulty with typing and playing the piano.

Examination at this time revealed evidence of a severe global dementia with loss of recent memory and temporal disorientation. His verbal and performance I.Q.s were 79 and <35 respectively on the Wechsler adult scale. He was agraphic and acalculic and showed evidence of a profound constructional dyspraxia with visuo-spatial disorientation. When reading aloud he frequently omitted words and phrases and was quite unable to explain the meaning of the text. His mood was often inappropriate and he showed lack of affective display when failing with simple tasks. Neurological examination and general
examination revealed no significant abnormalities. Investigations: cerebrospinal fluid pressure 130 mm; 1 lymphocyte/cmm; protein, 35 mg/100 ml.; Lange curve, 2211000000. The E.E.G. now showed bilateral recurring monophasic or diphasic slow waves, the left side always leading the right by 100 msec or more. Between the complexes the background record was within normal limits.

In view of the marked deterioration in his condition ventriculography and a right frontal cortical biopsy were performed in June 1958. The ventriculogram showed no abnormality of the ventricular system. Professor W. Blackwood reported the biopsy as follows: 'Subacute encephalitis, affecting both grey and white matter. It is either van Bogaert's subacute sclerosing leucoencephalitis or Dawson's inclusion body encephalitis. It is not possible at present, in frozen sections, to be certain whether inclusion bodies are present.' In subsequent paraffin sections no inclusion bodies were seen. The patient was finally discharged in June 1958 to continue Epanutin and Mysoline and, in addition, prednisone 2.5 mg three times a day.

Since 1958 the patient's condition has slowly improved. He began working in 1959 but has been dismissed from several jobs because of mental slowness and difficulty with reading and writing. The prednisone was gradually reduced, and finally discontinued in August 1965. When seen in February 1966 he was working as a gardener with the local council and had recently married. There were no abnormal neurological signs at this time and detailed intellectual testing revealed the following: he was orientated in both time and space and was able to give a reasonable account of recent national and international events. His verbal and performance I.Q.s (W.A.I.S.) were 82 and 40 respectively. When reading aloud, however, he continued to make frequent errors, often missing out a word or phrase and substituting one of his own choosing. He was able to understand the meaning of what he had read and his writing had improved, although he was still mildly dysgraphic. He was able to do simple calculations but showed a profound constructional apraxia, with visuo-spatial disorientation. In addition, there was now some degree of left-right disorientation and finger agnosia.

E.E.G. The first E.E.G. was in May 1957, at which time there was no significant general disturbance (Fig. 1) but low voltage slow waves recurred at intervals of about 8 sec. They were bilateral, though usually more evident on the left side. Nine weeks later these episodes were recurring at about 6-sec intervals and were then clearly left sided, though of very small amplitude (Fig. 1). During this second record two attacks occurred, with jerking of the arms and staring, lasting for about 30 sec; the E.E.G. showed mainly frontal slow activity, at first bilateral but left frontal in the post-ictal period, in contrast with the repetitive slow wave which was maximal in the left posterior temporal region.

In the third record, after admission to hospital, a left posterior temporal biphasic slow wave, recurring at 3-4 sec intervals, was well established, the background E.E.G. being virtually normal (Fig. 1). It was this focal repetitive slow wave which made us think that we might be dealing with a local lesion of the kind described by Lecasble and Dondey (1957), and independently by Dickson (1958) in this laboratory, and for this reason left carotid arteriography was performed, with negative results.

By the end of the patient's stay in hospital, the slow wave (hardly to be called a complex, the term appropriate in most cases of S.S.L.E.) had again become definitely bilateral and remained so in the next six records, up to June 1958 (Fig. 2). There were, however, always differences between the two sides, notably a delay of about 120 msec between the slow wave on the left and that on the right (Fig. 3). The form of the complex was little changed in light sleep. The mean interval between 'complexes' settled at less than 4 sec and on one occasion was as short as 2-6 sec (Fig. 3), the shortest in our experience of more than 25 cases and in the literature.

No repetitive jerks were ever seen in this patient and the occurrence of an episodic slow wave did not seem to interfere with continuous tests such as counting aloud. However, in the last recording before his discharge in June 1958 it was noted that eye movements observed through the closed lids corresponded in time with the slow waves; this was not the case with the eyes open, presumably because fixation overcame the effect.

An E.E.G. recorded in July 1959 showed no regular repetitive phenomena. In the right frontal region there was a small fast rhythm, some theta activity and occasional slow waves, enhanced by over-breathing (Fig. 4). It is possibly relevant that the biopsy was taken from this area. Records in 1963 and 1965 still showed episodic slow wave changes, with some right frontal emphasis, and without any constancy of form or interval.

