

CASE REPORT

Sustained normalization of cerebral blood-flow after iloprost therapy in a patient with neuropsychiatric systemic lupus erythematosus

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We report the case of a 30-year-old caucasian woman affected by SLE who developed neurological symptoms (prosopagnosia and visual-spatial agnosia) after nine years of disease. Brain MRI showed no abnormalities while a brain SPECT scan showed diffuse uptake defects and hypoperfusion areas in the right and left frontal-parietal regions. At that time the patient was on hydroxychloroquine (400 mg/day) and oral prednisolone (0.5 mg/kg/day) as maintenance therapy. One year later the patient showed worsening of Raynaud's phenomenon with digital dystrophic lesions and was therefore treated with an intravenous infusion of Iloprost (1.5 ng/kg/min per 6h/day for 10 days consecutively), while baseline treatment remained unchanged. One month later the patient showed a dramatic improvement in her cognitive function and subsequent SPECT scans showed the gradual disappearance of perfusion abnormalities. This first report of Iloprost treatment in CNS lupus suggests the potential therapeutic usefulness of this drug in patients with SLE and functional CNS involvement. *Lupus* (2002) 11, 52–56.

Key words: SLE; CNS; cognitive disorders; Iloprost; therapy; brain SPECT

Introduction

Nervous system involvement in patients with systemic lupus erythematosus (SLE) comprises a wide spectrum of neurologic and psychiatric features. The mode of presentation varies from overt neurological dysfunction, such as psychosis or stroke, to more subtle and subclinical abnormalities in neurocognitive functions, such as memory, intellect and learning.¹ The frequency of neuropsychiatric manifestations (NPM) in SLE has been estimated in around 25–70% of the patients.²

Single photon emission computed tomography (SPECT) studies have demonstrated a high incidence of functional abnormalities, particularly in SLE patients with overt neuropsychiatric manifestations, but also in those with mild symptoms or without any

neurological manifestations and/or lesions detectable upon magnetic resonance imaging (MRI).^{3–5} Current insights in the pathogenesis of NPM suggest a role for the following mechanisms: (i) vascular and perivascular immune-complex mediated damage;⁶ (ii) direct interactions of autoantibodies with antigens on neuronal cell membrane;^{7,8} (iii) local production of cytokines and induction of cell-mediated autoreactivity;⁹ and (iv) vasculopathy and antiphospholipid mediated thrombosis.^{10,11} Combined cell mediated and serological autoreactive factors possibly contribute towards the broad spectrum of NPM in SLE.^{2,12} Recently it has also been suggested that a possible vasospastic mechanism may be responsible for NPM in patients with SLE and Raynaud's syndrome.¹³

Iloprost is a chemically stable carbacyclin derivative of prostacyclin with a longer half-life.¹⁴ It has been shown to improve the microvascular functional capacity, with effects on leukocyte rolling, leukocyte-endothelium interaction, down-regulating adhesion molecules expression on neutrophils/monocytes and endothelial cells surface.¹⁵ Antiplatelet aggregation

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properties have also been advocated among its therapeutic effects.^{16,17}

We report the case of a patient with neuropsychiatric lupus manifested by severe cognitive dysfunction and diminished cerebral blood perfusion detected by brain SPECT in which a course of Iloprost infusion was effective in the normalization of the SPECT abnormalities and successful in the treatment of the neuropsychiatric manifestation.

Case report

A 30-year-old Caucasian woman was diagnosed as having SLE in 1990 at the age of 20, when she presented with non-erosive arthritis, malar rash, positivity for antinuclear antibodies (ANA) and anti-dsDNA antibodies (anti-dsDNA). Antiphospholipid antibodies (aPL) were negative. She also presented episodes of Raynaud's phenomenon. She was treated with a low dose of steroids and hydroxychloroquine from the onset of the disease. In August 1999 she complained of difficulties with concentration and memory loss. She also complained of acute episodes of headache resistant to conventional analgesic treatment and exacerbation of Raynaud's phenomenon. She was, therefore, admitted for evaluation in our department.

On admission her general condition was satisfactory. General and neuropsychiatric examination was normal, except for the presence of a mild asymmetry of the knee jerk (right > left). She was on hydroxychloroquine (400 mg/day) and oral prednisone (0.5 mg/kg/day). Complete neuropsychological evaluation was also performed. Time and place orientation, attention, frontal executive functions, memory, language, comprehension and calculation were all normal, but right hemisphere functions were severely impaired in the visual-perceptual tasks. The patient was unable to name and identify familiar faces, but was normal on face feature description and choosing examples of the same face in arrays (matching tasks). Knowledge of famous people and relatives was preserved, despite the inability to recognize and name them from photographs. The patient was also unable to name or identify famous buildings. A condition of prosopagnosia (inability to recognize familiar faces), in association with a visual-spatial agnosia (inability to recognize previously known places), was diagnosed in this patient.

