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Case report

Thalamic activation and cortical deactivation during typical absence status monitored using [^{18}F]FDG-PET: A case report

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ABSTRACT

We describe the ictal [^{18}F]FDG-PET study of a case of absence status showing bilateral thalamic hypermetabolism and frontal cortex hypometabolism. This is the first ictal assessment of absence status by [^{18}F]FDG-PET reporting this particular cortical and subcortical involvement. Our findings support the theory of corticothalamic circuitry involvement in the pathophysiology of absence seizures and stress the similarities of the clinical and metabolic pattern observed during absences with the pattern of task-induced interruption of the default state of brain function.

1. Introduction

Absence status epilepticus (AS) is a peculiar epileptic condition which has been defined as a prolonged, generalized absence seizure, lasting at least more than half an hour, but usually lasting for hours and even for days[6]; the impairment of consciousness is sometimes associated with automatisms or other subtle myoclonic, tonic, atonic, or autonomic phenomena.[12] AS has been distinguished in "typical", if occurring in the setting of idiopathic generalized epilepsy (IGE), and "atypical" in patients with symptomatic or cryptogenetic generalized epilepsy.[10] During "typical" AS continuous or almost continuous generalized spike wave (SW) or polyspike-wave (PSW) activity at 2–4 Hz is recorded on EEG. AS can occur spontaneously or as a consequence of drug withdrawal, sleep deprivation, alcohol intake or metabolic disturbances. We report a case of "typical" AS in which [^{18}F]FDG-PET and video-EEG (VEEG) were performed both ictally and interictally.

2. Case report

A 56-year-old man was referred to our Epilepsy Center for long-lasting episodes of consciousness impairment, characterized by abrupt onset, clouding of consciousness and long duration (up to 36–48 h). During these episodes he appeared confused and slowed, but able to continue automatic activities (such as walking, dressing, eating) and to answer simple questions, even if making many mistakes. The onset of such episodes could probably be dated to early adolescence, but being at that time extremely rare (1/year), they were overlooked. During adulthood their frequency increased progressively, up to about 1/month in the last 5 years. Moreover, he presented 2 generalized tonic-clonic (GTC) seizures which prompted him to seek medical attention. His family history, neurological examination and brain 1.5 T MRI were unremarkable. When first coming to our attention he presented normal clinical status; repeated basal VEEGs were unremarkable, while a post-sleep-deprivation VEEG showed normal background activity with frequent bursts of generalized SW and PSW discharges predominant on frontal areas, lasting 1–3 s, without clinical phenomena. Nearly 1 month after, he presented a long-lasting episode of consciousness impairment. An ictal VEEG showed almost continuous generalized SW or PSW activity at 2–3 Hz (Fig. 1), during which he was confused and slowed but able to answer simple questions (the date, his name); he showed impairment of working memory, comprehension and attention, thinking slowness and temporo-spatial disorientation. He did not present any ictal motor activities, nor any other neurological symptoms or signs. Ictal VEEG was interrupted after about 60 min and the patient, still slowed and confused, underwent a [^{18}F]FDG-PET study, which showed relative hypermetabolism in thalami bilaterally, mostly in

