

Creutzfeldt-Jakob disease treated with amantidine

A report of two cases

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SUMMARY The treatment of two cases of Creutzfeldt-Jakob disease with amantidine is described. The first case made a remarkable initial improvement which was sustained for two months, but then deteriorated and died. Histological examination of the brain showed changes consistent with early Creutzfeldt-Jakob disease. The second case which was clinically one of Creutzfeldt-Jakob disease has now been followed for 30 months since the start of treatment and appears to be cured. It is considered that amantidine has a definite effect in this disease and it is suggested that its mode of action, though unknown, is more likely to be metabolic than antiviral.

This paper presents two cases of Creutzfeldt-Jakob disease which have responded to treatment with amantidine in this hospital since September 1970.

CASE 1

Mr. R.D., aged 69 years, was admitted to a general hospital on 5 July 1971 with a three week history of increasing confusion, loss of memory, and unsteadiness of gait. On examination, he was mildly demented, his speech was slurred, there was inco-ordination of both hands, the tendon reflexes in the legs were increased, the plantar responses were flexor, and there was muscular fasciculation in both calves. Routine investigations, including examination of the cerebrospinal fluid (CSF) and brain scan were normal. An electroencephalogram (EEG) showed diffuse slow wave activity in all areas. His mental and physical condition rapidly deteriorated and he was transferred to this hospital on 26 July 1971. On admission, he was cachectic, lying in an attitude of flexion, doubly incontinent, and stuporose. He could be roused to take fluids, and when roused appeared to understand simple commands, but was mute and emotionally labile. There was extrapyramidal rigidity of all four limbs and the limb reflexes were increased but equal on the two sides. The plantar responses were flexor. There was fasciculation in the muscles of the calves and upper arms. Treatment was started the same day with amantidine 200 mg daily. By 28 July the rigidity of the limbs was less, but the right plantar response was extensor. By 30 July he was

eating and drinking and talking rationally, though his speech was very rapid and indistinct. On 2 August the dose of amantidine was increased to 300 mg daily. At this time he was walking with assistance, and the right plantar response was now flexor. He continued to improve mentally and physically, the muscular rigidity disappeared but fasciculation remained intermittently. On 25 August he began to deteriorate. He became alternately drowsy and restless and the right plantar response again became extensor.

On 3 September he began to improve again and by 22 September he was walking unaided and was continent. His speech was still rapid and difficult to follow but his conversation was rational. At this stage there was no muscular rigidity, the limb reflexes were still brisk and equal on the two sides, the plantar responses were both flexor and there remained some fasciculation in the calves.

On 24 September a boil on the buttock appeared which developed into a carbuncle. His condition again deteriorated, and on 22 October the dose of amantidine was increased to 400 mg daily. By 25 October he was drowsy, unable to walk, extrapyramidal rigidity had returned to his arms but not his legs, the tendon reflexes were no longer brisk, but present and equal, and the plantar responses were flexor. Fasciculation remained in the calves and his speech was more slurred and indistinct. On 26 October the dose of amantidine was increased to 800 mg daily. On 30 October, amantidine syrup in a dose of 400 mg daily was substituted for the capsules, and on 3 November the dose was increased to

600 mg daily. On 4 November he developed an olecranon bursitis which was treated with erythromycin and which subsided within a few days. By 5 November he appeared more alert, and though his speech was rapid and indistinct, he was rational. Fasciculation was still present in the calves and again in the upper arms. On 10 November he appeared to be hallucinated visually, and as it was thought that this might be due to amantidine, the dose was reduced to 400 mg daily. By 12 November his condition had deteriorated. He was no longer hallucinated, but he was more drowsy and had developed myoclonic movements of the arms. The dose of amantidine was increased to 800 mg daily, but his condition continued to deteriorate, he became stuporose and died on 16 November. Necropsy showed the immediate cause of death to be bronchopneumonia.

The report on the brain was as follows:

MACROSCOPIC APPEARANCE The brain weighed 1260 g. The dura mater was firmly adherent to the skull. Other membranes appeared normal. The gyri were well separated and were very small in both frontal and occipital lobes. There was no other obvious external abnormality. The vessels of the circle of Willis were patent and free from atheroma.

