

ities, pancytopenia or intestinal bleeding.⁴ Neuropathologic examination in patients with "Coats plus" shows abnormal small vessels with angiomatous proliferation and extensive calcinosis, similar to LCC.⁴ Recently, Linnankivi *et al.* reported patients showing LCC, and retinal vascular abnormalities, skeletal changes and haematological abnormalities, which overlap with features of the previously reported patients with "Coats plus" syndrome and LCC.⁴ This strongly suggests that LCC and "Coats plus" belong to the same spectrum.⁴ The occurrence of affected siblings and consanguinity in parents strongly suggests that these microangiopathic affections are autosomal-recessive disorders.^{2,4}

We report herein an adult-onset LCC case revealed by an acute hemiparesis due to a small, deep cerebral infarct. This presentation expands the clinical spectrum of this condition.

CASE REPORT

A 30-year-old woman was admitted due to an acute right-sided hemiparesis. Her family history was negative for neurological or ophthalmological illnesses, and no consanguinity was known. She had a past history of migraine without aura, according to the International Headache Society criteria, since the age of 25 years, without associated cardiovascular risk factors, mood disorders or cognitive dysfunction. On admission, 8 hours after onset, there was a right hemiparesis with an ipsilateral Babinski sign. Sensation to pain and touch was impaired on the right side. There was no cognitive dysfunction, visual-field defect or dysphasia. Her score on the National Institute of Health Stroke Scale was 6. The optic disk and retinal vessels were normal. Her blood pressure was 130/80 mm Hg. The routine laboratory workup was normal, including blood cell count, coagulation tests, creatinine, glucose, sedimentation rate, calcium, phosphate, alkaline phosphatase and lactate levels. Brain computed tomography (CT) showed numerous foci of calcifications scattered in the right thalamus, the left basal ganglia and the right part of the cerebellum, associated with a cystic formation on the right parietal lobe and asymmetric diffuse leucopathy (fig 1A). Magnetic resonance imaging (MRI) diffusion-weighted imaging revealed the presence of an acute ischaemic lesion in the posterior limb of the left internal capsule (fig 1B). T2-weighted imaging showed asymmetric white-matter hypersignals, always surrounding cysts and calcification foci (fig 1C). Gradient echo imaging revealed the extent of the calcifications, which were not seen on CT or conventional MRI (fig 1D). Ring-contrast enhancement of the cysts walls and adjacent to calcifications was observed (fig 1E–1F). Cerebral MRI angiography was normal. Electrocardiogram, cervical and transcranial Doppler, and transoesophageal echocardiography,

were also normal. Spinal MRI was normal, as well as cervical, thoracic and abdominal CT examinations. Complementary biological tests were obtained, including antinuclear, anticardiolipids and anti-β2GP1 antibodies, antithrombin III, protein C and S, prothrombin (G20210A) and factor V mutations (Leiden), cholesterolaemia, homocysteinaemia, endocrinology tests (including parathyroid hormone) and serological tests for cystercerosis, human immunodeficiency virus (HIV-1 and -2), *Treponema pallidum* haemagglutination and Venereal Disease Research Laboratory (TPHA/VDR) tests. All these tests were negative or in the reference range. Cerebrospinal fluid studies were normal. Treatment with aspirin was prescribed. Eight months later, the patient has only slight weakness in her right hand.

DISCUSSION

This young adult patient shows the classical LCC neuroradiological triad—namely, asymmetric calcifications, asymmetric abnormal white-matter signal and parenchymal brain cysts. However, she did not show any of the clinical symptoms that were previously reported in LCC, such as progressive extrapyramidal, cerebellar, pyramidal signs, slowed cognitive performances or seizures.^{1–5} Surprisingly, clinical onset was unusual as the patient presented an acute hemiparesis due to a small, deep, cerebral infarct. To our knowledge, this type of clinical manifestation has not been reported in LCC patients even in adult cases.^{1–5} We strongly believe that this lacunar infarct is a consequence of the disease as no other cause of cerebral infarct has been identified in this patient despite thorough investigations, and because LCC is characterised by a cerebral obliterative microangiopathy. In conclusion, these data suggest that LCC belongs to the group of hereditary causes of ischaemic small-vessel diseases of the brain, which already include Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL), Cerebral Autosomal Recessive Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CARASIL), cerebrotretinal vasculopathy, Hereditary Endotheliopathy with Retinopathy, Nephropathy, and Stroke (HERNS) and familial amyloid angiopathy.⁴

