International Journal of Infectious Diseases 51 (2016) 73–77

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Short Communication

Cerebral glucose hypometabolism in Tick-Borne Encephalitis, a pilot study in 10 Patients

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ARTICLE INFO

Article history:
Received 29 March 2016
Received in revised form 12 June 2016
Accepted 28 June 2016

Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
tick borne encephalitis
glucose metabolism
neuroinfection
FDG-PET

ABSTRACT

Background: Tick borne encephalitis (TBE) is an acute meningoencephalitis with or without myelitis caused by an RNA virus from the flavivirus family transmitted by *Ixodes spp* ticks. The neurotropic TBE virus infects preferentially large neurons in basal ganglia, anterior horns, medulla oblongata, Purkinje cells and thalamus. Brain metabolic changes related to radiologic and clinical findings have not been described so far.

Methods: Here we describe the clinical course of 10 consecutive TBE patients with outcome assessment at discharge and after 12 month using a modified Rankin Scale. Patients underwent cerebral MRI after confirmation of diagnosis and before discharge. ^{18}F-FDG PET/CT scans were performed within day 5 to day 14 after TBE diagnosis. Extended analysis of coagulation parameters by thrombelastometry (ROTEM® InTEM, ExTEM, FibTEM) was performed every other day after confirmation of TBE diagnosis up to day 10 after hospital admission or discharge.

Results: All patients presented with a meningoencephalitic course of disease. Cerebral MRI scans showed unspecific findings at predilection areas in 3 patients. ^{18}F-FDG PET/CT showed increased glucose utilization in one patient and decreased ^{18}F-FDG uptake in seven patients. Changes in coagulation measured by standard parameters and thrombelastometry were not found in any of the patients.

Discussion: Glucose hypometabolism was present in 7 out of 10 TBE patients reflecting neuronal dysfunction in predilection areas of TBE virus infiltration responsible for development of clinical signs and symptoms.

1. Introduction

Tick-borne encephalitis (TBE) is an acute meningoencephalitis with or without myelitis caused by an RNA flavivirus, transmitted by *Ixodes spp* ticks from western Europe to the eastern coast of Japan[1,2].

Typically TBE has a characteristic biphasic clinical course. After an initial incubation period of a median of 8 days signs and symptoms like fever, fatigue, general malaise, headache and arthralgia occur followed by a symptom-free interval [3–5]. Neurological manifestations hallmark the second stage ranging from mild meningitis with headache, to severe meningoencephalitis with impaired consciousness, epileptic seizures and, in severe cases, coma[3]. About 10% of all patients develop a meningoencephalomyelitis with acute flaccid paralysis and respiratory insufficiency requiring assisted ventilation[3]. The grade of severity in this acute phase is associated with poor outcome. Overall, up to 46% of patients suffer from long-term sequelae, such as headache, memory impairment, tremor or ataxia one year after TBE [4,5], with moderate to severe impairment of life quality in up to 30% of patients [4].

MRI studies[3,6–8] and histopathological examinations[9–14] suggest an affinity of the TBE virus for certain regions of the

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http://dx.doi.org/10.1016/j.ijid.2016.06.022

central nervous system including thalamus, basal ganglia, cerebellum and brainstem with associated neurological signs and symptoms such as tremor, ataxia, paresis and rigidity of extremities. However, changes in cerebral MRI are only evident in up to 18% of patients with TBE [3,6–8]. Pathophysiologic mechanisms leading to these clinical or radiological findings still remain unclear.

The two aims of this pilot study were 1) to investigate cerebral metabolic changes in TBE patients using [(18)F]2-deoxy-2-fluoro-D-glucose positron emission tomography (^{18}F-FDG PET) in combination with CT and to correlate these findings to clinical signs and symptoms and outcome. 2) To evaluate subtle coagulation changes by cell based rotational thrombelastometry (ROTEM®).

2. Material and Methods

The study was approved by the IRB of the Medical University of Innsbruck, Austria in (EK 01/2011).

Ten consecutive patients were enrolled prospectively after signing written informed consent when diagnosis of TBE had been confirmed by serological testing as well as RT-PCR with a direct Virus RNA detection in the patient's blood. Patient's clinical course was followed and reported closely according to protocol. Neurological signs and symptoms as well as standard laboratory values including red and white blood cell count, thrombocyte count, standard coagulation parameters (activated partial thromboplastin time, prothrombin time) were monitored according to clinical routine. At time of discharge and 12 months thereafter patients were evaluated by means of a modified Rankin Scale (mRS)[15]. Follow up was performed by telephone interview 12 months after discharge.