HISTOLOGY *Cerebral cortex* There was mild to moderate cortical atrophy that was patchy and most obvious in the posterior frontal, insular, and occipital regions. In the affected areas there was degeneration and loss of neurones and blurring of the normal laminar pattern. These changes were associated with a commensurate degree of astrocytic proliferation, though there was no gemistocytic transformation. The degenerate neurones showed mainly shrinkage and increased density of staining, granular disintegration, and/or excessive accumulation of lipofuscin. Chromatolytic features were seldom seen. In a few areas there was a suggestion of commencing status spongiosus. There was thinning of the subcortical white matter beneath the cortical areas that showed the most evidence of atrophy. Blood vessels were normal.

Corpus striatum and diencephalon There was patchy and mild neuronal atrophy, mainly in the caudate, paraventricular, and amygdaloid nuclei; the changes included satellitosis, vacuolation, and shrinkage. There was siderosis of vessels and pronounced formation of corpora amylacea in places.

Cerebellum and dentate nuclei These were unremarkable.

Brain-stem Gracile/cuneate complex showed well-marked neuronal loss and status spongiosus. Groups of medullary neurones were degenerated. The pons was not significantly involved. Glial reaction was minimal. The midbrain showed atrophic changes in the tectal plate nuclei, oculomotor nuclei, and substantia nigra, the neurones of which also contained hyaline Lewy-type inclusions.

Spinal cord There was mild loss of myelin in the posterolateral and dorsal columns and no other abnormality.

Muscle. There was no evidence of motor unit atrophy.

CASE 2

Mrs. L.B., aged 55 years, was well until January 1969 when she noted listlessness, poor concentration, and depression. In June 1969 she began to make mistakes at work, such as mixing up the figures on a job on which she had worked for 15 years. In July she developed diplopia which lasted for three weeks. In December she became ataxic and had frequent falls from which she was not able to rise. There was no loss of consciousness. In January 1970 she felt ill, complained of numbness in the back and legs and of severe headaches. She became strange in her behaviour, would not eat for days at a time, her speech became incoherent, and she was occasionally incontinent of urine. She was admitted to a general hospital in January 1970. On examination, she was ataxic. There was obvious intellectual impairment, tone was increased in the right leg with increased tendon reflexes and sustained ankle clonus, and an extensor plantar response on the left. Routine laboratory investigations, including the CSF, were normal. Bilateral carotid angiograms were also normal. In February she was transferred to another hospital where routine investigations, including brain scan, were again normal. On 9 March 1970 her EEG was very abnormal and rather difficult to interpret. The alpha rhythm was present, but intermixed with varying amounts of theta waves which sometimes appeared in runs and tended to show a predilection for the left side. More frontally delta waves appeared at first intermittently, but later in a more persistent fashion, maximal over the midline. The appearances were interpreted as consistent with a frontal tumour. Other possibilities included metastases or some form of diffuse cerebral disturbance of metabolic origin. On 26 March 1970, the EEG showed a marked improvement. There was a formed alpha rhythm which was rather irregular due to variation in amplitude and the admixture of con-

siderable fast activity. Only occasional random theta waves were apparent.

In April, she was transferred to another hospital for psychiatric assessment. At this time a neurologist described tremor of the tongue, so marked that he termed it lingual myoclonus, tremor of both arms, increased tone and reflexes in both legs with bilateral ankle clonus, and an extensor plantar response on the left. She was mentally agitated, emotionally labile, poorly oriented, and of poor memory. Her mental state varied from day to day and she had periods of greater confusion and disorientation in which she continued to fall, without loss of consciousness or convulsions.

Psychological testing carried out on 11 April 1970 showed signs of organic pathology limited to the functions of the anterior portion of the brain, implicating the frontal lobes.

