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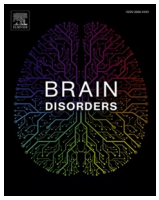

Early clinical, radiological and EEG improvement following L-arginine infusion in SMART syndrome

Arpan R. Mehta [a,b,*], Dermot H. Mallon [a,c], Jeremy H. Rees [a,c]

[a] National Hospital for Neurology and Neurosurgery, Queen Square, University College London Hospitals NHS Foundation Trust, United Kingdom
[b] Anne Rowling Regenerative Neurology Clinic, University of Edinburgh, United Kingdom
[c] Queen Square Institute of Neurology, University College London, United Kingdom

A B S T R A C T

Objectives: To report the clinical, radiological (MRI) and neurophysiological (EEG) changes in a case of SMART (stroke-like migraine attacks after radiation therapy) syndrome following treatment with intravenous L-arginine.
Methods: A 60-year-old woman had, ten years prior, been diagnosed with primary CNS diffuse large B cell lymphoma, and was successfully treated with curative chemotherapy and whole brain radiotherapy. She presented acutely with left-sided headache, teichopsia and dysphasia following a chest infection. MRI of the brain showed striking left parieto-occipital gyral swelling, diffusion restriction, leptomeningeal enhancement, and increased cerebral blood volume. Her EEG showed an excess of slow activity diffusely, particularly over the left temporal lobe. A diagnosis of SMART syndrome was made. Intravenous L-arginine (0.5 g/kg) was administered.
Results: A few hours post infusion, her migrainous headache subsided and her mentation improved. Her MRI brain performed six days post infusion showed reduced cortical swelling and hyperperfusion, and her EEG showed less temporal slowing. She continued to improve cognitively.
Discussion: This is the first report of SMART syndrome with a response to L-arginine, reflected clinically by a measurable improvement in cognition, brain perfusion and EEG parameters, encouraging further clinical studies.

A 60-year-old right-handed woman presented with a few days of left-sided headache, teichopsia and dysphasia following a chest infection. Ten years prior, she had rapidly progressive left-sided sensorimotor loss, brainstem symptoms and confusion, owing to primary CNS multifocal diffuse large B cell lymphoma, associated with right cerebral hemispheric focal slowing on EEG. She successfully received curative MATRIX chemotherapy (high dose methotrexate, cytarabine and rituximab), followed by whole brain radiotherapy (40 Gy in 22 fractions over 4.5 weeks). She subsequently developed idiopathic Parkinson's disease (confirmed by DaT scan) and had a history of psychotic depression. Prior to her present illness, she had some cognitive impairment, with a Mini Mental State Examination (MMSE) score of 28/30. She was on co-careldopa and rivastigmine.

On examination, higher mental function testing revealed anomia, ideational and ideomotor apraxia, dyscalculia, finger agnosia, right-left disorientation, and an MMSE of 5/30. She had conduction aphasia. She was disorientated to place and was unable to follow 2-step commands. She had broken smooth pursuit, and a right homonymous hemianopia, associated with decreased right-sided sensation. Right-sided tone and power were normal, despite pathologically brisk reflexes, with rigidity present on the left, consistent with her Parkinson's disease.

MRI of the brain showed prominent left parieto-occipital gyral swelling, diffusion restriction, leptomeningeal enhancement, and increased cerebral blood volume (rCBV; Fig. 1A-D). Her EEG showed an excess of slow activity diffusely, particularly over the left temporal lobe (Fig. 1E).

A diagnosis of SMART syndrome was made (stroke-like migraine attacks after radiation therapy). Intravenous L-arginine (0.5 g/kg) was administered. A few hours later, her migrainous headache subsided and her mentation improved. The next day, she still found it difficult to read, and had ongoing difficulty with two-stage commands. Three days post-infusion, her MMSE score had improved to 15/30. Six days post-infusion, her MRI brain showed reduced cortical swelling and hyperperfusion (Fig. 2A-D). Eleven days post-infusion, her EEG showed less temporal slowing (Fig. 2E). She was now able to follow two-step commands, read, write and name, and her topographical memory had returned. Her MMSE improved further to 24/30, with residual deficits in attention, calculation, recall and language. She was discharged on oral L-arginine (500 mg daily).