2.1. Cerebral MRI Scan

According to the study protocol two 3 Tesla MRI scans (Verio, Siemens, Erlangen, Germany) were performed after confirmation of the diagnosis and before discharge. For further description see Supplementary Material.

2.2. [(18)F]2-deoxy-2-fluoro-D-glucose positron emission tomography (^{18}F-FDG PET/CT)

^{18}F-FDG PET/CT imaging was performed at day 9 (median, range day 5 – 14) after hospital admission respectively day 14 (median, range 6 – 22) after onset of TBE meningoencephalitis characteristic signs and symptoms (onset of second peak in biphasic course of 7 patients and onset of first symptoms in 3 patients presenting without biphasic disease course). ^{18}F-FDG PET/CT scans of the brain were performed, without intravenous contrast application during the CT phase. Image interpretation was independently performed by two experienced nuclear medicine specialists blinded to clinical course and coagulation studies. In each of the 10 patients, regions of interest were defined and characterized according to the intensity of glucose utilization as glucose hypermetabolic or glucose hypometabolic regions, in comparison to the physiologic glucose metabolism of cerebral areas not affected by the disease in PET/CT and MRI. For further description see Supplementary Material.

2.3. Thrombelastometry

Extended analysis of coagulation parameters by thrombelastometry (ROTEM® InTEM, ExTEM, FibTEM) was performed every other day after confirmation of TBE diagnosis until day 10 after hospital admission or until discharge.

2.4. Statistical analysis

Due to the pilot nature of the study and the small number of enrolled patients statistics for ^{18}F-FDG PET/CT and clinical data are descriptive only. Comparisons of MRI perfusion in ROI were performed by Kruskal-Wallis Test with Dunn's post-hoc test. All analyses were performed by Graph Pad Prism 5.

3. Results

3.1. Patient's characteristics, clinical findings and outcome

Ten consecutive patients were enrolled from June 2011 until September 2012, four females and six males with a median age of 65.5 years (range 24 – 79). A detailed description of patient's characteristics and relevant clinical findings as well as outcome is given in Table 1. Only patients with a meningoencephalitic course of the disease were enrolled, whereof in two patients headache was the predominating clinical symptom, but both had moderate to severe EEG findings suggesting encephalitis. In 3 patients a Glasgow Coma Scale $\leq$ 9 during the course of disease in the hospital was reported, one patient necessitated mechanical ventilation due to bilateral paresis of nervus phrenicus. Median time of hospital stay was 17 days (range 7 - 69). Six patients had only mild symptoms without significant disability at discharge, two patients were slightly disabled and unable to carry out all previous activities and one patient was severely disabled, bedridden and required constant nursing care and attention (Table 1). At follow up one year after TBE four patients still reported mild symptoms such as hand tremor, headaches, impaired fine motor skills without disability to carry out all

Table 1
Demographics and clinical features

Patient No.	Sex	Age (years)	First onset (days)	Bimodal Course	Second onset (days)	Leading neurologic signs and symptoms	Time in Hospital (days)	mRS Discharge	mRS Follow up
1	F	25	28	yes	1	Tremor, ataxia	10	1	1
2	F	66	28	yes	7	Ataxia, rigid limb tonus, headache	17	1	na
3	F	29	28	yes	3	Epileptic seizures, cognitiv impairment	24	1	na
4	M	72	21	yes	2	Cognitiv impairment, depression	10	1	0
5	M	72	21	no	3	Gait disorder, headache, somnolence	30	0	0
6	M	80	11	no		Opsoclosnus, myoclonus, coma, non convulsiv status epilepticus, mechanical ventilation	69	5	4
7	F	61	10	yes	1	Rigid limb tonus, cognitiv impairment, desoriented	28	2	1
8	M	66	10	no		Headache, EEG changes	7	2	1
9	M	51	21	yes	7	Headache, EEG changes	14	1	0
10	M	70	14	yes	7	Somnolence, tremor, cognitive impairment	17	1	1

F, female; M, male; First onset (days), Days from first symptom onset until hospital admission; Second onset (days), Days from second symptom onset until hospital admission if disease course was bimodal; mRS, modified Rankin Scale; mRS, Follow Up one year after admission to hospital; na, Patients not assessable for mRS.

usual duties and activities. One patient was still severely disabled, unable to walk without assistance, unable to attend own bodily needs without assistance and unable to attend a normal conversation. Three patients reported no symptoms at all. Two patients were lost for follow up, both had moved back to their country of permanent residence and we failed to contact them in time. However, both patients had shown a mRS 1 at hospital discharge suggesting a further favorable course. Despite the severity of disease all 10 patients survived.