Case 2 (No. A.10717). D.T., a man aged 18, was first admitted to the National Hospital under the care of Professor R. Gilliatt in March 1963. His father was unknown and his mother died from hypertension in 1958; one half brother, aged 36, was alive and well. Little is known of his past history except that he attended Moorfields Eye Hospital in 1958 because of impaired vision in the left eye. Examination at that time revealed degenerative changes at both maculae. Since leaving school at the age of 14 he had held several jobs and, at the time of his first admission to hospital, he was employed as a lift attendant in a tobacco factory.

For about a year before admission the patient's colleagues at work had noticed a gradual deterioration in his behaviour. He had become mentally slow and forgetful and was frequently rude towards his friends and workmates. His conversation was often confused and disjointed and, in addition, he was noted to have frequent blank spells which occurred several times a day and in which he appeared to be inaccessible. According to the patient, who was a poor witness, his illness started in June 1962 when he began to have infrequent attacks, lasting a few seconds, in which he would feel strange—'as if the world is not there'—and his limbs would become momentarily arrested during movement—'my foot stopped and then started again.' During the attacks, which had occurred five or six times in all, he was unable to recognize friends but he denied losing consciousness. He also complained of being unduly forgetful and for
Non-fatal subacute sclerosing leucoencephalitis

FIG. 1. D.F. E.E.G.s from May, July, and August 1957, all with virtually normal background activity. The small complex is at first bilateral, but later confined to the left occipito-temporal region. The interval is initially about 8 sec but shortens to less than 4 sec, near which it remained throughout the illness.

several months he had found difficulty in recalling the date. On examination, he was mentally slow, with marked impairment of recent memory and poverty of emotional expression. His verbal I.Q. was 84 and his performance I.Q. was 46 (W.A.I.S.). In addition, he had certain specific defects which included a mild nominal dysphasia and dysgraphia, with acacluia, constructional apraxia, perceptual difficulties and a profound loss of topographic memory. His visual acuity was 6/36 on the right and 6/60 on the left, with bilateral central scotomata and pigmented degeneration of both maculae. There was a fine tremor of the outstretched hands and occasional jerking movements were seen which involved the face and arms and were usually associated with voluntary movements. Tone and power in the limbs were normal, the reflexes were symmetrical and both plantar responses were flexor. Sensory testing revealed no significant abnormality. The cerebrospinal fluid contained 5 lymphocytes/cmm and 65 mg/protein/100 ml; Pandy, weakly positive; Lange curve, 5544332100; W.R., negative. Radiographs of the skull and chest were normal.

The clinical picture, together with the E.E.G. abnorm-
FIG. 2. D.F. The complexes became bilateral though never symmetrical. In this record, about a year after the first, the steepest gradient is on the right side.

alities to be described and the paretic Lange curve, strongly suggested the diagnosis of subacute sclerosing leucoencephalitis. He was treated with Epanutin 1.5 gr twice a day and subsequently transferred to the care of Dr. R. Hunter at the Friern Hospital in April 1963.

The patient was readmitted to the National Hospital in July 1963, having had six generalized convulsions and several minor attacks in which he suddenly fell to the ground without convulsive movements, regaining his senses almost immediately. Examination at this time revealed evidence of further intellectual deterioration, with a verbal I.Q. of 79 and a performance I.Q. of 41 (W.A.I.S.). His behaviour was unpredictable and his mood inappropriate. His conversation was often confused and irrational and he had become obsessed with making phone calls to his friends and colleagues. In addition to the retinal changes, which were noted at his previous admission, the patient had now developed an irregular coarse action tremor of the upper limbs, particularly on the left side; the deep limb reflexes were exaggerated in the left arm and leg and his gait was a little unsteady. The plantar responses were flexor and sensory testing revealed no abnormality.

The patient continued to have frequent generalized convulsions associated with tongue biting and occasional incontinence of urine. In view of the deterioration in his condition a right frontal cortical biopsy was performed in August 1963. This was reported by Dr. W. Mair as follows: 'The white matter shows some increase of astrocytes. There is no demyelination. Occasional vessels in the cortex and the white matter are surrounded by round cells and scanty macrophages containing Scharlach R positive material.' The patient was treated with Epanutin and phenobarbitone and returned to Friern Hospital in September 1963.

His condition remained static for about a year, but since October 1964 there has been a gradual improvement in his mental state. When seen in November 1965 he
was orientated in time and place and able to give a reasonable account of current events. Formal intellectual testing revealed a verbal I.Q. of 98 and a performance I.Q. of 80. His writing had improved and he was able to perform simple calculations. There was considerable improvement in his memory and in his behaviour. His mood was somewhat euphoric and he still lacked insight into his previous behavioural disorder. On examination, the retinal appearances were unchanged and the fine tremor of the outstretched hands remained. The deep limb reflexes were now symmetrical but the left plantar response was extensor, the right one being probably flexor. The jaw jerk was also increased.

