Prolonged complex partial status epilepticus: a case report

Sir: Complex partial status epilepticus (CPSE) has been receiving increasing attention in recent years. Around 50 cases have been reported to date. However, few of these have lasted for longer than 24 hours. More recently the main areas of interest have been on the varying clinical manifestations of CPSE, the accurate definition of when a patient can be considered to be in CPSE, and the increasing awareness that it may produce persistent intellectual impairment after the attack has terminated. The following case report describes an episode of CPSE which lasted for 7½ months, our attempts to terminate the attack, the unusual feature of reflex mydodones occurring during the episode, and the presence of mild cognitive impairment persisting after the attack had terminated. We were also able to demonstrate histological evidence of cortical damage in the right frontal region.

The patient was a 54 year old female who had had four previous episodes of CPSE, three in 1984 and one in 1985. These previous episodes had lasted for either 3 or 4 days and each one had consisted of a fugue-like state with varying levels of responsiveness; the first two had been mistakenly diagnosed at a nearby hospital as aphasie stroke. The onset of the first and third episodes had not been seen to be associated with any visual or motor activity, but at the onset of the second one her husband had noticed that her eyes were conjugately deviated to the right. At the onset of the fourth, her eyes were “rolled upward” and on arrival in the Accident and Emergency Department weakness of the right side of the body was found. The third and fourth attacks had been confirmed by EEG; all the attacks had terminated spontaneously. There had been no other seizures in between these and she had never shown any marked post-ictal deficit, except that after the third attack it had been several months before she had felt able to return to work as a telephonist. She was otherwise in good health and there was no relevant past history. There was no family history of epilepsy. She was married with two children and was of average intelligence. The only drug therapy was carbamazepine, 200 mg bd, started after her third attack. General physical examination was always normal.

In January 1986 she had a spontaneous tonic-clonic seizure. She was immediately taken to a nearby District General Hospital and after 7 days was transferred to Walton Hospital. Over this initial period she demonstrated a fluctuating level of consciousness ranging from periods of complete psychomotor unresponsiveness, usually with the eyes open, to a more common trance-like state in which she was uncommunicative and inattentive, but was able to stand, walk and wash if accompanied; she did not return to her normal level of functioning at any time. She also had frequent twitching of the arms and face and when in bed would sit up and fumble with the bedclothes or perform imaginary tasks, such as reaching out for a glass that was not there. She was apraxial and the examination was otherwise normal. A CT scan and routine laboratory studies were normal. The CSF contained no cells and a normal glucose level, although the protein was slightly raised (0.84 g/l). The initial EEG (fig) on day 7 revealed mainly diffuse bilateral rhythmic slow wave activity with occasional sharp waves and intermittent runs of 5–7 Hz theta activity. It was felt that she was in CPSE and she was given 10 mg intravenous diazepam whilst having her EEG. This simply caused her to sleep and the EEG activity subsided. However, on waking her clinical state was unchanged and the abnormal EEG activity had returned. The carbamazepine was increased to 400 mg tds. On day 12 the clinical picture and EEG were unchanged and a further 5 mg IV diazepam, and then 1 mg IV clonazepam, again failed to terminate the attack. On day 13, 160 ml 0.8% chloromethide solution did not improve her and she was next loaded with phenytoin and started on phenytoin, 300 mg daily in addition to her carbamazepine, 400 mg tds. On day 16 a single intramuscular injection of 10 ml paraldehyde was unhelpful, so clonazepam was started in addition to the carbamazepine and phenytoin. Over the next 9 days the clonazepam was increased to 2 mg tds, and then reduced again to nil; the phenytoin was increased to 400 mg daily. For a period of several days whilst on the highest dose of clonazepam, the patient was continually asleep, but frequent twitching of the left arm persisted throughout. On withdrawing the clonazepam her EEG and clinical state had not improved. The phenytoin was increased to 450 mg daily. On days 25 and 26 she had several episodes of grand mal status which tended to start on the left side; this was controlled with IV chloromethide which was continued for 5 days in all; the lowest recorded arterial PO2 during this period was 57 mm Hg. On day 28 limited neuropsychological testing demonstrated that she was able to count from 1–20, recite the alphabet and supply her name correctly. She had no short-term memory recall and was disoriented in time and place. Over the
next 10 days she remained mostly alert but inattentive and appeared to be having frequent hallucinations, for example, ducking because she thought a ball was going to hit her or staring around and talking to imaginary people or voices. On day 37 her muscular twitching was more marked and more characteristic of myoclonus; the phenytoin was increased further. The myoclonus rapidly worsened and on day 39 there was very marked myoclonus which now had a prominent reflex component to it, in response to any sudden auditory or kinaesthetic stimulus. At this point sodium valproate was started in addition to the carbamazepine, 400 mg tds, and phenytoin, 550 mg daily. The dose of valproate was increased to 500 mg tds over the next 7 days and the myoclonus subsided. By day 63 she was persistently less responsive and showed signs of severe global cognitive impairment. On day 85 she had another grand mal seizure, following which she had moderate generalised myoclonus for a few days. On day 93 it was considered that her marked cognitive impairment may be partly due to the high dosage of anticonvulsants, although her serum levels were never in the toxic range. The carbamazepine was reduced to 400 mg bd. Three days later she had another grand mal fit and 2 days later, on day 102, she had a further grand mal fit. On day 110 high dose oral prednisolone was commenced and continued for 4 weeks before being withdrawn. This had no beneficial effect and again she was showing marked myoclonus. By now she had been bedbound for several weeks and was requiring naso-gastric feeding. We were becoming increasingly concerned about the underlying cause for her prolonged unresponsive state and the quality of life that she would have, even if the CPSE could be terminated. On day 159 a right frontal brain biopsy was performed. The histological examination showed a degree of cortical neuronal degeneration and some gliosis of the white matter. There was marked extracellular oedema and an increase in Virchow-Robin spaces but no true spongiiform encephalopathy. There was no neurofibrillary degeneration or senile plaques. The leptomeninges were slightly thickened and the small arteries showed minor atherosclerotic change. After the brain biopsy she seemed to have improved a little, she was no longer needing nasogastric feeding and was responding better to commands than at any time since the onset of the illness. However, this improvement was shortlived.