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REFERENCES

1. **Labrune P**, Lacroix C, Goutieres F, *et al.* Extensive brain calcifications, leukodystrophy, and formation of parenchymal cysts: a new progressive disorder due to diffuse cerebral microangiopathy. *Neurology* 1996;**46**:1297–301.
2. **Nagao-Poetscher LM**, Bibat G, Philippart M, *et al.* Leukoencephalopathy, cerebral calcifications, and cysts: new observations. *Neurology* 2004;**62**:1206–9.
3. **Sener U**, Zorlu Y, Men S, *et al.* Leukoencephalopathy, cerebral calcifications, and cysts. *Am J Neuroradiol* 2006;**27**:200–3.
4. **Linnankivi T**, Valanne L, Paetau A, *et al.* Cerebroretinal microangiopathy with calcifications and cysts. *Neurology* 2006;**67**:1437–43.
5. **Corboy JR**, Gault J, Kleinschmidt-DeMasters BK. An adult case of leukoencephalopathy with intracranial calcifications and cysts. *Neurology* 2006;**67**:1890–2.

Measuring the effect of amantadine in chronic anoxic minimally conscious state

The effect of pharmacological agents on recovery in chronic disorders of consciousness remains unsatisfactory.¹ Amantadine, a dopaminergic agonist, has been suggested to behaviourally improve recovery from both a vegetative state (VS) and a minimally conscious state (MCS).^{2,3} Here, we report the effect of amantadine in a chronic anoxic MCS patient using standardized behavioural evaluations, actigraphy and serial positron emission tomography.

CASE REPORT

Patient

A 23-year-old man was found comatose after ventricular fibrillation. A brain computed tomography scan was normal and electroencephalography showed an alpha-coma pattern. Somatosensory-evoked potentials detected no cortical (N20) responses. After 3 weeks, the patient evolved to a vegetative state (VS) and was transferred to a rehabilitation centre (where no cognitive-enhancing interventions were given). He returned home after 6 months, having been diagnosed as being in a VS. After 2 years, the family contacted us for re-evaluation. Using the Coma Recovery Scale-Revised (CRS-R),⁴ the patient was recognised as being in a minimally conscious state (MCS; that is, presence of visual pursuit). After written informed consent from the patient's legal representative, amantadine treatment (200 mg per day) in an ABAB design was proposed in conjunction with weekly CRS-R assessment, actimetry monitoring and serial FDG-PET (fluorodeoxyglucose-positron emission tomography) (3 weeks baseline period, amantadine administered during 6 weeks, stopped during 6 weeks and again resumed for 6 weeks). Throughout the observational period, the patient remained free of other centrally acting drugs. The study was approved by the Ethics Committee of the University of Liège.

Neuropsychological assessment, actimetry and PET

Behavioural changes were assessed unblinded during 21 CRS-R evaluations by an experienced neuropsychologist (CS). The patient was tested at home, once a week (on the same day and at the same hour).

An actiwatch (Cambridge Neurotechnology Ltd, UK) was placed on the extremity showing the best motor response. This device measures movements by means of a piezoelectric accelerometer integrating intensity, amount and duration of movements (1-min epochs; movements above 0.05 g counted; filters from 3 to 11 Hz). Three recording sessions were performed (each lasting 4 weeks): a) 2 weeks after beginning of treatment (B1); for technical reasons, baseline data (A1) could not be obtained; b) 2 weeks after stopping amantadine (A2); c) 2 weeks after re-institution of amantadine (B2). Mean data of motor activity were computed for each acquisition week. Treatment periods (B1 and B2) were compared to the period without amantadine (A2) using non-parametric Friedman ANOVA on paired samples.

