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References

1 **von Brevern M**, Seelig T, Neuhauser H, *et al*. Benign paroxysmal positional vertigo predominantly affects the right labyrinth. *J Neurol Neurosurg Psychiatry* 2004;**75**:1487–8.
2 **De la Meilleure G**, Dehaene I, Depondt M, *et al*. Benign paroxysmal positional vertigo of the horizontal canal. *J Neurol Neurosurg Psychiatry* 1996;**60**:68–71.
3 **Casani AP**, Vannucci G, Fattori B, *et al*. The treatment of horizontal canal positional vertigo: our experience in 66 cases. *Laryngoscope* 2002;**112**:172–8.
4 **Brandt Th**. Benign paroxysmal positioning vertigo. In: Brandt T, ed. *Vertigo*. London: Springer Verlag, 1999:251–83.

Aciclovir induced posterior leucoencephalopathy

Aciclovir is an extremely effective agent for the treatment of herpes simplex encephalitis and varicella–zoster infections in immunocompromised individuals.[1] Encephalopathy induced by aciclovir is an infrequent but well recognised adverse effect of aciclovir.[2] The predisposing factors to aciclovir induced encephalopathy (AIE) include age, acute or chronic renal failure, and other neurotoxic drugs.[2] Tremors (40–58%), disorientation (40–50%), agitation (22–38%), hallucinations (25%), and delirium (25%) are common presentations of AIE, whereas seizures (10%), cerebellar ataxia (11%), sensory symptoms (9%), speech disorders (9%), fever (3%), and cranial nerve palsies (0%) are much less frequent.[2] The supportive diagnostic criteria for AIE include a temporal association between the symptoms and aciclovir use, as well as acellular cerebrospinal fluid (CSF) in cases without herpes simplex or varicella–zoster encephalitis. In the majority of cases symptoms develop within 72 hours of starting aciclovir treatment, although up to 120 days has been reported.[2] The clinical recovery may take several days (five days in 57% of cases) following discontinuation of aciclovir.[2] The EEG typically shows diffuse slow wave activity rather than focal abnormalities.[2]

The radiological features are not well described in AIE. Case reports have identified multifocal white matter signal abnormalities involving the cerebellum, pons, and periventricular region as well as evidence of vascular encephalopathy on MRI.[2 3] We report a case of AIE with MRI features consistent with posterior leucoencephalopathy with clinical and radiological improvement following the discontinuation of aciclovir, along with raised serum and CSF concentrations of aciclovir and 9-carboxymethoxymethylguanine (CMMG), the main metabolite of aciclovir.

Case report

A 47 year old women with a 15 month history of $cANCA^+$ glomerulonephritis and chronic end stage renal failure (serum creatinine 957 μmol/l), managed on continuous ambulatory peritoneal dialysis, azathioprine (100 mg/day), and prednisolone (10 mg/day), developed a mid-thoracic varicella–zoster rash. She was given a reduced dose of intravenous aciclovir (250 mg three times daily). Within 48 hours she became agitated, developed visual hallucinations and drowsiness (Glasgow coma scale (GCS): overall 6; eye 1, motor 4, verbal 1). On admission to the intensive care unit she was apyrexial, the highest blood pressure recorded was 180/104 while agitated, and fundoscopy was unremarkable. The tendon reflexes were exaggerated, with extensor plantar responses. Oculocephalic and corneal reflexes as well as spontaneous respiration were present.

Laboratory investigations showed a haemoglobin of 9.7 g/l, white cell count 5.8×10^9/l, urea 22 mmol/l, ESR 90 mm/h, C reactive protein 27 mg/l, albumin 22 g/l, ammonia 10 mmol/l, and cANCA negative. Computed tomography of the head, done immediately after she became obtunded, showed posterior white matter hypodensities. The lumbar CSF contained no white cells and four red blood cells per mm^3, with a protein of 0.63 g/l and a CSF/serum glucose ratio of 3.9/6.4. The opening pressure was 41 cm. CSF cultures, including culture for acid fast bacilli, were negative. CSF testing by polymerase chain reaction was negative for herpes simplex virus I and II, varicella–zoster virus, cryptococcal antigen, and JC virus. An EEG showed excessive slow wave activity. Magnetic resonance imaging (MRI) of the brain and an MR venogram (done after five days on aciclovir) showed symmetrical posterior white matter changes predominantly in the occipital and parietal lobes (fig 1A and 1B) without evidence of venous sinus thrombosis, gadolinium enhancement, or matched defects in diffusion weighted images.