On day 181 it was decided to induce a barbiturate sleep with pentobarbitone, which was increased over a 2-week period to a maximum dose of 400 mg tds. Whilst on the highest dose she was continually asleep. After 3 weeks (day 202) the dose of pentobarbitone was gradually reduced and on day 227 it was noted that she was definitely more responsive again. At this time she was taking valproate, 500 mg five times a day, carbamazepine, 400 mg tds, and pentobarbitone, 200 mg bd.

She now began to improve gradually and after 2 weeks was alert and fully orientated; her understanding and production of speech were slowed but otherwise normal; she was able to perform simple calculations; her memory was still poor but had improved compared with earlier testing. She was also able to give a rational account of why she was in hospital. At 7 weeks she was fully mobile around the ward, socialising with the other patients and mildly disinhibited. There was no myoclonus. Psychometry showed WAIS verbal IQ 98, performance IQ 89 and WMS memory quotient 93. The 11-point discrepancy between her verbal and performance IQ was caused by specific difficulties in visuo-spatial abilities; she also performed very poorly on tests of visual memory. At 10 and 24 weeks respectively testing showed WAIS verbal IQ 98, then 99, and performance IQ 92 then 93. The only event that she remembered during her illness was having her head shaved for the burr-hole biopsy. Her pre-morbid IQ was estimated to be about that of her present level of functioning. The only specific areas of mild deficit remaining were of verbal fluency, visual memory and constructional skills. Her only subjective complaints at present (30 weeks) are of a degree of slowness in her thoughts. Her family notice her to be clumsy and slow with some tasks, such as cooking, and she is still mildly disinhibited. However, despite this, she is managing to function adequately in all aspects of daily life.

Other investigations performed whilst she was in CPSE were: two contrast enhanced CT scans were normal; CSF protein: episode No. 2—0.94 g/l, episode No. 3—0.77 g/l; episode No. 4—0.93 g/l, day 17—0.84 g/l, day 41—1.64 g/l, day 62—0.94 g/l. On days 51–58 there was an electrolyte abnormality consistent with inappropriate ADH production; this corrected with fluid restriction and did not recur. From day 27–41 there was a mild hypocaemia (minimum 2.02 mmol/l corrected for albumin) for which no cause was found. This corrected with calcium and Vitamin D. The alkaline phosphatase and phosphate remained normal.

The following serum results were normal: ESR, liver function tests, thyroid function tests, autoantibodies, magnesium, aluminium, zinc. The following infections were excluded: Epstein Barr virus, measles, HSV, CMV, mumps, V and S, mycoplasma, TB, treponema, fungi.

Prior to 1987 the longest reported case of CPSE was 4 weeks and there had been only 81–88 or possibly 11 cases reported which had lasted for over 24 hours. In 1985 Mikati et al. described a previously unrecognised possible form of CPSE in an 11-year old boy with a florid encephalopathic illness lasting for 3 months associated with paroxysmal EEG seizure activity in the temporal and frontal regions. In the same report Lee also mentioned a similar illness which he had seen in a 3½ year old boy. The episode in our patient was, in the earlier stages, more similar to those of the earlier reported cases that did not manifest solely as aphasia. However, since the episode was of longer duration the clinical picture subsequently changed.