A complete biochemical and haematological profile was normal. The erytrosedimentation rate and C-reactive protein were normal. C3 and C4 complement fractions were reduced. ANA titre was 1:320, with a homogeneous pattern (detected by IFI on a Hep2 cell

substrate). Anti-dsDNA were positive with a value of 37 U/ml (detected by Farr test, for a normal value < 7 U/ml). Anti-ENA antibodies, detected by dot-blot method, were negative. IgG and IgM anti-cardiolipin antibodies, detected by a standardized ELISA, were negative. Kaolin clotting time and dilute Russel's viper venom time were within normal limits.

The patients underwent a brain magnetic resonance imaging (MRI) using a conventional 1 T MR imager Magnetom (Siemens, Erlangen) by standard spin-echo techniques (transverse slices, 5 mm thick, with axial orientation). T1-weighted ($TR/TE = 600/15$), proton-density ($TR/TE = 3000/25$) and T2-weighted images ($TR/TE = 3000/90$) were assessed. No abnormalities were found on the MRI (Figure 1).

Brain SPECT was performed by a rotating single-head γ camera system (Elscint, Haifa, Israel) equipped with a high-resolution parallel-hole collimator, 30 min after intravenous administration of 740 Mbq of 99m Tc-ethyl cysteinate dymer (ECD). Data were acquired in a 64×64 matrix through 360° rotation at 6° intervals, for 30 s per arc interval. Approximately 8 million counts were acquired. Data storage and reconstruction of transaxial, sagittal and coronal slices was

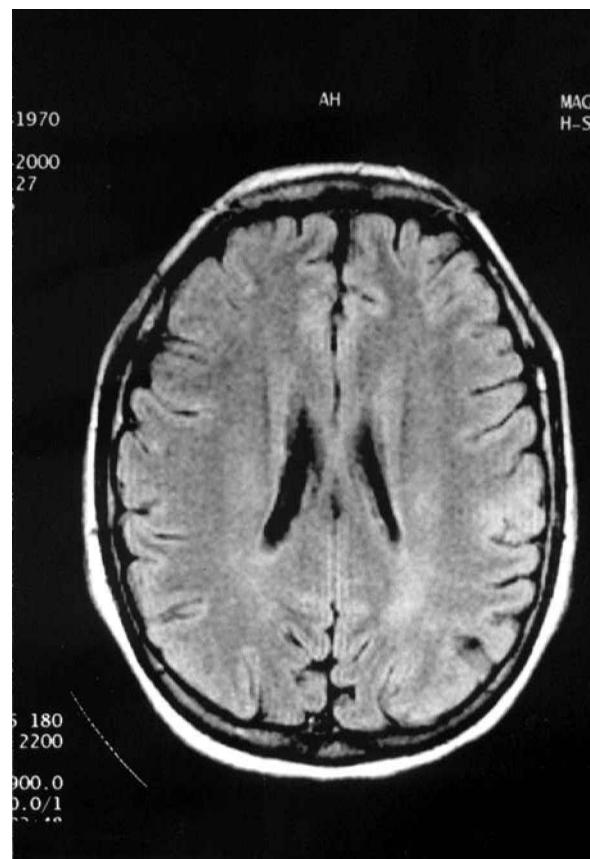


Figure 1 MRI picture shows no brain morphological abnormalities.

performed along the orbitomeatal line using a computer system (Micro Delta-Max Delta) coupled to the γ camera on a 64×64 matrix. The brain was subdivided into six circular regions of interest (ROIs) for each hemisphere: frontal, temporal, parietal, occipital, basal ganglia and cerebellum. Areas of hypoperfusion were considered pathological when abnormal uptake was present in almost six slices and their anatomical sites were recorded. The SPECT scan showed diffuse uptake defects and hypoperfusion areas in the right and left frontal-parietal regions (Figure 2).

The patient was discharged with unchanged steroid and hydroxychloroquine treatment and followed-up in our outpatient clinic. Although she did not present signs of lupus flare, she continued complaining of the persistence of memory loss.

