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ORIGINAL PAPER

Split-brain syndrome after hepatic transplantation: a tacrolimus-related vasculitis?

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Abstract An unusual case of inter-haemispheric disconnection syndrome occurring in a patient who had undergone hepatic transplantation is presented. The underlying disorder, at first wrongly interpreted as encephalitis, was found to be severe, diffuse cerebral vasculitis. The hypothesis that treatment with tacrolimus might have caused, or at least favoured the vascular damage is discussed.

Keywords Cirrhosis · Hepatitis C · Transplantation · Tacrolimus · Corpus callosum · Split-brain · Vasculitis

Abbreviations

HCV	hepatitis C virus
ITT	inter-haemispheric transmission time
MELD	model end stage liver disease
MRI	magnetic resonance imaging
OLTx	orthotopic hepatic transplantation

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Introduction

Split-brain is the term used to describe the clinical consequences of a complete or partial section of the corpus callosum, the main brain structure that allows information transfer between the two haemispheres. The syndrome has been reported after ischaemic/haemorrhagic vascular accidents (Berlucchi and Aglioti 1999; Marzi et al. 1991) and the elective section of the corpus callosum was also utilised as a therapeutic measure to contain the generalization of seizures from one haemisphere to the other in treatment-resistant epilepsy (Wilson et al. 1977). Corpus callosum damage has also been related to alcohol misuse, although mostly as a post-mortem (Marchiafava and Bignami 1903) or an imaging (Hommer et al. 1996) rather than a clinical finding.

Crucial elements for the diagnosis of split-brain syndrome are: *i)* left hand tactile agnosia, or the inability to recognize objects placed in the left hand in the eyes-closed condition, since this function requires information transfer from the right sensory cortex to the left parietal associative cortex, and *ii)* prolonged inter-haemispheric transmission time (ITT), as measured by the difference between left/right hand reaction times to lateralised stimuli (Mooshagian et al. 2009). As a consequence, also the early sensory evoked potential components produced in response to a visual stimulus presented to one visual haemifield segregate within the stimulated, contra-lateral haemisphere, since the damage stops these components from spreading contralaterally. In contrast, the later components, such as the P300, spread to both haemispheres, suggesting that information related to late stimulus processing is transferred via alternative inter-haemispheric pathways, such as the anterior commissure and/or the superior colliculus (Yovel et al. 2003).

Case history

A 53-year-old male was referred to our centre 22 months after orthotopic hepatic transplantation (OLTx) with worsening neuropsychiatric performance.

He had been diagnosed with hepatitis C virus (HCV)-related cirrhosis at the age of 36. He was a non-insulin dependent diabetic and had an otherwise unremarkable medical history. He had never misused alcohol and was completely abstinent since the diagnosis of cirrhosis. At the age of 48 he had undergone trans-jugular intra-hepatic portal-systemic shunt because of diuretic-resistant ascites. The procedure had been well tolerated and he had not developed overt nor minimal hepatic encephalopathy (normal psychometric performance and electroencephalogram (Amodio et al. 1999)). He had subsequently been transplanted at the age of 51, when he was classified as Child-Pugh class C/10 (Pugh et al. 1973) and Model End Stage Liver Disease (MELD) 14 (Kamath et al. 2001).

Eighteen months after OLTx, he had started to develop disorientation in time, anxiety, bizarre behaviour, fatigue, insomnia, mild left haemiparesis, followed by severe frontal-temporal headache and vomiting. He had been admitted into a local district hospital and treated with prednisone on a presumptive diagnosis of viral encephalitis, with no benefit. Meanwhile, he had also developed severe systemic hypertension.

When we first reviewed him, he reported that his left hand performed actions that were somehow 'independent' of his will and of those of the right hand (i.e. attempting to close a door with his right hand whilst opening it with his left hand). In addition, he complained of gait disturbance. On clinical examination he was vigilant, cooperative, orientated in time and space, with apparently normal mood and nutrition status. No lung, cardiac or abdominal abnormalities were detected. Mild pitting oedema was present bilaterally. Neurological examination revealed a remarkable lack of motor coordination, a mild deficit of the inferior branch of the left VII cranial nerve and a mild strength reduction in both the upper and the lower left limb. Laboratory exams revealed microcytic anaemia (haemoglobin 7.3 g/dL; erythrocyte mean cellular volume 76 fL), renal impairment (creatinine 509 μmol/L, urea 31 mmol/L), massive proteinuria (5 g/day), good glycemic control (glycaeted haemoglobin 6.0%), traces of cryoglobulin; smooth muscle antibodies were positive at low titre, rheumatoid factor and anti-neutrophil cytoplasmic antibodies were negative. Tacrolimus plasma levels were adequate at 4.2 μg/L.