It has been suggested by Ballenger and colleagues that recurrent CPSE (episodes of prolonged confusion or aphasia associated with recurrent electroencephalographic seizures with or without clearly defined recurrent clinical seizures) tends to persist longer than continuous CPSE (episodes of prolonged confusion associated with continuous focal epileptiform activity). However, the episode in our patient does not support this suggestion, since there was only one short period when the activity may have ceased and other than this there was nothing to suggest that the illness was due to recurrent episodes.

Treiman and Delgado-Escueta suggested that there is no fundamental difference between recurrent and continuous CPSE, and that they probably constitute two ends of a continuum. They stated that CPSE may start with a continuous twilight state during which there may be partial and amnestic responsiveness, partial speech and quasi-purposeful complex automatisms. This is often interrupted by staring, total unresponsiveness, speech arrest and stereotyped automatisms with the patient eventually failing to completely recover from the longer state of partial and amnestic responsiveness before the next cycle of staring and stereotyped automatisms begins. The frequency of these cycles may increase until the patient appears to be in a continuous epileptic fugue state. In our patient we were unable to witness the first 7 days of her illness but after this her responsiveness definitely fluctuated from hour to hour and
she exhibited various automatism. However, as her illness progressed this variability became less obvious and any possible cyclicity still present was on a day to day level rather than hour to hour.

The EEG recordings have always shown bilateral slow wave activity with multi-focal sharp waves and spikes but no apparent rhythmic patterns or paroxysms. This picture is consistent with CPSE of longer duration. In the earlier stages and at seizure onset the picture is usually one of recurring cycles of activity similar to that seen in isolated complex partial seizures.

It has recently been demonstrated that CPSE can originate in the frontal lobes and, in fact, many previous reports of CPSE lend support to this when reviewed retrospectively.1,2 We were unable to record the onset of any of our patient's five episodes of status. However, on reviewing the clinical features of the seizure onsets, it is possible that the 2nd, 4th and 5th episodes may have had a frontal origin.

There is increasing experimental evidence that repeated electrical discharges may produce neuronal damage, even in the absence of motor convulsive activity.1,3,4 In our patient a biopsy of the frontal region after 5 months of CPSE merely showed non-specific changes. There had been a 48 hour period of recurrent episodes of grand mal status earlier in the illness. The changes were not necessarily directly due to the CPSE.

Of the approximately 60 cases of CPSE documented in the literature so far, five have had impairment of higher mental functioning persisting after the attack.5,8,9,15 Three of these6,15 had as their main feature a marked impairment of memory function. One was the atypical case of CPSE mentioned earlier.9 The area of deficit in this case was not specified. One was a 60 year old diabetic male with "aphasic status epilepticus", in whom the authors believed there had probably been a small cerebral infarct during the ictal activity.6 In our patient neuro-psychological testing demonstrated that memory was severely impaired in the first few weeks after the episode had terminated, but that memory function is now probably approaching the pre-morbid level. There are still mild deficits in verbal fluency, visual memory and constructional skills, and the patient remains mildly disinhibited, possibly reflecting the frontal lobe damage.

The increasing reports of persisting post-ictal impairment has further consequences. The importance of accurate case definition is paramount and in their recent review Treiman and Delgado-Escueta14 suggested that a patient can be considered to be in CPSE if there are repeated complex partial seizures without full recovery between seizures to a completely normal state with no signs of residual deficit. This statement, therefore, must be revised since full recovery between attacks can no longer be a requisite to stating that the attack has terminated.

Myoclonus was a prominent feature of the illness in our patient and reflex myoclonus also occurred in the latter stages. Action myoclonus may occur after cerebral anoxia, but we feel that this was unlikely to be the cause in our patient since the myoclonus eventually subsided. Movement disorders may also occur with anticonvulsant usage; however, our anticonvulsant levels were never in the toxic range, although we were not able to measure free levels. It is not possible to be sure whether the myoclonus was due to the anticonvulsants or the CPSE. However, we favour the latter explanation.

There is no rigid strategy of drug therapy for terminating CPSE except that diazepam is the drug which most often successfully ends attacks. The recommended treatment at present is intravenous diazepam and loading with phenytoin. On review of other cases of CPSE there does not appear to be any other drug which is regularly successful in terminating episodes of CPSE. It seems that our patient's attack terminated when barbiturates were introduced.

In conclusion, our case serves to reinforce further the point that CPSE should be treated vigorously at the earliest possible opportunity, since it may convert to major motor status and even in the absence of this CPSE on its own may produce persisting changes in higher mental functions after the attack has terminated. The illness in our patient was very prolonged and latterly we felt that we must have been dealing with an irreversible and progressive process. On many occasions we felt that any further therapeutic manipulations would be futile. However, this was not so and the patient is now almost completely recovered.

References


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Akinetic mutism in Wernicke-Korsakoff disease: a case report

Sir: Akinetic mutism, first described by Cairns et al., may be seen in three types of
Prolonged complex partial status epilepticus: a case report.

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