Cerebral metabolic rates for glucose metabolism (CMR_{glu}) were measured in wakeful, resting conditions using FDG-PET.⁵ Four CMR_{glu}-PET acquisitions were performed: a first baseline scan (A1); a second scan, 5 weeks after the beginning of treatment (B1); a third scan, 5 weeks after stopping amantadine (A2); and a final scan, 6 weeks after starting a second period of treatment (B2). PET data were analysed using statistical parametric mapping (SPM2; <http://www.fil.ion.ucl.ac.uk/spm>). The design matrix separately modelled each patient's scan (A1, B1, A2, B2) and 40 control subjects' scans (20 men; mean age 46 ± 16). Global uptake normalisation was performed by proportional scaling. A conjunction analysis identified brain regions in which glucose metabolism was significantly lower in the patient (A1) compared with controls, and in which glucose metabolism showed amantadine-related CMR_{glu} changes (A1 < B1 > A2 < B2). The resulting set of voxel values for each contrast, constituting a T statistics map [SPM{t}], was transformed to the unit normal distribution SPM{Z} and thresholded at p < 0.001 (Z = 3.09).

RESULTS

Compared with the baseline (A1), CRS-R total scores increased during the first period of treatment (B1) (mean scores of 9.0 ± 0.6 vs 12.5 ± 2.4, respectively). During the second treatment period (B2), there was no substantial improvement but an increase in the frequency of the patient's best CRS-R score (13.0 ± 1.5 vs 14.0 ± 0.0) (fig 1, lower panel). Changes were observed during B1 after 1 week of treatment in the motor function scale (ie apparition of automatic motor response) and after 3 weeks in the auditory function scale (ie emergence of responses to verbal order) (see Supplementary data). These behaviours did not disappear

during washout (A2), thereby explaining the high scores observed.

Mean motor activity increased following the first amantadine administration (B1) compared with the subsequent recording sessions without treatment (A2) (p < 0.05) and following the second amantadine treatment (B2) compared with A2 (p < 0.05) (fig 1, lower panel).

Prior to amantadine administration (A1), a significant hypometabolism (compared with controls) was observed in the bilateral dorsolateral prefrontal, temporo-parietal and mesiofrontal cortices, and in right-sided sensori-motor areas. A conjunction analysis showed that this cortical network showed significant (p < 0.001) amantadine-related increases in metabolic activity, approaching the normal range (fig 1, upper panel).

COMMENT

Two years after the brain insult, our patient recovered consciousness and remained in a

MCS (ie presence of visual pursuit) but failed to obey commands, as assessed by standardised testing.⁴ After 3 weeks of amantadine treatment, the patient showed reproducible movement to command and consistent automatic motor responses (ie opening of the mouth following the presentation of a spoon), permitting mouth feeding. Figure 1 (lower panel) illustrates the increase in the frequency of the patient's best CRS-R score. Similarly, actimetry monitoring showed a significant increase in limb movements during treatment periods. Discontinuation of amantadine resulted in a reduction of motor activity and treatment reintroduction induced a small but significant increase in actigraphic activity. Surprisingly, we have not observed amantadine-related increases in arousal as previously described.²

Even after 2 years post-anoxia, natural recovery cannot be excluded. However, serial FDG-PET scanning and the ABAB