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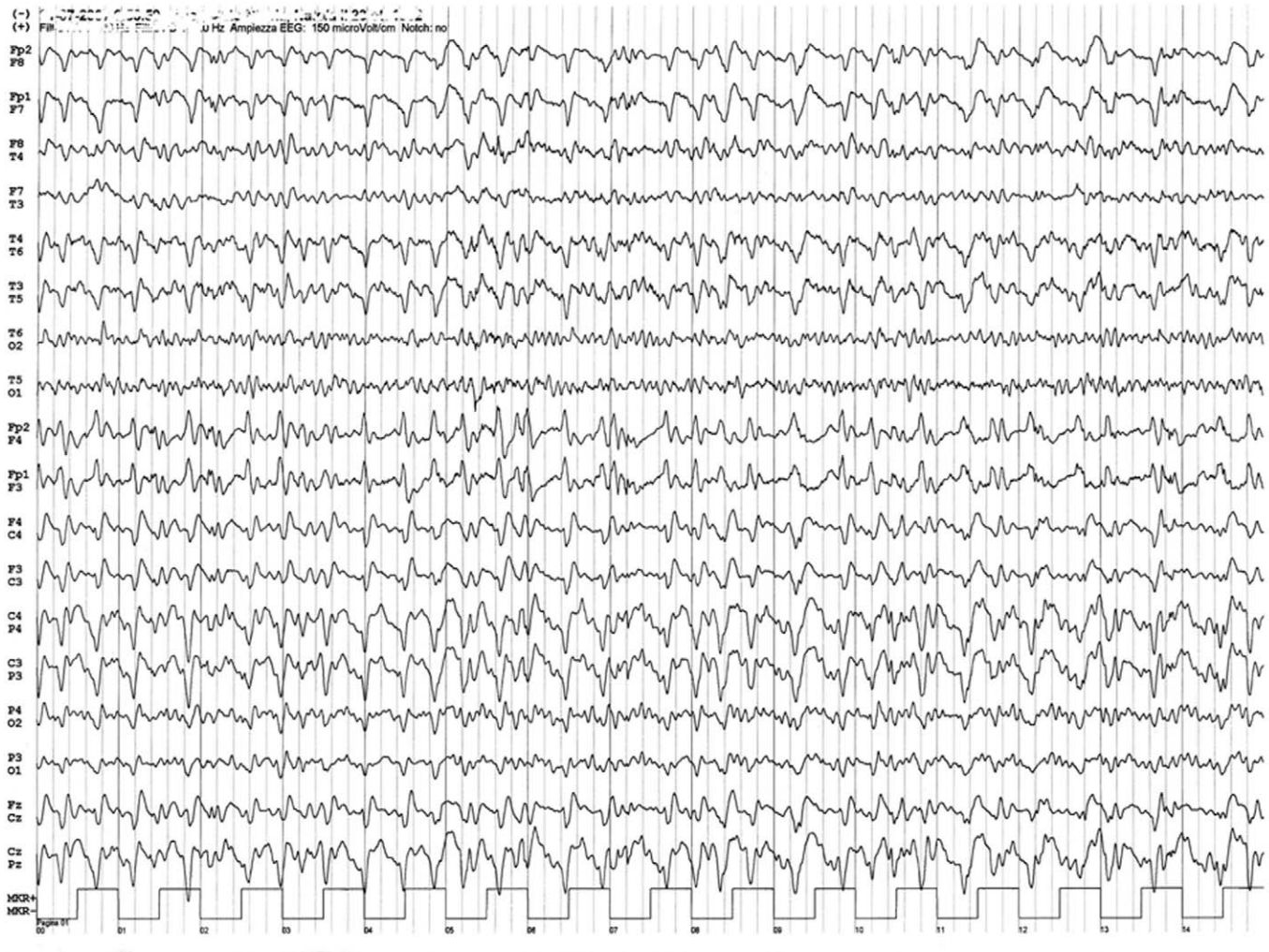

Fig. 1. Ictal EEG showing continuous generalized 2–3 Hz spike/multiple spike slow wave activity, with a predominance over the anterior areas; the patient appeared confused, slow, drowsy.

the anterior nuclei, and relative hypometabolism in bilateral frontal cortex and, to a lesser extent, relative hypermetabolism in the cerebellar vermis and relative hypometabolism in parietal and posterior cingulate cortices and in cerebellar hemispheres (Fig. 2A, C and D). Immediately after the [^{18}F]FDG-PET study the patient was submitted to a VEEG, which confirmed the persistent status. The status lasted about 40 h. An interictal [^{18}F]FDG-PET, performed several days after AS resolution, showed normal cerebral glucose metabolism (Fig. 2B). The VEEGs performed immediately before and after this interictal [^{18}F]FDG-PET study were normal.

3. Discussion

Previous ictal [^{18}F]FDG-PET studies in absence seizures reported diffusely increased metabolism during single absence seizure or generalized interictal SW[4,11] and decreased metabolic rates throughout cortical and subcortical structures in a patient with AS, suggesting different pathophysiologic mechanisms.[11] More recent studies, which studied clinical absences or generalized SW by fMRI and H_2 ^{15}O-PET, reported an increase of blood flow in the thalamus and a broad decrease in the neocortex, reflecting activation and suppression of neuronal activity, respectively.[7,9,1,5] On the whole, these results confirm the key role of the thalamus for the generation of generalized SW discharges and support the concept of thalamocortical circuitry abnormalities as the underlying pathophysiological substrate of IGE.[2,3] In particular, an increase of thalamic blood flow during typical absences was reported in patients studied with H_2 ^{15}O-PET[7] and bilateral activation within the thalami and widespread but symmetrical cortical deactivation was described during prolonged runs of generalized SW in a single patient assessed through EEG-correlated fMRI.[9] In 2 subsequent studies from the same group[1,5] the blood oxygen level-dependent (BOLD) responses to interictal generalized epileptic discharges were assessed through EEG-correlated fMRI in 15 IGE patients with short SW bursts (1–14 s). The first study,[1] which analyzed individual patients, reported a variety of patterns of BOLD response, with thalamic responses present in most patients, most often as activation, posterior cortical responses appearing frequently and most often as deactivation, and anterior cortical responses presenting sometimes as activation and sometimes as deactivation. The second study[5] analyzed the same patients performing a group analysis with the aim of assessing the activations and deactivations which were consistent across the patients. Results showed that activation was prominent bilaterally and symmetrically in the thalamus but also involved insula, mesial midfrontal cortex and cerebellum, while deactivation was prevalent in the anterior frontal, parietal and posterior cingulate cortices.