E.E.G. Fourteen records over the period from March 1963 to September 1964 showed only minor evidence of progressive change, though transient variations occurred from time to time. The alpha rhythm, at first at 8-9 c/sec, became a little slower in subsequent records. Generalized complexes occurred at regular intervals, initially about 10 sec but shorter in most later records, usually 5-6 sec. At first sight these complexes were more variable than is usual in S.S.L.E. but, in fact, they could be resolved into two components, one a series of low voltage slow waves lasting about 1 sec and the other a rhythm at 8 c/sec. Most of the variation was in the latter, the amplitude ranging from zero to 200 μV even from one complex to the next (Fig. 5); the number of detectable waves was also variable but never more than 8 or 9. In later records the frequency of this rhythm fell to 6 c/sec, distinguishing it absolutely from the alpha rhythm.

No periodic motor disturbance was ever demonstrated and, to inspection, there were no related changes in cardiac and respiratory rates. On one occasion it was shown, however, that the mean reaction time to 73 light stimuli presented during complexes was 0·37 sec, whereas to 100 stimuli between complexes it was 0·28 sec, indicating a recurrent transient delay at some point in the visuomotor pathway.

In one of the 14 waking records six months after the first, the fast component of the complexes was absent. However, on the several occasions when sleep was induced with Seconal, this component disappeared at the same time as the alpha rhythm. The slow components became more variable and prolonged and the intervals
between them tended to be shorter. The most striking change during sleep was the occurrence of sigma (sleep) spindles, not only at random but also regularly, associated with the latter half of each complex. K complexes could be evoked by clangs and occurred spontaneously; their distribution and form were normal. These two unusual features are discussed and illustrated (Figs. 6 and 7) by Cobb, 1966.

On one occasion the patient had an attack during recording, in which he opened his eyes and slowly flexed the arms and trunk. It lasted only 16 sec and after it he was confused and had no memory of the attack. During this episode there was no change in the E.E.G., including the regular recurrence of complexes, apart from blocking of the alpha rhythm, which was probably associated with eye opening.

The E.E.G. was recorded again on two occasions, in June 1965 and in November 1965. In both the alpha rhythm remained rather slow (7-8 c/s) and irregular and there was some low voltage theta activity, but this background was only mildly abnormal, as it had always been. In the first of the two records, though not in the second, there were short low-voltage episodes of 6 c/s waves superimposed on some slower components which, if not being the same as the earlier complexes, were reminiscent of them. However, they occurred only in association with stimuli or with activities such as eye opening or closing, and there were no regular complexes in this or the subsequent record.

Comment There were pathological changes in the cortical biopsy material indicative of a subacute inflammatory process, not such as to make a specific diagnosis possible though in no way reducing the probability that this was a case of S.S.L.E. That the disease can run this
Non-fatal subacute sclerosing leucoencephalitis

FIG. 5. D.T. Typical of the waking records in this man, the background is little disturbed and complexes recur at about 6-sec intervals. They are rather variable in form, the main variation being in the amplitude of the 8 c/s component, seen near its maximum in the first complex and absent from the next.

type of course is illustrated by the previous confirmed case. Strongly in favour of the diagnosis are the nature of the E.E.G. and the paretic type of Lange curve, which is almost invariably found at some stage of the disease, though not necessarily throughout it. In the E.E.G. the complexes were admittedly unusual in containing a relatively fast rhythmic component and in varying from one to the next, even though through a restricted range. However, we know of no other condition in which regular complexes could be found, so little changed in many records over the course of 18 months. It is of interest that an E.E.G. recorded as early as August 1962, in the department of Professor Sir Denis Hill at the Middlesex Hospital, showed very similar complexes but at such rare intervals that, with their variable form, their special association could hardly have been recognized.

A point which caused some diagnostic doubt at first was the presence of pigmented macular degeneration. The patient said that he had never been able to see straight ahead with the left eye and, in fact, he had been attending hospital since 1958 because of this. In the unlikely event of the two conditions being related there are nevertheless precedents for the association (Malamud, Haymaker, and Pinkerton, 1950; Otradovec, 1963; Cobb, 1966). We feel that, despite the lack of absolute pathological confirmation, the diagnosis is most probably correct.

