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FDG-PET hyperactivity in the striatum in anti-NMDAr encephalitis

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Introduction

Encephalitis with Anti-NMDA receptor (NMDAr) antibodies is a recently described, subacute severe condition occurring mostly in young women. Its course typically presents with initially prominent psychiatric symptoms followed by seizures, movement disorders, and eventually consciousness impairment, as well as dysautonomia[1]. The predominance of psychiatric symptoms observed at onset can render the identification of the condition challenging. Identification of anti-NMDA receptor antibodies in the cerebrospinal fluid (CSF) and serum is diagnostic. As a proportion of cases are paraneoplastic, ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) of the body is used to screen potential neoplasia in patients. Several reports showed a characteristic cerebral FDG-PET pattern in this condition, with a rostral cortical hypermetabolism as compared to posterior regions[2]. Clinically, movement disorders[1] also suggest involvement of subcortical structures, which has been demonstrated in MRI[3].

The determination of specific cerebral metabolic changes translating into FDG uptake could provide an additional diagnostic tool alongside the auto-antibodies level to help early diagnosis and monitor disease activity.

Methods

We retrospectively reviewed the brain FDG PET results of 5 episodes of anti-NMDAr encephalitis in 4 patients. All PET were performed as part of the clinical work-up. To ascertain that the exam was performed interictally, all scans were performed under EEG monitoring beginning 20 minutes before the intravenous injection of 150 to 250 MBq of ^{18}F-FDG, until 20 minutes thereafter. A 20-minute 3D PET image of the brain was acquired (Discovery 690 VCT, GE Healthcare, Waukesha, Wisconsin, USA). All patients had a brain MRI as part of the clinical evaluation; T1 weighted images were fused to the FDG PET using the PMOD Software (version 3.403, PMOD Technologies Ltd., Zurich, Switzerland). MRI images were used to fit a 67 voxels of interest model to individual anatomical features for which FDG uptake was measured. The patient group was compared to 10 controls of the same mean age from a database of 25 healthy probands[4] . The healthy subjects were

processed the same way using the PMOD software, and a voxel based group comparison was performed using SPM8 (P-value < 0.001, corrected for the cluster).

Results

The details of the 5 episodes (4 patients, 1 relapse) are summarised in Figure 1a. Figure 1b shows the comparison of FDG uptake in patients versus healthy probands, where the cortical anteroposterior gradient and an increased uptake in the striatum are seen. Figure 1c shows the FDG uptake ratio, normalized to global uptake, in the caudate nuclei, the occipital, parietal and frontal cortex, using cerebellar vermis as normalisation reference, highlighting statistical differences.

Discussion

This series confirms the cortical anterior-posterior decreasing FDG uptake gradient outlined in patients with NMDAr encephalitis [2, 5]. However, the majority of reports did not describe subcortical structures: our study pooling 5 episodes matched with healthy controls clearly shows selective, bilateral striatal hypermetabolism. Abnormalities in striatum have been previously described in structural imaging [5]: caudate nuclei diffusion alterations in MRI were shown in a patient with strikingly prominent dystonia[6] and in another case with transient hypoxemia[3].

This metabolic pattern seems to be consistent throughout the course of the disease, as it was found in all cases at varying delay from the onset of the disease, and appears also to be independent of the concomitant EEG overall activity or the administered sedation. There are suggestions that the intensity of the PET abnormalities correlates with the severity of the disease at least within the course of a single episode[5, 7]. This may render FDG-PET a useful addition to the diagnostic of relapses. Anti-NMDAr antibodies may indeed not normalise between relapses, their detection alone being therefore potentially not sufficient to conclude to a relapse in the presence of dubious symptoms. It is moreover not uncommon

for patients who recovered from a first episode of encephalitis not to undergo another lumbar puncture to assess the normalisation of the autoantibodies. In our series, the FDG-PET abnormal pattern was found already 2 weeks in the course of a relapse with only mild psychiatric symptoms (episode 1), suggesting indeed that PET abnormalities can prove clinically useful when assessing people with suspected anti-NMDAr encephalitis.

Although this pattern appears to be highly suggestive of NMDAr encephalitis, some cases showing different abnormalities such as lateralised/focal areas of hyper- or hypometabolism were also reported[7]. This discrepancy seems not to be explained by parenchymal lesions in cases with focal alteration of metabolism. Further trials should be performed this population to first confirm our observations and precise the role of PET.

Figure 1 Legend

a. Clinical details of the episodes, episodes N= 1 and 2 occurred in the same patient. *Quantitative data were not available at the time of this episode. b. FDG uptake ratio in different regions in patients (dots) compared with healthy probands (bars show mean ± SD). c. SPM analysis of FDG uptake pattern showed on superimposed MRI, with red corresponding to hypermetabolism, and blue to hypometabolism compared to the healthy probands (FDG uptake normalized to the whole cortex; a normalization to the cerebellar vermis led to similar results). Please note that in this SPM voxel-based analysis, hypermetabolism of the striatum predominated in the putamen.

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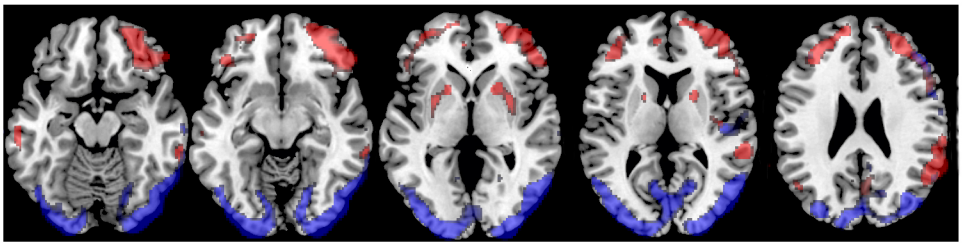
a.

N	Gender	Age	Days from onset	Consciousness impairement	Movement disorder	Psychiatric symptoms	Dysautonomic symptoms	Seizures	Consciousness level during PET	Sedation during PET	EEG activity during PET	MRI findings	Antibodies CSF titer	Antibodies serum titer
1	F	30	16	no	no	yes	no	no	alert	no	alpha rythm, theta slowing	slight global atrophy	1/3	absent
2	F	26	72	yes	yes	yes	yes	yes	somnolent	no	alpha rythm, delta slowing	slight global atrophy	n/a	+*
3	F	22	22	yes	yes	yes	yes	yes	somnolent	propofol	alpha rythm,theta-delta slowing	normal	1/128	1/2000
4	F	23	60	no	no	yes	no	yes	alert	no	alpha rythm	normal	1/32	1/375
5	F	23	22	yes	yes	yes	yes	no	somnolent	no	theta-delta discontinuous	normal	1/2	1/100



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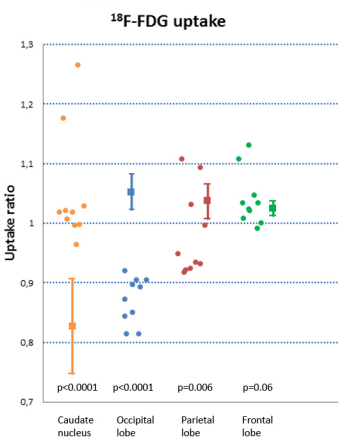

c.