FDG-PET/CT Brain Findings in a Patient With Macrophagic Myofasciitis

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Abstract Brain Positron Emission Tomography/Computed Tomography with ¹⁸F-fluorodeoxyglucose (FDG PET/CT) was performed in a 44-year-old woman with marked cognitive impairment, diffuse myalgias, sensory, memory and visual disorders, and chronic fatigue, presenting with histopathological features of macrophagic myofasciitis (MMF) at deltoid muscle biopsy. Cerebromedullary Magnetic Resonance Imaging (MRI), electromyography, ophthalmic examination, and cerebrospinal fluid analysis were normal. Visual analysis of FDG PET/CT images showed an atypical pattern of hypometabolism, involving symmetrically the occipital cor-

tex, temporal lobes, and limbic system (including in particular amygdalo-hippocampal complexes), and the cerebellum. Posterior cingulate cortex and parietal areas were preserved. This pattern was confirmed by a voxel-based procedure using Statistical Parametric Mapping (SPM12) that compared a patient's images to normal reference samples from six healthy subjects with adjustment to age obtained using the same PET/CT camera. These results provide a glucose metabolism substrate for cognitive complaints in patients with long-lasting aluminium hydroxide-induced MMF.

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Introduction

Macrophagic myofasciitis (MMF) is a longstanding inflammatory lesion found at deltoid muscle biopsy assessing the persistence of aluminum hydroxide adjuvant particles within macrophages following intramuscular vaccine injections [1, 2]. Clinical manifestations associated with MMF typically include arthromyalgias, chronic fatigue, and a cognitive dysfunction, occurring several months or years after the last vaccine injection combining impaired verbal long-term memory, dysexecutive syndrome, and more rarely an alteration of dichotic listening [3–6]. Only a very limited number of functional studies using the Single-Photon Emission Computed Tomography (SPECT) technique have investigated these cognitive disorders. Recently, in a large series of 76 patients, Van Der Gucht et al. [7] described a pattern of diffuse cortical and subcortical perfusion changes including in particular the occipital cortex and the cerebellum. We present Positron Emission Tomography/Computed Tomography with ^{18}F -fluorodeoxyglucose (FDG PET/CT) brain images of a patient with a known MMF, referred to our center for marked cognitive disorders.

Case Report

Brain FDG PET/CT was performed in a 44-year-old woman with marked cognitive impairment, diffuse myalgias, sensory, memory and visual disorders, and chronic fatigue, which occurred after anti-hepatitis B immunization. Deltoid muscle biopsy diagnosed MMF lesions 28 months after the last vaccine injection (Fig. 1). Cerebromedullary Magnetic Resonance Imaging (MRI), electromyography, ophthalmic examination, and cerebrospinal fluid analysis were normal.

Acquisition of PET images was performed on a Gemini XL instrument (germanium oxyorthosilicate-based PET+16-slice CT; Philips) after a planned intravenous injection of 2.5 MBq/kg of FDG. The patient was required to fast for at least 6 h before undergoing the scan, have a normal blood sugar level, and an update neurosensory rest for 30 minutes. A low-dose helical CT was first performed for anatomical correlation and attenuation correction with the following parameters: x-ray tube tension of 120 kV, current of 80–100 mAs, rotation time 0.5 s, pitch 0.938, and slice thickness 2 mm. Images were reconstructed using line of response-row action maximum likelihood algorithm (two iterations, 28 subsets, postfilter 5.1 mm), with and without CT attenuation correction (matrix size of 512×512 , voxel size $4 \times 4 \times 4 \text{ mm}^3$). Visual analysis of FDG PET/CT images (Fig. 2) showed an atypical pattern of

Fig. 1 Deltoid muscle biopsy: Macrophagic myofasciitis (MMF) lesion. **a** Multifocal infiltration (stars) of endomysium by well-circumscribed and cohesive sheets of large mononucleated cells corresponding to macrophages intermingled with some lymphocytes. **b** Higher magnification showing the characteristic granular appearance of macrophages cytoplasm (arrow); no multinucleated giant cells were observed. **c** PAS staining showing strong positivity of MMF macrophages (arrow); Pm: perimysium. Paraffin sections; hematoxylin-eosin (**a**, **b**) and PAS (**c**) staining; bars: 100 μm (**a**), 20 μm (**b**), 40 μm (**c**)

hypometabolism, involving symmetrically the occipital cortex, temporal lobes, and limbic system including in particular amygdalo-hippocampal complexes, and the cerebellum (white arrows). Posterior cingulate cortex and parietal areas were preserved. This pattern was confirmed by a voxel-based analysis using Statistical Parametric Mapping (SPM) (Fig. 3).

All PET brain image volumes were spatially normalized onto the Montreal Neurological Institute (MNI) template (McGill University, Montreal, Canada) using a 12-parameter affine transformation, followed by non-linear transformations.