DISCUSSION

Although it is exceptional in S.S.L.E. for the disease to last for more than a year or so, there are a number of cases in the literature with durations measured in years. Malamud et al. (1950) reported three examples of what they called the chronic variety of the disease, and one of their patients, a 10-year-old girl, survived for seven years after the onset of symptoms.
Necropsy confirmed the presence of numerous intranuclear inclusion bodies but in addition there were widespread neurofibrillary changes resembling those seen in Alzheimer's disease. Gutewa and Osetowska (1961) reviewed most of the reported cases of chronic S.S.E. up to that time and added one of their own patients, a 4-year-old boy in whom the clinical illness ran a rather fluctuating course with a total duration of five years. (In passing it may be mentioned that the cited case of Cobb and Hill (1950) ended in death after about three years and post-mortem examination confirmed the diagnosis.)

In several of the more prolonged cases the disease has apparently become stationary for long periods, only to start up again and lead finally to death (Eicke and Ziegler, 1950; Krucke, 1957; Osetowska and Torck, 1962). However, the possibility has to be considered that the pathological process may cease, leaving the patient with permanent gross disabilities. Since full pathological confirmation is necessarily lacking in such cases, they are less likely to be reported than others and may be more common than is apparent from the literature. Terzian (personal communication), for example, has two cases, clinically and electrically typical, alive after six and 10 years respectively of illness. We also have a patient (J.W., in Cobb, 1966) whose active illness probably lasted three years, but who then lived in an unchanged condition for at least another seven years; unchanged, that is, except for the normal processes of growth between the ages of 7 and 14 years, although he is totally demented, helpless, and incontinent.

Recovery from the disease has only rarely been reported in the past. Kurtzke (1956) described the case history of a 20-year-old army private who developed an acute febrile illness leading in three days to coma. The patient remained in this state for four months before making a gradual though incomplete recovery. Although the brain biopsy in this case showed intranuclear inclusions, several atypical features, including the acute onset and the marked pleocytosis in the cerebrospinal fluid, must cast doubt on the diagnosis. Simpson (1961) mentions briefly another case in which apparent recovery occurred and Pearce and Barwick (1964) reported a young schoolboy with E.E.G. changes and findings in the cerebrospinal fluid which were highly suggestive of the disease; examination nine months after the onset of symptoms, however, revealed no psychiatric or neurological abnormalities.

In our two cases described above, it would seem likely that the disease became arrested at a time when the cerebral damage was relatively slight. Their subacute illnesses, however, were far from being brief: D.F. appears to have deteriorated continuously for 15 months and D.T. for probably more than two years before improvement began. In both cases the disabilities, both during the illness and subsequently, were largely in the psychiatric sphere. D.F., as a university student, may be supposed to have had an I.Q. of 120 or better, which fell to 57 in April 1958. D.T.'s initial intelligence is unknown, though we suspect below average; his verbal and performance I.Q.s were 79 and 41 at their worst and rose to 98 and 80 respectively. Even such a retention of intellectual faculties as this is remarkable, the usual course being one of rapidly progressive dementia, going on to coma in a matter of weeks or months.

Equally unusual is the insignificance of the motor disturbance in both cases. In D.F. there was the single observation of recurrent eye movements and in D.T. there were minor reflex changes and tremor. At one time he was noticed to have occasional jerking movements of the face and arms but they never became regular or stereotyped.

It seems clear that these two patients had the disease in a mild form which not only allowed them to survive but also to recover their previous intellectual abilities to some degree. In seeking a reason for this unusual outcome the most obvious point of difference shown by these two is that they were older than the majority with this disease. The oldest reported have both been 23 years (Usunoff, Crigel, Bojinov, Georgiev, and Atzev, 1961; Cobb, 1966) and the average age of Osetowska's patients was 9-8 years. However, we have had five patients, apart from these two, aged 16-23 years, in whom the disease ran a fatal course indistinguishable from that in the younger patients, so that there is little cause for optimism when the disease affects older subjects.

SUMMARY

Two patients are described, aged 21 and 18 years, who had slowly progressive illnesses lasting at least 15 months and two years respectively, from which they gradually recovered to a considerable extent during the following years. In both cases there were epileptic attacks; they were also similar in the predominance of intellectual deficits and the triviality of motor disturbances; neither patient had regularly recurrent jerks.

In both cases the Lange curve showed a first zone rise which disappeared with recovery. The E.E.G.s, recorded on numerous occasions, were, with minor variations, characteristic of subacute sclerosing leucoencephalitis.

A frontal biopsy confirmed this diagnosis in the older patient but was equivocal in the younger.
It is unlikely that the age of these patients, about twice the average, contributed to their avoidance of the usual fatal outcome.

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Non-fatal subacute sclerosing leucoencephalitis.

W A Cobb and J A Morgan-Hughes

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