3.2. Routine laboratory Parameters and ROTEM®

The median White Blood Cell Count was expectedly elevated at 10.950/μl (range 7.800 – 17.000/μl), the median hemoglobin level was within the normal range of 134,5 g/l (range 95 – 177 g/l). One patient had decreased thrombocyte count on admission (105.000/μl) and the day after admission (96.000/μl). All other patients had thrombocyte counts within the normal range (150.000 - 400.000/μl) on admission and every other day of routinely performed measurement of thrombocyte cell count. Activated partial thromboplastin time was within normal range (28-40 sec) in all 10 patients (mean on admission 32 ± 3.5 sec, mean overall patients during hospitalization 34.7 ± 4.5 sec). Prothrombin time was within normal range in all 10 patients (mean on admission 94.6 ± 14%, mean overall patients during hospitalization 86 ± 11.2%; normal range 70-120%, INR 1.0 – 1.3).

EXTEM, INTEM and FIBTEM every other day until day 10 of hospitalization revealed no significant impairment of coagulation (detailed data not shown). In six patients FIBTEM showed elevated maximal clot firmness due to hypofibrinogenemia.

3.3. ^{18}F-FDG PET/CT

One patient showed increased glucose utilization in the right cerebellar hemisphere (figure 1). 6 patients showed decreased ^{18}F-FDG uptake in different brain regions such as bifrontal, fronto-temporal left, temporopolar left, temporoparietal left, bitempor-obasal, hippocampal left. One patient showed global decreased ^{18}F-FDG uptake, however this patient has been intubated and analgosedated previously to the scan. In 2 patients, no change of ^{18}F-FDG uptake was seen on ^{18}F-FDG PET/CT (detailed data shown in Table 2, Supplementary Material).

3.4. MRI findings

Corresponding to literature MRI findings on admission were uncharacteristic with diffuse and unspecific signal alterations in the nucleus caudatus (n = 1), putamen (n = 1), nucleus dentatus