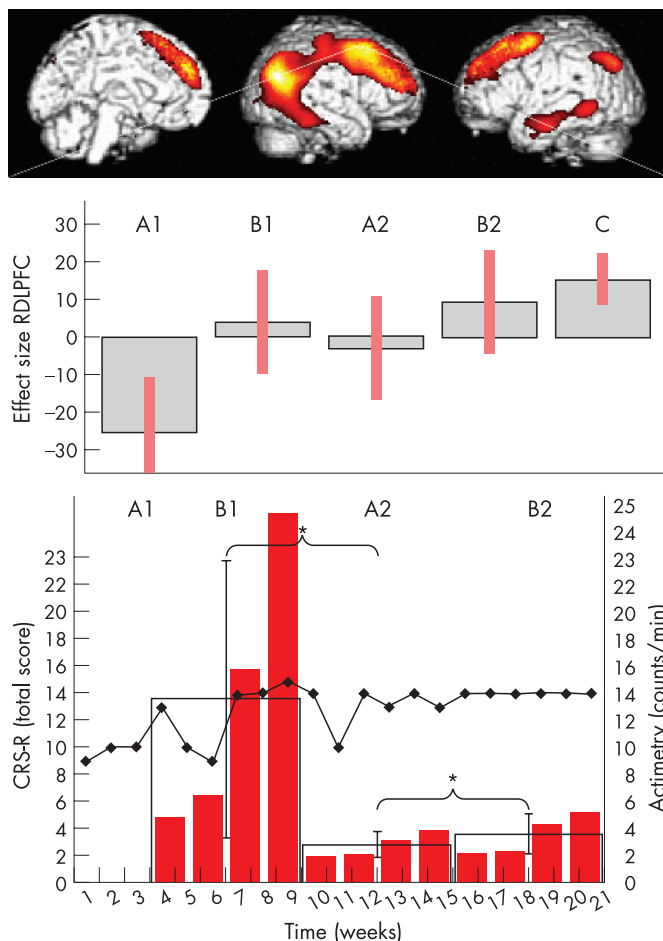


Figure 1 Upper panel: ABAB design illustrating treatment-related metabolic changes compared with controls (C) in widespread bilateral fronto-temporo-parietal associative and right-sided sensori-motor areas. Note that metabolic dysfunction, compared with controls (C), prior to amantadine administration (A1), increases after 5 weeks of treatment (B1), decreases after withdrawal (A2) and resumes near-normal values after amantadine reintroduction (B2). Lower panel: Behavioural changes as assessed by Coma Recovery Scale-Revised (CRS-R) during 21 weeks (CRS-R total scores ranging from 0 to 23 shown as black diamonds). Actimetry monitoring represented as mean motor activity counted per week (red bars) or per month (white bars). Asterisks represent the significant difference of motor activity between conditions (B1 > A2 < B2). RDL/PFC, right dorso-lateral prefrontal cortex.

design objectively measured treatment-related metabolic changes in a widespread fronto-temporo-parietal network and in the sensori-motor area. These data suggest a modulation of polymodal associative cortical metabolism and motor function by amantadine. The metabolic decrease after cessation of the drug did not return to baseline level (A1), possibly reflecting persisting long-term effects. This is conferred by the consistently higher CRS-R scores observed after treatment reintroduction.

In conclusion, using serial behavioural assessments, actigraphy and PET scanning, we here showed that pharmacological intervention in chronic anoxic MCS can result in cognitive and motor improvement. Large-scale studies on the efficiency of amantadine in this challenging patient population are warranted.

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REFERENCES

1. **Laureys S**, Giacino JT, Schiff ND, *et al*. How should functional imaging of patients with disorders of consciousness contribute to their clinical rehabilitation needs? *Curr Opin Neurol* 2006;**19**:520–7.
2. **Whyte J**, Katz D, Long D, *et al*. Predictors of outcome in prolonged posttraumatic disorders of consciousness and assessment of medication effects: A multicenter study. *Arch Phys Med Rehabil* 2005;**86**:453–62.
3. **Zafonte RD**, Lexell J, Cullen N. Possible applications for dopaminergic agents following traumatic brain injury: part 1. *J Head Trauma Rehabil* 2000;**15**:1179–82.
4. **Giacino JT**, Kalmar K, Whyte J. The JFK Coma Recovery Scale-Revised: measurement characteristics and diagnostic utility. *Arch Phys Med Rehabil* 2004;**85**:2020–9.
5. **Laureys S**, Faymonville ME, Degueldre C, *et al*. Auditory processing in the vegetative state. *Brain* 2000;**123**:1589–601.

Acute necrotizing encephalopathy: a relapsing case in a European adult

Acute necrotizing encephalopathy (ANE) is a rare disease, which is characterised by the rapid development of multiple, symmetrical brain lesions. These lesions affect the thala-

mus bilaterally, the brainstem tegmentum and the cerebellar medulla. The clinical picture consists of a rapidly deteriorating encephalopathy that develops 1–3 days after a prodromal febrile illness. Indeed, ANE has been related to influenza A virus infection, but to date it has also been associated with other viruses and mycoplasma.¹

We report a case of ANE, characterized by a combination of unusual features.