SMART syndrome is a rare, delayed complication of brain radiotherapy of unknown cause, characterised by a rapid onset of complex neurological impairment unrelated to tumour recurrence or ischaemic

* Corresponding author: Dr Arpan R. Mehta, National Hospital for Neurology & Neurosurgery, Queen Square, London WC1N 3BG, United Kingdom.
E-mail address: amehta@exseed.ed.ac.uk (A.R. Mehta).

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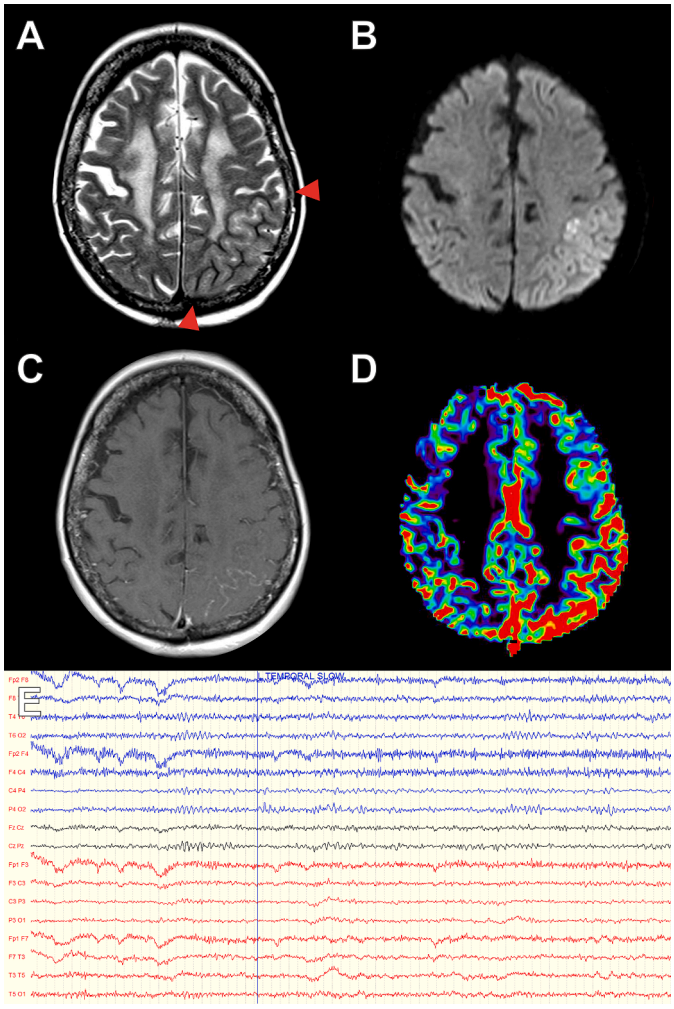

Fig. 1. Pre L-arginine infusion radiological and EEG data. The left parietal and occipital lobes were swollen on T2-weighted imaging (A) and hyperintense on diffusion weighted imaging (B). Post-gadolinium T1-weighted imaging showed leptomeningeal enhancement (C). (D) There was evidence of hyperperfusion on the dynamic susceptibility contrast cerebral blood volume map (rCBV of 1.7 relative to the right striatum). (E) 18-channel digital EEG trace (longitudinal bipolar montage; red channels are left and blue channels are right hemispheric) shows an excess of slow (delta) activity diffusely, particularly over the left temporal lobe (bottom 4 channels). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