The [^{18}F]FDG-PET pattern of activation/deactivation observed in our patient is strikingly similar to the fMRI pattern emerging

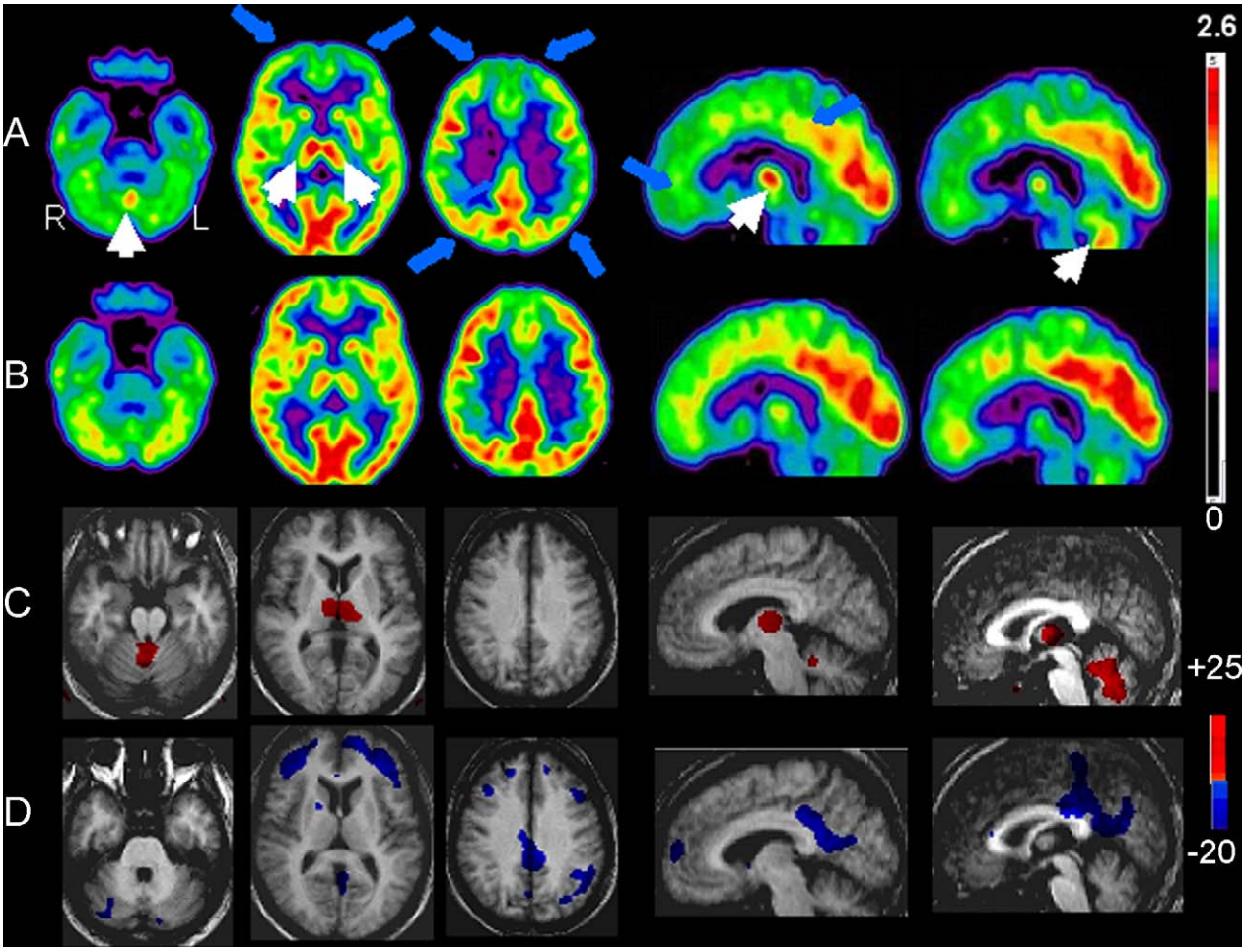

Fig. 2. Axial and sagittal [^{18}F]FDG-PET images obtained during the absence state (A) and in the intercritical state (B). Images were spatially normalised into the Montreal Neurological Institute (MNI) space using SPM2 (Wellcome Department of Imaging Neuroscience, UK, London). The images represent regional [^{18}F]FDG concentration values normalised to those measured in the whole brain (globals). In (C) and (D) are reported the areas of relative hypermetabolism (red) and of relative hypometabolism (blue) obtained by the subtraction of normalised PET images (absence state–intercritical state) and superimposed on 3D-T1 MRI axial and sagittal images obtained in a volunteer in the MNI space. L = left side; R = right side; the percentage thresholds for increase and decrease were arbitrary settled at +25% and −20%, respectively. White arrows: relative increase; blue arrows: relative decrease. During the absence state the cerebral glucose metabolism appears relatively increased in the thalamus and cerebellar vermis and relatively decreased in the fronto-parietal and posterior cingulate cortices.

from the above group analysis.[5] In fact, the ictal [^{18}F]FDG-PET in our patient showed relative increase of metabolism in the thalamus bilaterally and symmetrically (and to a lesser extent in the cerebellar vermis), and relative hypometabolism in frontal cortex bilaterally and symmetrically (and to a lesser extent in the parietal and posterior cingulate cortices and cerebellar hemispheres). It must be underlined that, when the fMRI data of subjects from Gotman et al.[5] were examined separately in individual patients, the "complete" pattern of thalamic/insula/cerebellum activation coupled with anterior (frontal)/posterior (parietal and posterior cingulated cortices) deactivation was never observed, but it emerged only through whole group analysis. Interestingly, we observed this "complete" pattern in a single patient, probably because, while in the study of Gotman et al. (2005)[5] the individual paroxysmal discharges were never longer than 14 s, our patient was studied during a very long, uninterrupted epileptic activity which probably allowed metabolic cerebral changes to become detectable. This is the first report in which AS is, without ambiguity, accompanied by a contemporaneous, but opposite, involvement of thalamus (activation) and frontal, parietal and posterior cingulated cortices (deactivation). It must be underlined that, differently from most studies assessing cerebral blood flow during SW discharges, our patient presented a definite and persistent clouding of consciousness during the neuroimaging study. This pattern of metabolic activation/deactivation has been interpreted by Gotman et al. (2005)[5] as an interruption of the default state of brain function, causing the reduced