A complete neuropsychological examination was performed. The Mini Mental State Examination (Folstein et al. 1975) was abnormal with a score of 22/30 (reference range ≥ 24/30), while the Brief Neuropsychological Examination (Mondini et al. 2003) showed that short/long term verbal memory, attention, working memory, executive function and language (comprehension, visual naming, verbal fluency) were substantially preserved. In contrast, severe constructional apraxia, or the inability to draw with/without a model, was detected (Fig. 1). Eyes-closed, left hand tactile anomia was also observed: while all 13 three-dimensional objects presented to the right hand were correctly named, only five of those presented to the left hand were correctly named. In addition, the patient exhibited lateralised ideational apraxia, being unable to make a 'military knot' or to cross himself with his left arm.

Split-brain syndrome was therefore suspected and the ITT measured utilising a simple lateralized reaction time task, according to Poffenberger (Poffenberger 1912). The ITT was prolonged at 37 ms (reference range ≤ 4–10 ms) (Fig. 2), confirming the clinical suspicion. To further characterize the disorder, visual event-related potentials were measured under the same task. The evoked components P1 and N1 were significantly larger contra- compared to ipsi-laterally (contra-P1: 3.6±0.4 μV; ipsi-P1: 2.6±0.3 μV; F [1,9]=39.0, $p<$ 0.0001) (contra-N1: -4.9±0.2 μV; ipsi-N1: −2.9±0.2) μV; F [1,9]=160.6, p<0.0001) (Fig. 3).

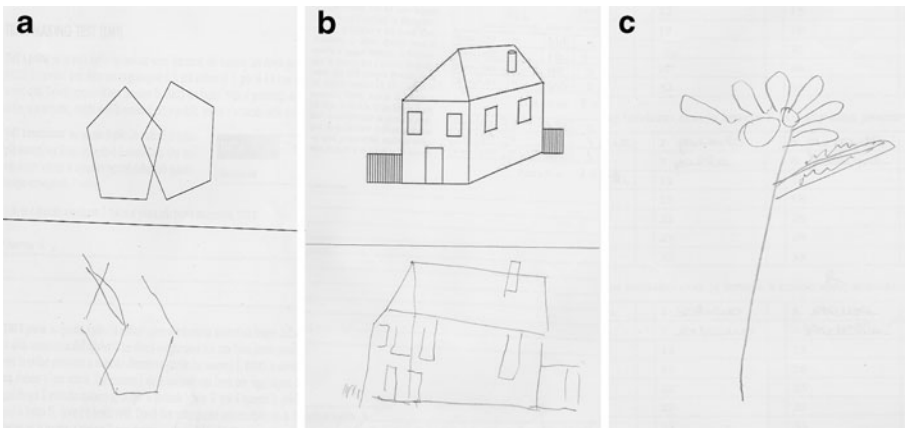

Fig. 1 Performance of the patient in the drawing copying section of the Mini Mental State Examination (overlapping pentagons; **a**), the drawing copying section of the Brief Neuropsychological Examination (a house; **b**) and the free drawing section of the Brief Neuropsychological Examination (daisy with stem and leaf; **c**). The patient shows a piecemeal, fragmented approach and seems to miss the overall picture and the aim of the construction task

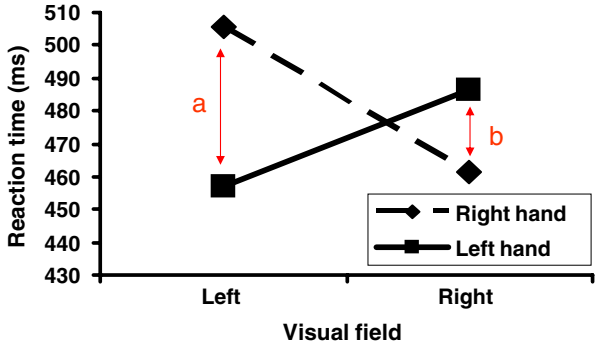

Fig. 2 The interaction between hand-position and stimulus-position in the Poffenberger task. Reaction times are faster for the uncrossed responses (same hand- and stimulus-position) compared to the crossed (different hand- and stimulus-position). The average of the crossed-uncrossed difference [(a+b)/2], or inter-haemispheric transmission time, was prolonged at about 37 ms (reference range ≤ 4–10 ms)

Both acute encephalitis and cerebral vasculitis were considered as potential causes for the observed clinical syndrome.