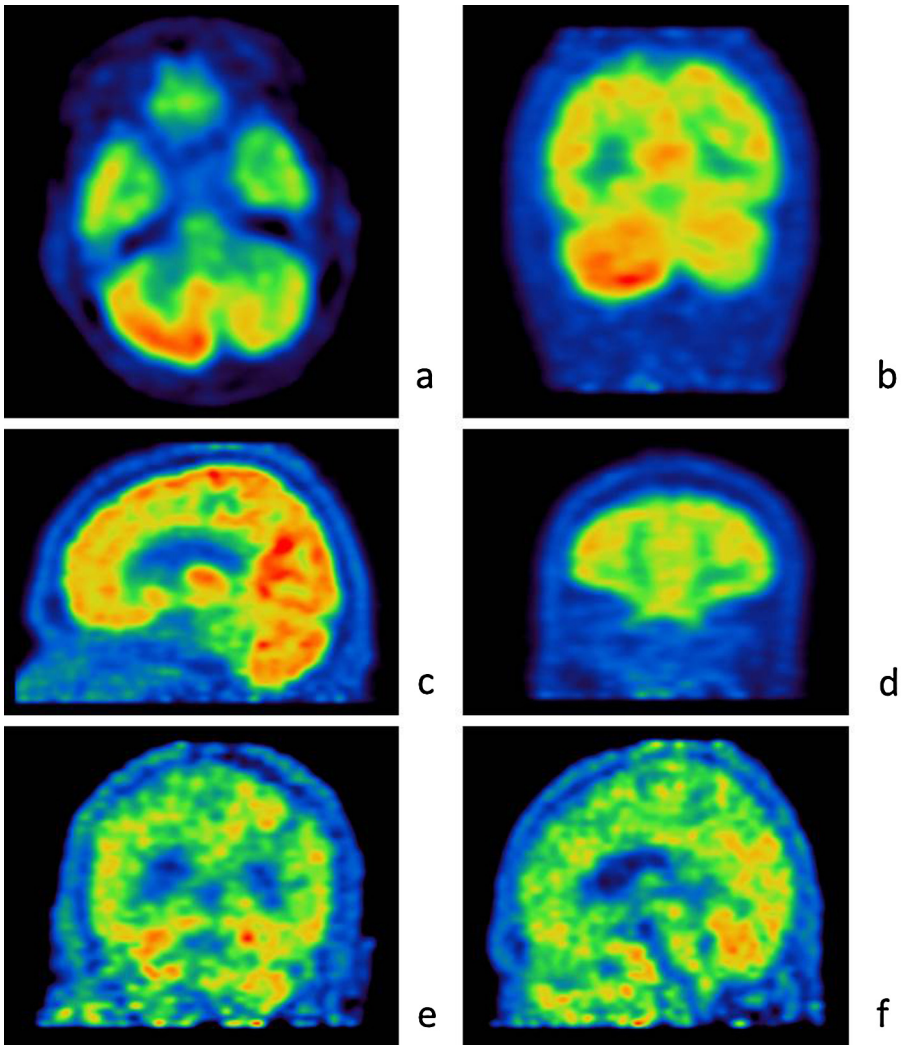

Figure 1. ^{18}F-FDG PET/CT scans: (a, b) 25 year old patient suffering TBE with region of glucose hypermetabolism to the right cerebellum, (c, d) 72 year old patient with a region of glucose hypometabolism including the frontal lobe on both sides and (e, f) 80 year old patient with global cerebral glucose hypometabolism, however, the patient was intubated and analgosedated previous to the scan.

(n = 1) and, enhancement of leptomeningeal structures (n = 3). Comparison of MRI-perfusion in specific brain areas yielded no significant difference (Supplementary Material, Table 3). At discharge MRI findings revealed no significant change and were unspecific in all patients.

4. Discussion

To our knowledge, this is the first report on brain metabolic changes using ^{18}F-FDG PET/CT in a series of ten patients suffering from meningoencephalitic course of TBE. We found a hypometabolic glucose uptake pattern in 7 out of 10 TBE patients. One patient showed a hypermetabolic ^{18}F-FDG pattern in the right cerebellum correlating with clinical findings of ataxia. Interestingly, this patient was examined at the earliest time point after onset of TBE specific signs and symptoms (day 6 vs. median 14 days). Therefore, it is tempting to speculate that cerebral glucose metabolism might change with duration of disease. Early glucose hypermetabolism has been related to active inflammation, while hypometabolism later in the course of disease might be a sign of neuronal dysfunction or even neuronal loss [16,19,20]. One patient had an impressive global hypometabolism, however, during ^{18}F-FDG PET/CT this patient was analgosedated with midazolam and sufentanil. Therefore, a generalized hypometabolic pattern is probable rather due to decreased overall cerebral metabolism under analgosedation than specific for TBE.

However, we were not able to demonstrate neither a TBE specific glucose uptake pattern, a correlation between glucose metabolism and clinical signs and symptoms nor brain MRI scan, most likely to the small number of included patients.

Literature on cerebral metabolism in encephalitis or meningoencephalitis is limited; most publications are case reports only. In the largest study so far on patients with clinically suspected encephalitis ^{18}F-FDG PET revealed glucose hypermetabolism in most cases of definitive diagnosis of encephalitis in the acute phase, however also hypometabolic patterns were found [16]. Alavi et al. described glucose hypometabolism with two different patterns of either specific temporal lobe hypometabolism or a diffuse cortical hypometabolism in 17 out of 24 patients with confirmed Lyme disease[17]. To our knowledge only one study investigating regional cerebral blood flow measured by SPECT has been published on TBE so far [18], describing a moderately decreased regional cerebral blood flow with a patchy or multifocal pattern in almost 50% of TBE patients. Findings were more common in patients with encephalitis compared to meningitis [18].

Members of the flavivirus family such as yellow fever virus or Dengue virus may cause hemorrhagic fever [23]. Decreased thrombocyte counts are frequently seen early in TBE virus infection without bleeding complications later in disease course [3,24]. Therefore, in addition to routinely performed laboratory plasma hemostasis tests we performed rotational thrombelastometry (ROTEM®). Thromboelastometry records the continuous profiles of whole blood coagulation by measurement of the viscoelastic changes associated with fibrin polymerization, and thereby provides a global assessment of hemostatic function [25].

Hemostatic function measured by thrombelastometry as well as routinely performed plasma test such as activated partial thromboplastin time and prothrombin time was found not impaired in any of our 10 patients.

In conclusion, our results underline once more that the TBE virus, despite being a member of flavivirus family, has no detectable influence on hemostasis and does not cause clinically important bleeding complications. PET/CT revealed a predominance of hypometabolic but not TBE specific glucose metabolism pattern. Although we could not identify a clear TBE specific pattern, these findings may provide important information regarding pathophysiologic mechanisms of TBE infection. Glucose hypometabolism may reflect neuronal dysfunction in predilection areas of TBE virus infiltration responsible for development of clinical signs and symptoms. Further investigations in bigger cohorts are needed to define whether this hypometabolism represents functional inactivation or irreversible brain damage.

Conflict of Interest statements and funding: The Authors declare no Conflict of Interest. This Project was financially supported by the ASEA UniNet Programm, Austria.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijid.2016.06.022.

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