On admission, azathioprine was stopped and intravenous methylprednisolone (500 mg/day for three days) was started for presumed CNS vasculitis. There was no improvement 72 hours after this treatment and after eight days of aciclovir. Aciclovir was discontinued when AIE was suspected, and peritoneal dialysis was maintained. Within 48 hours of discontinuation of aciclovir, the GCS improved (eye score 3, motor score 6, verbal score 3) and neurological examination showed bilateral upper limb postural tremor, which resolved over 24 hours. The Addenbrooke's score was 77/100. Repeat MRI (fig 1C, 1D) showed a significant improvement. Analysis of aciclovir and CMMG levels in the serum and CSF showed high values, at levels generally associated with neurotoxicity.[4] The serum aciclovir and CMMG concentrations were, respectively, as follows:

- 5 days post-aciclovir initiation: 34.9 μmol/l and 91.7 μmol/l;
- 6 days post-aciclovir: 35.4 μmol/l and 148.5 μmol/l;
- 7 days post-aciclovir: 17.2 μmol/l and 141 μmol/l.

The CSF aciclovir and CMMG concentrations four days post-aciclovir initiation were, respectively, 5.99 μmol/l and 2.25 μmol/l (CMMG levels are not detectable in CSF unless there is neurotoxicity (Helldén A, submitted for publication)), supporting a diagnosis of AIE.[4]

Comment

The clinical presentation of our patient, her rapid recovery, and the CSF and EEG findings are characteristic of AIE in cases without herpes simplex or varicella–zoster encephalitis.[2 5] The lack of significantly raised blood pressure or papilloedema excludes hypertensive posterior leucoencephalopathy. $ANCA^+$ vasculitis causing posterior leucoencephalopathy has been reported but only in the presence of severe hypertension. AIE, an infrequent but well recognised adverse effect of aciclovir, has until now been diagnosed

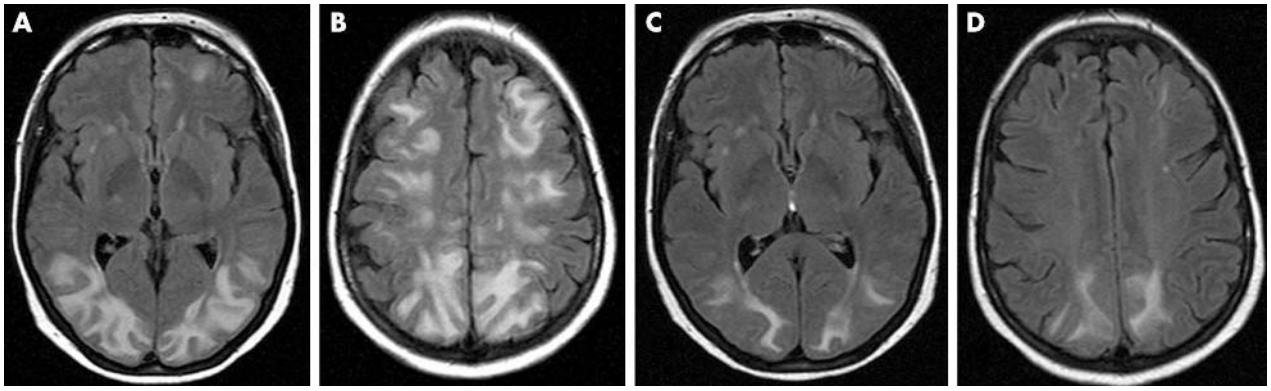

Figure 1 Fluid attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) of the brain done five days after initiation of aciclovir treatment, showing features consistent with posterior leucoencephalopathy (panels A and B). Repeat MRI five days after discontinuation of aciclovir showed a marked improvement (panels C and D).