Cerebral magnetic resonance imaging (MRI) was performed, which documented frontal para-saggital abnormalities extending to the gyrus cinguli and involving the posterior part of the corpus callosum, potentially consistent with both diagnostic hypotheses. Cerebrospinal fluid was examined: no biochemical abnormities were detected and microbiological investigations were negative for bacteria, fungi and viruses, with the exception of HCV-RNA. This might have been related to blood contamination but quasi-species determination was not obtained.

At this stage, the hypothesis of viral encephalitis was abandoned and that of vasculitis pursued with an angio-MRI scan. This showed signs of cerebral vasculitis with multifocal, impressive narrowing of the main cerebral arteries. A tacrolimus-related vasculitis was suspected and thus tacrolimus was stopped and replaced with mycophenolate mofetil, cyclophosphamide and methylprednisolone. However, the clinical condition worsened further and after 10 days the patient was dysarthric, dysphagic and the left haemisyndrome had become more obvious. A second cerebral MRI was performed, which showed a further ischemic right lesion within the pons, while the previously detected lesions had evolved into atrophic-degenerative areas. The corpus callosum was heavily involved (Fig. 4). The diagnosis of cerebral arteritis was eventually confirmed by angiography (Fig. 5). Treatment with mycophenolate mofetil, cyclophosphamide and methylprednisolone was continued. However, both the renal failure and the neurological syndrome worsened and the patient self-discharged and died at home after a few days, with severe renal impairment and coma. The relatives did not consent to post-mortem examination.

Discussion

To our knowledge, this is the first time that a split-brain syndrome is reported after OLTx. The patient developed systemic hypertension, progressive renal impairment with proteinuria and, finally, inter-haemispheric disconnection. Although histopathological confirmation was not available, there is sufficient evidence to support the hypothesis that a vasculitis involving at least the kidneys and the brain was the most likely cause for transplant failure and, ultimately, death.

Fatal cerebral vasculitis was reported during treatment with tacrolimus in a diabetic patient who had been trans-

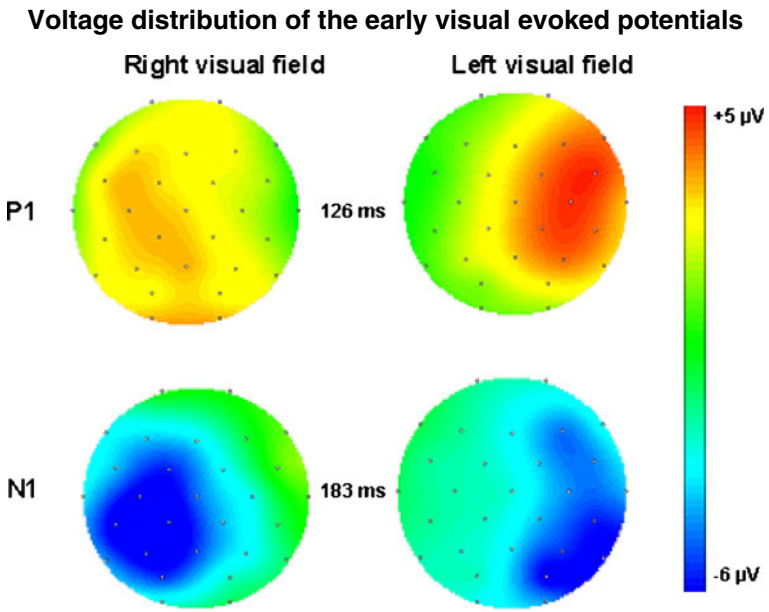

Fig. 3 The voltage distribution across the scalp of the P1 and N1 responses evoked by stimuli presented in the right/left visual fields. The responses are considerably attenuated in the hemisphere ipsi-lateral to the stimulus position due to the lesion in the corpus callosum

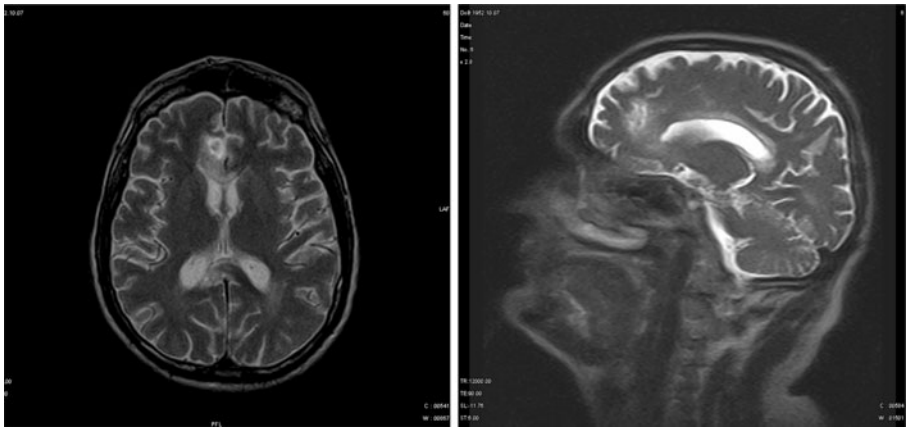

Fig. 4 Cerebral magnetic resonance: T2 axial and sagittal images showing diffuse involvement of the corpus callosum