In May, she was transferred back to the original hospital. Her condition appeared to fluctuate but on the whole was deteriorating. By July she was wholly incontinent of urine and, by August, doubly incontinent. On 15 September 1970 she was transferred to this hospital. On 18 September one of us (W.L.S.) saw her for the first time and started treatment with amantidine 100 mg daily. At this time, she was severely demented, emotionally labile, and doubly incontinent. She spoke little and her speech was rapid and indistinct, she was unable to stand, walk, dress, or feed herself. On examination there was extrapyramidal rigidity in the legs with increased reflexes and clonus in the left ankle, but the left plantar response was flexor. By 22 September she was more alert mentally and was speaking more. On 25 September the dose of amantidine was increased to 200 mg daily. By 28 September her speech was clearer, her incontinence was less, she answered questions rationally, and she was beginning to walk. By 14 October she was well oriented and able to carry on a rational conversation. By 16 October she was able to walk with assistance. By 30 October she had only occasional urinary incontinence and was walking with a frame. By 11 November she was walking unaided, her incontinence had gone, there were no abnormal physical signs, and her mental state was normal. Psychological testing carried out over a four week period in October–November indicated left hemisphere involvement and suggested a frontal and parietal lobe focus. The testing showed progressive improvement over the period. She was transferred back to the original hospital on 16 November and discharged home on 11 December 1970.

Since discharge from hospital she has been followed as an outpatient. Psychological testing on 16 August 1971 showed no detectable organic path-

ology. An EEG in January 1972 was normal. The dose of amantidine was reduced to 100 mg daily in February 1972 and in April it was stopped. She was last seen in January 1973. She had remained well, was leading a normal life, and was not incontinent. There were no abnormal physical signs and she was normal mentally.

DISCUSSION

Braham (1971) has described one case of Creutzfeldt-Jakob disease in which there was improvement after treatment with amantidine. The degree of improvement remained at the level described for some nine months until the patient died of sepsis. There was no necropsy (Braham, 1972). In both cases of the present report there was a remarkable degree of improvement after starting treatment with amantidine. The first case relapsed twice while under treatment. It is thought that the first period of relapse may have been due to inadequate ingestion of amantidine as he was reluctant to swallow the capsules, and that this responded to stricter nursing supervision. The second relapse from which he never recovered may have been precipitated by the intercurrent infection of the carbuncle or may have been failure to respond further to amantidine in the natural course of the disease. The second case made an uninterrupted recovery from the start of the treatment, and from the length of time (30 months) which has passed without relapse from the start of treatment, it seems permissible to speak in terms of cure.

Clinically the first case conforms to the description of the subacute spongiform encephalopathy variant of Creutzfeldt-Jakob disease (Nevin, 1967). Histologically the cerebral lesions are mainly non-specific but could well represent an early stage of the same process; it is relevant in this respect that the history is relatively short (about four months). The Lewy bodies that were present in the substantia nigra are a well-recognized feature of idiopathic Parkinsonism. In the second case, there is no proof of the diagnosis but, clinically, this case is characteristic of the classical type of the disease. In neither case was the EEG characteristic but May (1968) reviewing 68 cases from the literature concluded that the EEG may vary during the course of the illness and may be normal in the presence of neurological abnormalities. In both the present

cases it may be that the EEG was recorded before permanent changes were established.

Amantidine has an antiviral action, particularly against influenza A2 virus (Galbraith, Oxford, Schild, Potter, and Watson, 1971), but its action in Parkinsonism is unknown (Parkes, Baxter, Curzon, Knill-Jones, Knott, Marsden, Tattersall, and Vollum, 1971). Creutzfeldt-Jakob disease is known to be transmissible (Gibbs, Gajusek, Asher, Alpers, Beck, Daniel, and Matthews, 1968), but whether the action of amantidine in this condition is antiviral or metabolic is impossible to say. Braham (1971) favours a metabolic action, and subsequent attempts in his patient to lower the dose of amantidine caused temporary relapse (Braham, 1972).

It appeared that the response in our first patient was also dose related, and this variability in response to dosage would indicate a metabolic rather than an antiviral action.

From the recorded cases, there seems no doubt that amantidine has some action in Creutzfeldt-Jakob disease, and that its use is justified in an otherwise universally fatal condition. If treatment is to be effective before permanent damage has occurred it would seem essential to start amantidine therapy as soon as a clinical diagnosis can be made.

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