responsiveness and the clouding of consciousness observed during SW discharges. The term of "default state of the brain" has been first used by Raichle et al. (2001)[8] to describe a resting condition in which a subject is not performing any specific task, but is awake and conscious; when the subject concentrates on any task, the default state is interrupted and this is accompanied by a cortical deactivation involving the fronto-parietal cortical regions, including the posterior cingulate gyrus. Gotman et al. (2005)[5] stress the similarities of this pattern of task-induced deactivation with the deactivation accompanying generalized SW discharge, hypothesizing that also an epileptic discharge can result in a partial suspension of the default state of the brain. They also underline[5] that the suspension from the default state observed in an absence seizure is accompanied by a peculiar mental state characterized by altered consciousness and unresponsiveness resulting from activation in the thalamus, midfrontal regions, and insula, which cannot be described as "loss of consciousness". Our observation, with the limitation due to the report of a single case, supports this theory, as we have documented through VEEG

assessment, how the pattern of thalamic activation/cortical deactivation was accompanied by a very peculiar mental state in which the patient was partially unresponsive, considerably slow, but still able to perform automatic activities, even if with frequent mistakes.

However, it must be underlined that, since the pathophysiology of AS is not necessarily identical to that of typical absences, the information that can be drawn from our study are not necessarily relevant to interpret the impairment of consciousness associated to absence seizures. In fact, the short duration and abrupt cessation of typical absences suggest the activation of a powerful controlling mechanism, which is not operating in AS: this suggests the possibility that thalamocortical interactions might not necessarily be the same in the two conditions.

A shortcoming of our study is the lack of a simultaneous EEG-PET assessment. However, the VEEGs were carried out less than 1 h before and immediately after the ictal [^{18}F]FDG-PET assessment, in both cases showing generalized, uninterrupted SW discharges consistent with AS; moreover, the clinical picture of clouding of consciousness observed during the VEEGs persisted unmodified during the [^{18}F]FDG-PET study. Similarly, after resolution of the AS, the interictal [^{18}F]FDG-PET was immediately preceded and followed by a VEEG recording, normal in both cases. In conclusion, our [^{18}F]FDG-PET findings confirm the findings coming from functional neuroimaging studies, further supporting the pivotal role of thalamocortical circuitry in generating the AS unresponsiveness.

Conflicts of interest

None.

Acknowledgment

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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