Fig. 2 Visual analysis. FDG PET brain in axial slices showing a decreased uptake of FDG in a symmetrical and atypical pattern involving the occipital cortex, temporal lobes, and limbic system including, in particular, amygdalo-hippocampal complexes, and the cerebellum (white arrows)

Dimensions of the resulting voxels were $2 \times 2 \times 2 \text{ mm}^3$. Images were smoothed using a Gaussian filter (FWHM 10 mm) to blur individual variations in anatomy and to increase the signal-to-noise ratio. Spatial preprocessing and statistical analysis were performed using the SPM12 software implemented in Matlab version R2014a (Mathworks Inc., Sherborn, MA). Using ANCOVA analysis, FDG PET brain images of patient were compared to those from six healthy subjects (one man and five women, mean age: $54 \pm 19 \text{ y}$) obtained using the same PET/CT camera. Results were collected at a $P\text{-value} < 0.005$ at the voxel level, for clusters $k \geq 150$ voxels (corrected for cluster volume) with adjustment for age. Representations and detailed results of the abnormalities are given in Fig. 3 and Table 1, respectively, including the individual $k\text{-value}$, which represents the number of significant voxels in the particular

cluster (cluster size), the brain regions, the side of the hemisphere, the Brodmann areas (BA) involved, the peak value coordinates, the peak T-value, and the peak Z-value.

Discussion

This case showed diffuse cortical and subcortical metabolic abnormalities in a patient with MMF and marked cognitive disorders. This patient presented typical cognitive dysfunction, referred to as MMF-associated cognitive disorder (MACD). Hypometabolism of occipital cortex is consistent with visuospatial impairment found at neuropsychological assessment. Cerebellar hypometabolism may be related to the numerous connections between the cerebellum and cortical

Fig. 3 SPM analysis. MMF hypometabolic pattern by the SPM12 analysis after comparison with reference samples from six healthy subjects confirming a significant decreased uptake of FDG in a symmetrical and atypical pattern involving the occipital cortex, temporal lobes, limbic system, and cerebellum. Abnormalities are

displayed with T-score value on 2-dimensional “Glass-brain” projection-images (a), slices of MRI template in axial, coronal, and sagittal orientations (b) and projected onto a brain rendered by 3D-MIP (c). $P\text{-value} < 0.005$ at the voxel level for clusters $k \geq 150$ contiguous voxels (corrected for cluster volume). A, anterior; P, posterior; L, left; R, right

Table 1 Brain areas with significant decreased uptake of FDG after comparison with reference samples from six healthy subjects. Results were collected at a P-value<0.005 at the voxel level, for clusters $k \geq 150$ voxels (corrected for cluster volume) with adjustment for age

K	Brain areas	Side	Labels	Peak value coordinates (mm)			T-value	Z-value
				x	y	z		
1822	Occipital lobe, Cerebellum, Temporal lobe	L, R	BA19, BA18, BA37, BA17, CAL, CPL	-24	-86	-18	33.22	4.01
1214	Occipital lobe, Cerebellum, Temporal lobe	R	BA18, BA19, BA17, BA37, CAL, CPL	26	-86	-18	30.97	3.96
865	Cerebellum	L, R	CAL, CPL	18	-70	-60	27.98	3.89
606	Occipital lobe, Temporal lobe	L	BA19, BA18, BA17	-24	-74	28	26.52	3.85
721	Temporal lobe, Limbic lobe	R	BA20, BA21, BA38, amygdalo-hippocampal complex, BA36	38	-2	-46	25.79	3.83
318	Limbic lobe, Temporal lobe, Cerebellum	L	BA36, BA20, amygdalo-hippocampal complex, CAL	-32	-8	-28	23.96	3.78
500	Occipital lobe, Temporal lobe	R	BA18, BA19, BA7	22	-82	24	23.11	3.75
218	Temporal lobe	L	BA21, BA38, BA22	-52	16	-8	20.73	3.67
157	Temporal lobe	R	BA21	68	-14	-4	13.84	3.35

BA, Brodmann area; CAL, cerebellum anterior lobe; CPL, cerebellum posterior lobe; L, left; R, right

areas through the cortico-ponto-cerebellar pathways [8]. Also, memory disorders are probably explained by the involvement of amygdalo-hippocampal complexes, which are involved in the Papez circuit [9].

This pattern has been described recently on a population level using perfusion SPECT technique and SPM12 analysis [7], but is now apparent to the naked eye using FDG PET/CT, on an individual level. Therefore, FDG PET/CT appears more sensitive than SPECT to detect posterior cortical and subcortical abnormalities in this setting. The main difference is the absence of visualization of periventricular involvement, but the present patient showed no argument for an impairment of inter-hemispherical connection typically revealed by left ear extinction on dichotic listening test and suggests the involvement of different metabolic and brain perfusion mechanisms. Cortico-subcortical brain lesions are possibly of inflammatory or toxic origin. Experimental data evidenced that after intramuscular injections of aluminum hydroxide, aluminum particles can translocate into the brain tissue where they remain trapped [10]. However, to our knowledge, there is no pathological or radiological evidence for brain damage specifically associated with MMF. In particular, except in the subset of patients who have co-occurring multiple sclerosis, standard MR brain imaging failed to explain cognitive dysfunctions in MMF, and no post-mortem brain examination of MMF patient has been reported so far.

To our knowledge, this is the first report showing FDG PET/CT brain metabolic changes in a patient with MMF and providing a glucose metabolism substrate for cognitive complaints in patients with long-lasting aluminium hydroxide-induced MMF. Further studies on larger populations are warranted.

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Conflict of interest Axel Van Der Gucht, Mehdi Aoun-Sebaiti, Paul Kauv, Eric Guedj, Jessie Aouizerate, Antoine Verger, Romain K. Gherardi, Anne-Catherine Bachoud-Levi, François-Jérôme Authier, and Emmanuel Itti declare that they have no financial or other relation that could lead to a conflict of interest. The manuscript has not been published before or is not under consideration for publication anywhere else and has been approved by all co-authors.

Ethical statement All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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