planted for hepatitis B and C cirrhosis (Pizzolato et al. 1998). In this individual, the brain lesions were characterised by neutrophilic infiltration of the walls of the small cortical arteries and perivascular spaces; recent thrombi were detected in the vessels with ensuing focal foci of cortical necrosis (Pizzolato et al. 1998). Fatal cardiac failure due to severe large/small coronary arteritis was also reported after treatment with high doses of tacrolimus in a child who had undergone liver/bowel transplantation (Atkison et al. 1997).

Tacrolimus is also known to accelerate the progression of other vascular diseases (Morioka et al. 1999), probably by limiting nitric oxide production (Diaz-Ruiz et al. 2005) and thus causing a reduction in the ratio between vasodilating substances and endothelin. Interestingly, the vascular effects of tacrolimus seem to be more common at relatively low doses rather than at immunosuppressant doses, at least in the animal models (Ochiai et al. 1993).

In our patient, who had HCV infection and whose graft showed HCV-related hepatitis, tacrolimus might have caused a vasculitis or possibly worsened/accelerated an HCV-related vasculitis (Hartge et al. 2006). Within the context of HCV infection, the most common vasculitis is related to mixed cryoglobulinemia. However, its clinical presentation is generally limited to cutaneous purpura and arthralgia (Cacoub et al. 2001; Dammacco et al. 2001). A different, more severe type of HCV/cryoglobulinemia-related vasculitis shares some clinical features with periarteritis nodosa: it has an acute onset and it is associated with poor general conditions, severe multifocal sensorimotor mono-neuropathy, high blood pressure and central nervous system or gastro-intestinal involvement (Cacoub et al. 2001). The presence of renal impairment, high cryocrit and complement activation represent negative prognostic factors (Ramos-Casals et al. 2006). Our patient had renal impairment, but very low cryoglobulin levels, probably indicating that an additional factor, most likely treatment with tacrolimus, might have contributed. Based on these considerations, the choice of replacing tacrolimus with an immunosuppressive regimen including mycophenolate mofetil, cyclophosphamide and methylprednisolone seemed reasonable, but was made at a fairly late stage and did not prove beneficial.

The current understanding of the pathophysiology and the management of vasculitis in transplanted patients is limited and further research is needed.

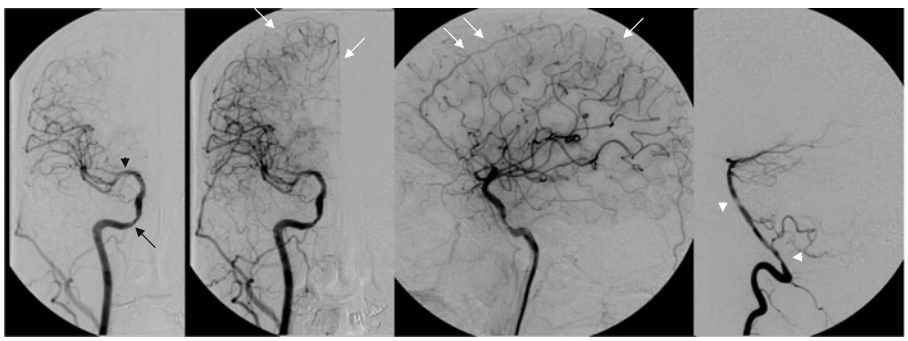

Fig. 5 Digital subtraction cerebral angiography showing severe stenosis of the intracranial segment of the right carotid artery (*black arrow*) and minor alterations of the lumen of the right middle cerebral artery (*black arrowhead*). There were also severe perfusion defects within the territories of the right anterior cerebral artery, which were supplied by anastomotic lepto-meningeal collaterals (*white arrows*); multiple stenoses were apparent along the basilar artery (*white arrowheads*) and the intracranial segments of the vertebral arteries. Cerebral veins and sinuses were unremarkable (not shown)

Conflict of interest Nothing to declare.

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