mainly on clinical features.[2 5] Factors predisposing to AIE include age, acute or chronic renal failure, and other neurotoxic drugs.[5] The diagnosis is facilitated by analysis of aciclovir and CMMG in serum and CSF. In cases with renal failure, the half life of aciclovir extends from 3 to 20 hours and as a result aciclovir is metabolised to CMMG by alcohol and aldehyde dehydrogenases.[4] At present, reliable dose recommendations are not available for patients with renal failure.

In a case study of 93 patients, mainly with renal failure,[4] we found mean (SD) serum aciclovir concentrations of 21.0 (30.7) μmol/l (in 49 patients with neurotoxicity) and 7.2 (6.7) μmol/l (in 44 asymptomatic patients receiving aciclovir), while CMMG concentrations were 34.1 (39.4) μmol/l in patients with neurotoxicity and 4.7 (4.7) μmol/l in asymptomatic patients. CMMG levels of >10 μmol/l seemed to be associated with neurotoxicity. A high CMMG level is a strong predictor of AIE in patients with renal failure.[4] Haemodialysis is effective in clearing aciclovir and CMMG, and to a lesser extent so is peritoneal dialysis.[4]

This case highlights the difficulties in diagnosing AIE and the value of measuring aciclovir and CMMG levels in making the diagnosis.[4] In cases with renal failure and herpes simplex or varicella–zoster encephalitis, aciclovir should not be discontinued prematurely, but a total daily dose exceeding 400 mg is not generally recommended in patients with renal impairment. Pharmacokinetic studies of aciclovir and CMMG are being undertaken at Karolinska University Hospital, Sweden, with the aim of achieving dose recommendations for patient with renal failure.

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References

1 **Dorsky DI**. Clyde S, Crumpacker S. Drugs five years later: acyclovir, *Ann Intern Med* 1987;**107**:859–74.
2 **Rashiq S**, Briewa L, Mooney M, *et al*. Distinguishing acyclovir neurotoxicity from encephalomyelitis. *J Intern Med* 1993;**234**:507–11.
3 **Braun JS**, Apel I. Schaffer S, *et al*. Delirium during oral therapy of herpes zoster with acyclovir: case report and brief review of central nervous system side-effects of acyclovir. *Nervenarzt* 1998;**69**:1015–18.
4 **Hellden A**, Odar-Cederlof I, Diener P, *et al*. High serum concentrations of the acyclovir main metabolite 9-carboxymethoxymethylguanine in renal failure patients with acyclovir-related neuropsychiatric side effects: an observational study. *Nephrol Dial Transplant* 2003;**18**:1135–41.
5 **Cohen SM**, Minkove JA, Zebley JW, *et al*. Severe but reversible neurotoxicity from acyclovir. *Ann Intern Med* 1984;**100**:920.

Normal memory and no confabulation after extensive damage to the orbitofrontal cortex

Subarachnoid haemorrhage caused by the rupture of an anterior communicating artery (ACoA) aneurysm is often followed by amnesia, confabulation, and personality change including social decision making.[1–3] However, the regions responsible for each symptom have not been determined conclusively. We describe a patient who showed personality change, but neither memory impairment nor confabulation, after extensive damage to the bilateral orbitofrontal cortex demonstrated by magnetic resonance imaging, providing evidence that the destruction of the medial orbitofrontal cortex alone cannot cause amnesia and confabulation.

Case report

The patient was a 45 year old, right handed man with a 16th grade education. He was not an apathetic person and worked hard as a manager before the onset. His past medical history was unremarkable and he had no medication. He had sudden onset of headache, became unconscious, and was admitted to an emergency hospital. Brain computed tomography showed a subarachnoid haemorrhage in the cisterns around the brainstem, longitudinal cerebral fissure, and bilateral Sylvian fissure caused by a ruptured aneurysm of the ACoA. On the same day, he underwent an operation to repair the ruptured aneurysm. There were slight brain oedema and vasospasm (four to 10 days). He did not become delirious, agitated, or suspicious. He had 200 mg of phenitoin each day to prevent secondary seizures. His family noted that he showed mild anterograde amnesia, which improved over two months, but no retrograde amnesia.