CASE REPORT

First episode

In July 2001, a 17-year-old previously healthy Italian boy was admitted to his local hospital due to a state of deep unconsciousness, with a sudden onset, after 1 day of high fever and cough. He had not been given any aspirin. Neurological examination revealed no pupil abnormalities, no abnormal postures or focal and lateralising signs, no Babinski sign and no signs of meningeal irritation. Computed tomography (CT) of the brain was normal. An electroencephalogram (EEG) showed generalised slow-wave activity. Urinalysis, and all biochemical and haematological parameters were normal. Cerebrospinal fluid (CSF) showed normal pressure, no increase in cells, normal glucose levels and an increase in proteins (55 mg/dl, normal values 20–40). CSF cultures showed no bacterial growth; immunoelectrofocusing for oligoclonal bands revealed a normal pattern. Serum antibody titres against common viruses were absent except for coxsackie virus, which was negative on day 1 and raised to 80 (determined by complement fixation test) on day 5. No specific therapy was administered; consciousness level and body temperature gradually returned to normal after 36 hours and the patient had no neurological sequelae. Magnetic resonance imaging (MRI) of the brain, performed after 1 week, showed no abnormalities and the patient was discharged without a definite diagnosis.

Second episode

Five years later, in April 2006, a similar episode of high fever and altered consciousness occurred and the patient was admitted to our hospital. Urinalysis, and all biochemical and haematological parameters were normal, except for alanine transaminase of 66 U/l (normal values 7–45) and creatine kinase of 619 UI/l (normal values 30–170); both were within normal limits after 4 days. Ammoniaemia and serum lactate at rest and after muscular exercise were normal. Extensive laboratory evaluation for coagulation disorders and for vascular, autoimmune, toxic, traumatic, nutritional and metabolic causes were negative. Enzyme-linked immunosorbent assay revealed IgA against influenza A virus, whereas specific IgG were absent, thus confirming a recent infection. Serum and CSF antibodies against other common viruses were within normal

limits. Biochemical and immunoelectrofocusing studies of CSF were normal except for an increase in proteins (69 mg/dl, normal values 20–40). EEG, on admission, showed generalised slow-wave activity; after 12 days, it was normal. Brain MRI on admission (fig 1A–F) showed bilateral and symmetrical central thalamic lesions; neither thrombi nor congenital vascular abnormalities were seen with MRI angiography. A follow-up brain MRI, 17 days after clinical onset (fig 1G–I), showed a complete resolution of the abnormal findings. While awaiting a definite diagnosis, we empirically administered cephtriaxone and acyclovir in case the patient was affected by bacterial meningitis or herpes simplex virus encephalitis. Consciousness level and body temperature gradually returned to normal after 2 days. Memory impairment and paraesthesias of the face and hands persisted for 1 month before complete recovery.

DISCUSSION

Our case represents a unique form of ANE, which is characterised by onset in adulthood in a Caucasian boy with a relapsing course. The majority of cases occur among young children in the Far East countries (mainly Japan and Taiwan). Nevertheless, to date, sporadic cases have been reported in North America and Europe as well,^{2,3} and onset in adulthood has been reported in only four Japanese cases (see additional references online—refs 6–9). In addition, so far, only two cases have been reported as being relapsing: a 4-year-old Japanese boy with two episodes of ANE—the first after an influenza A infection, and the second, 1 year later, after an adenovirus infection⁴; and a European girl with two episodes, both after an influenza A infection at the age of 3 and 11 years.⁵

Our patient fulfills the diagnostic criteria for ANE.¹ The distinction of ANE from viral encephalitis is based on CSF analysis as, in the latter, CSF pleocytosis is common. Leigh syndrome is distinguished by its neurodegenerative course, persistent lactic acidosis and other sites of disease localisation such as optic nerves and spinal cord, which are not involved in ANE. Wernicke encephalopathy, caused by thiamine deficiency, is accompanied by lesions in the thalamus and mammillary bodies. Reye syndrome is an acute encephalopathy, associated with fatty degeneration of the liver, hyperammonaemia and hypoglycaemia; MRI generally shows diffuse brain oedema with only patchy, if any, necrosis. Other possible causes of thalamic involvement include thalamic infarction and deep cerebral-vein thrombosis. However, the most resembling condition to be considered in the differential diagnosis is acute disseminated encephalomyelitis (ADEM), an acute post-infectious/post-vaccine inflammatory demyelinating disease. As well as the fact that ADEM is more common among children (see additional reference online—ref 10), our case