In February 2000 the patient developed severe Raynaud's phenomenon with initial cutaneous dystrophic lesions. She was then readmitted and received treatment with intravenous infusion of Iloprost (1.5 ng/kg/min per 6 h/day for 10 days consecutively). Her baseline treatment was unchanged. On review 1 month later the patient was noted to have a dramatic improvement on her cognitive function. A second brain SPECT examination was then carried out, showing the presence of a small focal uptake defect confined to the left occipital region (Figure 3). A third SPECT scan performed 8 months after Ilo-

prost infusion course did not reveal any perfusion defects and was completely normal (Figure 4). The brain MRI remained normal. A repeat neuropsychological evaluation was completely normal.

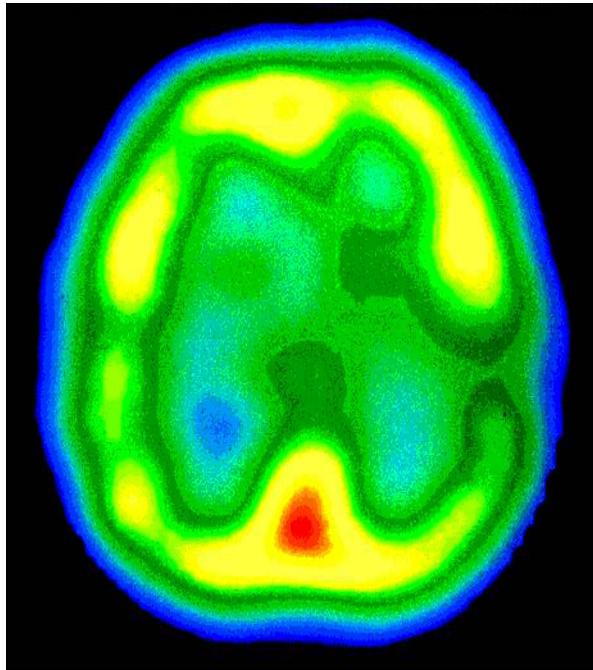


Figure 2 Baseline 99m Tc-ECD brain SPECT scan shows diffuse uptake defects and hypoperfusion areas in the right and left frontal-parietal region.

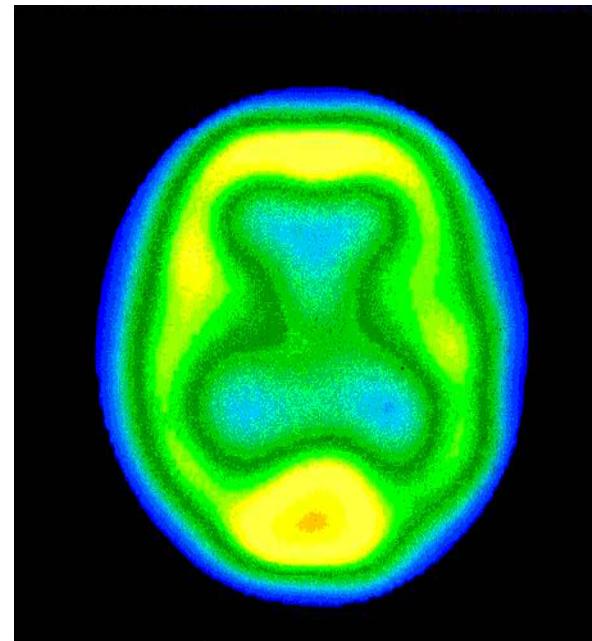


Figure 3 99m Tc-ECD brain SPECT scan 1 month after Iloprost infusion: presence of a small focal uptake defect confined to the left occipital region.

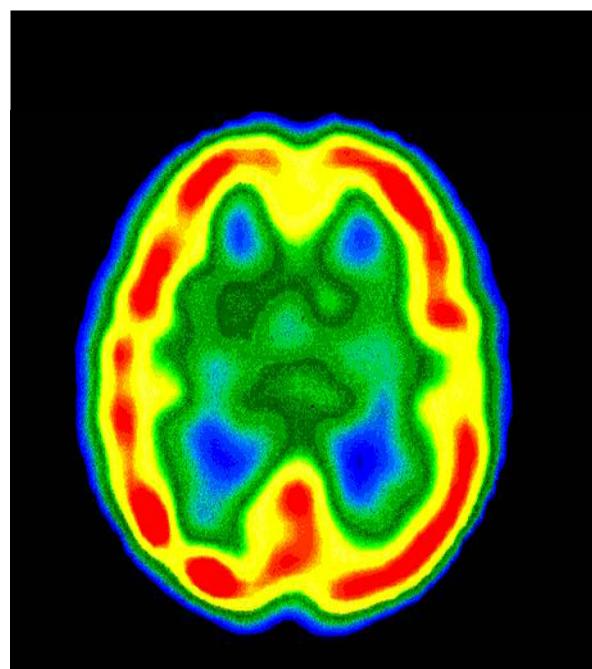


Figure 4 99m Tc-ECD brain SPECT scan 8 months after Iloprost infusion: no perfusion defects are detectable.

