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Brain perfusion alterations in tick-borne encephalitis—preliminary report

Zuzanna Tyrakowska-Dadełło[a,b,*], Eugeniusz Tarasów[a,b], Dariusz Janusek[c], Anna Moniuszko-Malinowska[d], Joanna Zajkowska[d], Sławomir Pancewicz[d]

[a] Department of Radiology, Medical University of Bialystok, Bialystok, Poland
[b] TMS Diagnostyka, Bialystok, Poland
[c] Nalecz Institute of Biocybernetics and Biomedical Engineering, Polish Academy of Sciences, Warsaw, Poland
[d] Department of Infectious Diseases and Neuroinfections, Medical University of Bialystok, Bialystok, Poland

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ABSTRACT

Background: Magnetic resonance imaging (MRI) changes in tick-borne encephalitis (TBE) are non-specific and the pathophysiological mechanisms leading to their formation remain unclear. This study investigated brain perfusion in TBE patients using dynamic susceptibility-weighted contrast-enhanced magnetic resonance perfusion imaging (DSC-MRI perfusion).
Methods: MRI scans were performed for 12 patients in the acute phase, 3–5 days after the diagnosis of TBE. Conventional MRI and DSC-MRI perfusion studies were performed. Cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT), and time to peak (TTP) parametric maps were created. The bilateral frontal, parietal, and temporal subcortical regions and thalamus were selected as regions of interest. Perfusion parameters of TBE patients were compared to those of a control group.
Results: There was a slight increase in CBF and CBV, with significant prolongation of TTP in subcortical areas in the study subjects, while MTT values were comparable to those of the control group. A significant increase in thalamic CBF ($p < 0.001$) and increased CBV ($p < 0.05$) were observed. Increased TTP and a slight reduction in MTT were also observed within this area.
Conclusions: The DSC-MRI perfusion study showed that TBE patients had brain perfusion disturbances, expressed mainly in the thalami. These results suggest that DSC-MRI perfusion may provide important information regarding the areas affected in TBE patients.

Introduction

Tick-borne encephalitis (TBE) is an acute meningoencephalitis with or without myelitis caused by an RNA flavivirus (TBEV), transmitted by *Ixodes* spp. ticks (Lindquist and Vapalahti, 2008; Suss, 2008). In endemic areas, TBE has an incidence of 1.2 per 100 000, and mortality in Europe ranges between 0.5% and 4% (Günther and Haglund, 2005). Pathological magnetic resonance imaging (MRI) changes in the course of TBE are non-specific and only evident in up to 18% of patients (Horger et al., 2012; Lorenzl et al., 1996; Marjelund et al., 2004). Pathophysiological mechanisms leading to these radiological findings remain unclear. Some publications have indicated that changes in TBE and long-term effects may be associated with blood flow, perfusion, and metabolism disturbances (Lee et al., 2004; Kao et al., 1994).

Dynamic susceptibility-weighted contrast-enhanced magnetic resonance perfusion imaging (DSC-MRI perfusion) is a powerful, commonly used technique that provides important information regarding cerebral haemodynamics. DSC-MRI perfusion has been widely applied to diagnose and grade central nervous system (CNS) tumours, differentiate between various brain tumour types, distinguish tumour recurrence from radiation necrosis, and evaluate the response to therapy (Griffith and Jain, 2016). DSC perfusion is a widely accepted technique to identify the presence of perfusion abnormalities in patients with acute ischemic brain stroke (Khalil et al., 2017). Perfusion imaging can also be used to study the progression of lesions in multiple sclerosis or perfusion changes in several degenerative diseases of the CNS such as Alzheimer's disease (Eskildsen et al., 2017; Peruzzo et al., 2013). DSC perfusion may also serve as a useful additional tool in the

* Corresponding author at: Department of Radiology, Medical University of Bialystok, Sklodowskiej 24a St, 15-276 Bialystok, Poland.
E-mail address: zuza1405@op.pl (Z. Tyrakowska-Dadełło).

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differentiation of infectious from neoplastic brain lesions (Floriano et al., 2013).

No DSC-MRI perfusion studies in patients with TBE have yet been reported in the literature. The aim of this study was to evaluate MRI brain lesions in patients in the acute phase of TBE combined with the presence of perfusion disorders assessed by DSC-MRI perfusion.

Materials and methods

Study group

Twelve patients (six male, six female) aged 31–58 years (mean age 48.0 ± 9.5 years) in the acute phase of the disease were included in this study. The diagnosis of TBE was based on the clinical presentation, serum and cerebrospinal fluid (CSF), and laboratory and serological test results.

The clinical presentation of TBE was defined as (1) meningitis, i.e. patients without focal neurological symptoms; or (2) meningoencephalitis, i.e. patients with meningitis and focal neurological symptoms, a disturbance of consciousness, and/or other brain disorders (Kaiser, 1999).

Control group

The control group comprised 10 healthy individuals (five male, five female) who were matched for age and sex ($p > 0.05$); their mean age was 45.5 ± 10.5 years. Subjects with organic CNS damage confirmed on routine neurological and MRI examinations were excluded.

Methods

Antibodies against TBE in serum and CSF were determined by enzyme-linked immunosorbent assay (ELISA; Virion/Serion, Wurzburg, Germany).