The patient was discharged home after three months. He began working again as a manager at his company, but could not do his job as well as before the onset. Twenty months after the onset, he was admitted to our hospital for assessment of his problems.

On admission, the patient was fully alert and oriented. General physical and neurological examinations were unremarkable. During his stay in hospital, he had no problems communicating with others, kept his appointments and could find his way around the hospital. His family and his superior at his company reported that his personality had changed since the onset of his illness (in terms of lack of concern for others including his family, his appearance, and his future; the loss of spontaneity, initiative, and self motivation; disinhibition; and rigidity of thought).

General neuropsychological assessments were performed between the second and 12th hospital days. He was attentive, cooperative, and showed no confabulatory response. His intelligence level was normal on the Wechsler Adult Intelligence Scale-Revised (full IQ, 113; verbal IQ, 114; performance IQ, 109), Mini Mental State Examination (30 of 30), and Raven Progressive Colored Matrices (35 of 36). He showed no linguistic deficit on the Western Aphasia Battery. The results of the Wisconsin Card Sorting Test (six categories achieved) and Verbal Fluency Test (animals, initial syllables ''A'', ''Fu'', and ''Ni'': 15, 10, 10, and 15/minute, respectively) were normal. His immediate memory spans were normal (forward: verbal, 7; spatial, 6; and backward: verbal, 6; spatial, 6). The indices on the Wechsler Memory Scale-Revised were above average, except for a somewhat low score for delayed index (general, 112; verbal, 110; visual, 108; attention/concentration, 112; delayed, 85). He showed no retrograde amnesia in a structured interview, on the Autobiographical Memory Interview (incidents 9, 9, 8 and personal semantic 21, 20, 21 for childhood, early adult life, and recent, respectively), and on the Public Events test (14, 15, 14, and 16/16 for 60th, 70th, 80th, and 90th, respectively).

Brain magnetic resonance imaging performed 20 months after the onset (fig 1) showed bilateral lesions in the ventromedial prefrontal lobe extending to the frontal pole and subcortical regions under the middle and superior frontal gyri. Additional lesions were seen in the left insula and the right ventral anterior nucleus of the thalamus.

Discussion

After extensive damage to the bilateral orbitofrontal cortex, with no concomitant lesion in the basal forebrain, the patient showed personality change as a result of a subarachnoid haemorrhage, but neither memory deficits on comprehensive neuropsychological assessment nor confabulation. His personality change could be classified as a combined type (apathetic and disinhibited) and was consistent with those (lack of concern, loss of spontaneity, disinhibition, impaired decision making, and rigidity of thought) generally agreed in the literature to be the result of dysfunction of the frontal lobe, particularly the orbitofrontal cortex.[1–3]

Importantly, the patient showed no memory deficit. Damage to the basal forebrain without damage to the frontal lobe causes amnesia.[4] With regard to the orbitofrontal cortex, it has been argued that destruction of this region is not necessary for the development of amnesia or basic cognitive function.[1 3] However, there has so far been no conclusive evidence as to whether or not damage to the orbitofrontal cortex alone (especially the medial caudal part of it) gives rise to amnesia.[1] Our present study provides evidence that damage to the orbitofrontal cortex alone does not result in amnesia and therefore strengthens the notion that the basal forebrain is one of the crucial sites for human memory.

It should be noted that the assessment of memory in our present study is based on standardised tests. This means that memory that is not measurable using these standardised tests (for example, temporal context memory) may be related to the function of the orbitofrontal cortex. In addition, we cannot draw a strong conclusion regarding frontal lobe function, because we did not use tests sensitive to damage to the ventromedial prefrontal cortex (for example, the Iowa Gambling Task[3]).

The patient showed no confabulation. Damage to the orbitofrontal lobe alone might not be sufficient for confabulation to be