Discussion

Many factors might be involved in central nervous system (CNS) hypoperfusion, probably in relation to microcirculatory functional abnormalities and neuronal metabolic changes. Among these abnormalities a cerebral vasospasm can play a role, at least in the category of SLE patients suffering from Raynaud's phenomenon.

Ferraccioli *et al*¹⁸ have recently reported about the appearance of CNS vasospastic features in patients affected from SLE and Raynaud's phenomenon. They showed that after a cold stressor test, perfusion defects were detected in two SLE patients with Raynaud's syndrome who had no baseline defects. Seven patients, also with SLE and Raynaud's syndrome, who had defects at the baseline showed worsening of them after the cold test. On the other hand, no SLE patients without Raynaud's syndrome showed any response to the cold test. In this study the authors gave evidence that vasospasm may occur indeed in the CNS and can be detected by means of SPECT analysis.

Our group¹³ described the high occurrence of NPM and SPECT abnormalities in patients suffering from SLE and Raynaud's phenomenon. In this study, patients with SLE and Raynaud's syndrome had marked SPECT abnormalities, overt neuropsychiatric signs and active neuropsychiatric symptoms when compared with patients without Raynaud's syndrome. Our data suggest that abnormal vascular reactivity could be linked with CNS involvement in SLE.

Evidence of clinical benefit of Iloprost treatment in patients suffering from peripheral ischaemia in course of different conditions, like Raynaud's phenomenon, thromboangiitis obliterans and atherosclerosis are known, as well its efficacy in the pulmonary hypertension secondary to connective tissue diseases.¹⁹

There is no reports in the literature regarding the use of Iloprost in patients with CNS hypoperfusion, only some evidence has emerged from animal model studies. Egemen *et al*²⁰ showed resolution of cerebral vasospasm and protection of endothelial damage, suggesting a prophylactic effect of Iloprost in the prevention of chronic cerebral vasospasm in dogs. Keskil *et al*²¹ showed evidence of a potent antagonistic effect of Iloprost against endothelin-1 induced cerebral vasospasm in the rabbit as evaluated by angiography, light microscopy and electron microscopy.

This case reports for the first time the efficacy of Iloprost in a patient with SLE suffering from severe cognitive dysfunction and cerebral hypoperfusion probably secondary to hyporeactivity of the cerebral endothelium. In this particular case, Iloprost given as

treatment for Raynaud's syndrome proved of clinical benefit with the consequent impact as a possible therapeutic option in patients with SLE and functional CNS involvement. However, although the clinical improvement was prompt, SPECT imaging was not completely normal until 8 months after the treatment. These findings suggest that vasodilation alone has only a small part to play in the mechanism by which Iloprost improved cerebral perfusion, in view of its short half-life. Although the use of Iloprost alone cannot explain the sustained improvement seen in this patient, it is well known that this drug is able to maintain Raynaud's remission.²²⁻²⁴

Several mechanisms by which Iloprost could exert its clinical efficacy have been advocated. Among them vasodilatation and inhibition of platelet aggregation are certainly important, but they are transient. It has also been recently suggested that Iloprost can be effective in the long-lasting modulation of the cytokine network.

Della Bella *et al*²⁶ compared the long-term effects of intermittent infusion of Iloprost with those of oral nifedipine on the *in vitro* production of cytokines in patients with systemic sclerosis (SSc) and found that the production of IL-1- β was significantly lower in the Iloprost group than in the nifedipine group.

It has also been showed that Iloprost is effective in decreasing the expression of adhesion molecules on phagocytes in patients suffering from peripheral arterial occlusive disease and/or from skin ulcers due to systemic sclerosis. Mazzone *et al*²⁷ demonstrated a significant decrease in the expression of the α M β 2 integrin adhesion receptor after Iloprost infusion, confirming that the drug modifies the expression of an integrin that play a key role in leukocyte–endothelium interactions in the course of inflammation and thrombosis.

This case showed clinical benefit of Iloprost, suggesting for the first time its potential usefulness as a therapeutic option in patients with SLE and functional CNS involvement. Further controlled studies are needed to assess the use of Iloprost in these patients.

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