MRI examinations were performed using a 3.0 T scanner (Titan; Toshiba Medical, Japan) with a 32-channel phased-array head coil. The imaging protocol included the following conventional sequences: (1) axial T2-weighted turbo spin echo (TSE) sequence: echo time (TE)/repetition time (TR) = 84/5500 ms, flip-angle (FA) = 90°, field-of-view (FOV) = 240 × 240 mm, matrix = 386 × 320; slice thickness = 5 mm; (2) axial fluid attenuated inversion recovery sequence with fat saturation (FLAIR FSat): TE/TR = 15/8000 ms, inversion time (TI) = 2700 ms, FOV = 240 × 240 mm, matrix = 256 × 224; slice thickness = 5 mm; (3) axial three-dimensional T1-weighted field echo (3D FE) sequence: TE/TR = 4.6/10 ms, FA = 8°, FOV = 240 × 240 mm, matrix = 256 × 256, 180 slices with 2 mm slice thickness; (4) axial diffusion-weighted (DWI) sequence, single-shot echo planar imaging: TE/TR = 90/5000 ms, FA = 90°, FOV = 240 × 240 mm, matrix = 160 × 192; slice thickness = 5 mm, with b values of 0 and 1000 s/mm^2; (5) sagittal T1-weighted spin echo inversion recovery (SE IR) sequence: TE/TR = 15/2150 ms, TI = 950 ms, FA = 90°, FOV = 240 × 240 mm^2, matrix = 320 × 256, slice thickness = 5 mm.

DSC-MRI perfusion was performed with an axial field echo-echo planar imaging (FE-EPI) sequence with the following parameters: TE/TR = 30/2000 ms, FA = 90°, FOV = 240 × 240 mm, matrix = 96 × 96, with 10 slices, 5-mm thickness.

Twenty millilitres of the contrast medium gadobutrol (Gadovist 1 mmol/ml; Bayer Pharma AG, Leverkusen, Germany) was administered with an intravenous automatic injection MR system (Medrad, Spectris Solaris; Bayer Healthcare, Medrad Europe BV) at a rate of 3 ml/s, followed by a 20-ml saline flush with a rate of 2 ml/s. A total of 300 dynamic T2*-weighted images were acquired with the contrast injection, starting at the 10th image.

A post-contrast axial 3D FE T1-weighted sequence was acquired 10 min after intravenous injection of the contrast medium, as described above.

DSC data analysis

DSC images were processed using Olea Sphere software (Medical SAS, France). The arterial input and venous output functions were selected automatically using a cluster analysis algorithm, and the deconvoluted perfusion parameters were calculated using the oscillation index cSVD (singular value decomposition, oSVD) technique. Parametric maps of cerebral blood flow (CBF), cerebral blood volume (CBV), time to peak (TTP), and mean transit time (MTT) were generated and used for the qualitative and quantitative analyses. The quantitative analysis was performed using a region-of-interest (ROI)-based analysis, using FLAIR images for the identification of anatomical landmarks.

A total of eight 50–100 mm^2 ROI were placed symmetrically in both hemispheres of the brain in normal-appearing grey and white matter regions, i.e. without any focal lesions: subcortical frontal, subcortical parietal, subcortical medial temporal, and dorsal thalamus.

Statistical analysis

The arithmetic mean was calculated for the quantitative variables and the standard deviation (SD) was used as a measure of scatter. The Mann–Whitney *U*-test for differences and Spearman's rank correlation test were used in this study. A *p*-value of ≤ 0.05 was considered statistically significant for all analyses.

Results

Clinical data

The mean duration of the disease before hospitalization was 3.6 ± 1.2 days, while the average duration of hospitalization was 13.5 ± 3.0 days. Among the most common symptoms were fever ($n = 12$; 100%), headache ($n = 12$; 100%), vertigo ($n = 4$; 33.3%), nausea ($n = 8$; 66.7%), and vomiting ($n = 6$; 50%). Weakness, consciousness disorders, drowsiness, and visual disturbances were also confirmed in individual cases. Meningeal signs, i.e. neck stiffness, Kernig's sign, and Brudzinski's sign, were observed in all patients (100%). Moreover, other neurological symptoms were reported: focal signs ($n = 2$; 16.7%), sensory impairment ($n = 4$; 33.3%), pyramidal signs ($n = 2$; 16.7%), and cranial and peripheral nerves disorders ($n = 1$; 8.3%). Eight patients (66.7%) were diagnosed with meningitis and four (33.3%) with meningoencephalitis (Kaiser, 1999).

Peripheral blood examinations revealed leukocytosis ($>10 \times 10^9$ leukocytes/l) in eight of the patients examined (66.7%), an elevated erythrocyte sedimentation rate (ESR; >20 mm/h) in six (50%), and raised C-reactive protein (CRP; >6.0 mg/l) in nine (75%). CSF examination revealed pleocytosis in the initial phase of TBE amounting to 122.5 ± 69.2 cells/mm^3 (with a percentage of lymphocytes of 59.2 ± 22.8%), a protein concentration of 73.96 ± 44.09 mg/dl, and a glucose concentration of 64.7 ± 6.7 mg/dl.

Serum IgM and IgG antibodies against TBEV were detected in nine (75%) and six (50%) patients, respectively. In CSF, IgM class antibodies were present in 10 patients (83.3%) and IgG in six (50%) patients.

There were no statistically significant differences in laboratory or serological tests results between patients with meningitis and patients with meningoencephalitis, except for the protein