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Original Article

Increased working memory related fMRI signal in children following Tick Borne Encephalitis

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ABSTRACT

Objective: Tick Borne Encephalitis (TBE) is a viral infection in the central nervous system endemic in Europe and Asia. While pediatric infection may carry a lower risk for serious neurological sequelae compared to adults, a large proportion of children experience long term cognitive problems, most markedly decreased working memory capacity. We explored whether task related functional magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) could reveal a biological correlate of status-post TBE in children.
Methods: We examined 11 serologically verified pediatric TBE patients with central nervous system involvement with 55 healthy controls with working memory tests and MRI.
Results: The TBE patients showed a prominent deficit in working memory capacity and an increased task related functional MRI signal in working memory related cortical areas during a spatial working memory task performed without sedation. No diffusion differences could be found with DTI, in line with the reported paucity of anatomical abnormalities.
Conclusion: This study is the first to demonstrate functional MRI abnormalities in TBE patients that bears similarity to other patient groups with diffuse neuronal damage.

1. Introduction

TBE is a vector born disease endemic in areas throughout Europe and Asia that may cause meningoencephalitis in children and adults.[1] For the European TBEv subtype, the course is biphasic in 75–85% of cases with CNS symptoms developing after an initial phase with influenza-like symptoms.[1,2] The severity of the CNS symptoms varies from mild meningitis to severe encephalitis and the mortality rate is reported to be 0.5–2% for the European subtype.[3,4]

TBEv-infection is described to have a milder clinical course in children and myelitis which has a poor prognosis in adults is rarely seen during TBEv infection in children.[5–8] This has led to an assumption that children are less affected by TBE than adults. However, in recent years, reports of long term cognitive problems after infection with TBEv in pediatric patients have surfaced. Studies show mild to moderate cognitive and learning deficits in the absence of focal neurological findings.[9,10] We also recently demonstrated that a large proportion of children experience an incomplete recovery following TBE with CNS involvement, with residual problems

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Abbreviations

TBE	Tick Borne Encephalitis
TBEv	Tick Borne Encephalitis Virus
BOLD	Blood Oxygen Level Dependent
DTI	Diffusion Tensor Imaging
WM	Working Memory
GLM	General Linear Model

such as cognitive problems, headache, fatigue and irritability.[11] This corresponds to findings in the adult population[12] and indicates that the clinical course in the acute phase is a poor predictor of long-term outcome.

On detailed neuropsychological testing, deficits have been shown to be prominent in Working Memory (WM) with a normal performance in reasoning, processing speed and verbal comprehension.[11] Despite these findings, no clear clinical, laboratory or radiological correlates to later deficits have been reported.

In order to direct medical or psychological interventions with the aim of preventing or mitigating later cognitive problems it is of greatest importance to understand the neural mechanisms underlying the symptoms.

Only a few case reports have studied MRI findings associated with the acute phase of the disease, with thalamic involvement being the most commonly reported.[13,14] However, it appears from the scarce data available that structural pathology is only present in a limited number of children and may only partly correlate to later cognitive symptoms.[11,15] From the non-focal nature of the symptoms one would expect any structural underpinnings to be distributed and subtle in nature and possibly not be detected in standard clinical radiological evaluations.

WM function is known to increase during development and is associated with fMRI Blood Oxygen Level Dependent (BOLD) signal in parietal and pre-frontal cortical areas while performing a WM task.[16–18] Furthermore, white matter structure in tracts connecting parietal and prefrontal cortices measured with DTI also correlates with the WM associated BOLD signal in these areas.[19]

In order to explore and characterize changes in the networks underlying WM function among pediatric TBE patients we therefore performed WM related fMRI and DTI scanning in a cohort of children who went through TBE.

2. Patients and methods

Children were recruited from Astrid Lindgren Children's Hospital in Stockholm as a part of a larger cohort study to study the long term outcome of children with TBE.[11] The study was reviewed and approved by the ethical board of Astrid Lindgren Children's Hospital. As TBEv infection is a reportable disease in Sweden, all children (0–17 years old) with TBEv infection from 2004 to 2008 were identified at the local Swedish Institute for Communicable Disease Control in Stockholm. Medical records were studied retrospectively and in order to only include TBEv infections with CNS involvement the inclusion criteria were: 1) children aged 4 weeks to 17 years 2) febrile illness and clinical symptoms of meningitis (headache, nuchal rigity, nausea/vomiting) or encephalitis (altered mental status, focal neurological signs, seizures, EEG changes) 3) significant titers of specific TBEv antibodies IgM/IgG in serum (analyzed by Enzyme immunoassay in local, accredited laboratories) and 4) lumbar puncture with pleocytosis ($\geq 6 \times 106$/L) or confirmed CNS involvement by other methods (i.e. EEG, CT/MRI or presence of symptoms of CNS involvement such as encephalopathy, focal neurological symptoms or seizures). Within this group 17 patients were invited for an MRI examination, out of which 13 responded positively and attended MRI scanning. Among the scanned patients two had to be excluded due to dental bracer artifacts. This resulted in 11 patients with usable MRI data. These patients had a mean age of 12 ± 2years. The mean time that had passed since the acute phase of illness was 3.8 ± 1.4 years. Patient data is summarized in Table 1.

55 age matched individuals participating in a larger longitudinal study of healthy brain development[20] were included. These individuals were scanned in the same scanner using the same sequences and fMRI stimulus.

MRI scanning was carried out on a 1.5 T Siemens scanner. The scan aimed to analyze DTI as well as fMRI as these have previously been found to be tied to cognitive development in childhood.[21] The stimulus during the fMRI consisted of 2 sessions of 4 min and 54 s during which the subjects were instructed to remember the positions of a sequence of dots on a 4×4 grid and subsequently confirm or deny a statement on the position of one of the dots. The trials were divided into levels consisting of either 2 or 4 dots. For the current study these levels were combined to study the effect related to WM. A control condition without WM load was also included. In this condition the dots were of a blue color and always presented in the corners. The subjects was instructed prior to the scanning that the blue dots should always be answered with 'no'. No sedation was used during MRI scanning. The fMRI sequence consisted of T1* echo-planar imaging volumes TR = 3000, TE = 50 ms was gathered with a 20×220 FOV, 64×64 grid and a voxel size of $3.44 \times 3.44 \times 4.5$ mm. After motion correction and normalization a General Linear Model (GLM) analysis was carried out. In the first level, single subject analysis a linear model was fit to each voxel. A block design was used. Each block was defined as the onset of showing the sequence of dots and to end when the subsequent question was displayed. The block thus included the presentation of the stimulus and the following delay. During this time the subjects had to keep the sequence in their WM. Only trials where the subjects gave a correct response were included in the regressors. The block design was then convolved with the canonical hemodynamic response function. The regressor for the control condition was constructed in the same manner. A contrast map was calculated between the WM regressor and the control regressor for each subject. Additional regressors that were used were the temporal derivative of the WM and control conditions as well as the movement parameters derived from the realignment.

The DTI sequence consisted of a field of view of 230×30 mm, 128×128 grid, 1 mm3 voxels and 20 gradient directions. Data was corrected for eddy currents and