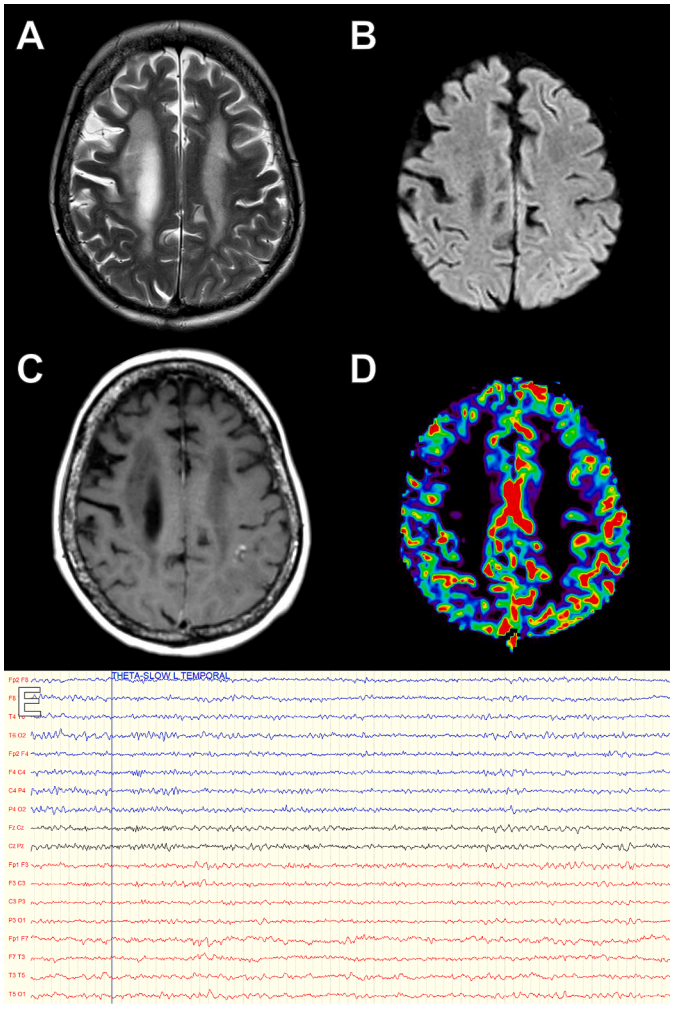

Fig. 2. Post L-arginine infusion radiological and EEG data. Repeat imaging performed 6 days later showed improvement in the left parietal and occipital swelling on T2-weighted imaging (A), regression of the diffusion-weighted hyperintensity (B), almost complete resolution of the leptomeningeal enhancement (C) and reduction in the hyperperfusion on the dynamic susceptibility contrast cerebral blood volume map (D; rCBV of 1.1 relative to the right striatum). (E) EEG trace shows a reduction in the degree of left temporal slowing (fragmentary theta, which is less abnormal than pre-infusion). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

infarcts. Recovery may be incomplete. The interval between radiotherapy and the onset of sympoms of SMART syndrome can range from 1 to 35 years. The hallmark features on MRI are reversible abnormal signal on T2/FLAIR (fluid attenuated inversion recovery) sequences, associated with post-gadolinium cortical/leptomeningeal enhancement, which persist for weeks to months. Perfusion imaging usually shows high rCBV [1–3].

This is the first report of SMART syndrome with a dramatic response to intravenous L-arginine, reflected clinically by a measurable improvement in her MMSE, perfusion and EEG abnormalities, drawing parallels with MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes) syndrome [4]. One other report described a probable acute case of SMART syndrome with reversible cerebral hypoperfusion on CT perfusion treated with L-arginine 6-hours post-onset, but MRI perfusion was not performed [5].

Contributorship

ARM and JHR contributed to the diagnosis and treatment of this patient. DHM contributed neuroimaging expertise. ARM wrote the first draft and all authors approved the final manuscript.

Research ethics and informed consent

Written informed consent from both the patient and her next of kin was obtained both during the course of her treatment and also prior to submission of this manuscript. No research ethics approval was required.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] D.F. Black, J.D. Bartleson, M.L. Bell, et al., SMART: stroke-like migraine attacks after radiation therapy, Cephalalgia 26 (9) (2006) 1137–1142, https://doi.org/10.1111/j.1468-2982.2006.01184.x [published Online First: 2006/08/22].

[2] A. Shuper, R.J. Packer, L.G. Vezina, et al., Complicated migraine-like episodes' in children following cranial irradiation and chemotherapy, Neurology 45 (10) (1995) 1837–1840, https://doi.org/10.1212/wnl.45.10.1837 [published Online First: 1995/10/01].

[3] M. Kosmin, J. Rees, Radiation and the nervous system, Pract. Neurol. 22 (6) (2022) 450–460, https://doi.org/10.1136/pn-2022-003343 [published Online First: 2022/08/23].

[4] A.W. El-Hattab, M. Almannai, F. Scaglia, Arginine and citrulline for the treatment of MELAS syndrome, J. Inborn. Errors Metab. Screen 5 (2017), https://doi.org/10.1177/2326409817697399 [published Online First: 2017/07/25].

[5] K. Wai, A. Balabanski, N. Chia, et al., Reversible hemispheric hypoperfusion in two cases of SMART syndrome, J. Clin. Neurosci. 43 (2017) 146–148, https://doi.org/10.1016/j.jocn.2017.05.013 [published Online First: 2017/06/25].