



## Case report

## Amyloid PET in pseudotumoral multiple sclerosis



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## ARTICLE INFO

## Keywords:

Multiple sclerosis  
Amyloid  
Positron emission tomography  
Myelin

## ABSTRACT

**Background:** Pseudotumoral multiple sclerosis is a rare form of demyelinating disease of the central nervous system. Positron emission tomography (PET) using amyloid-tracers has also been suggested as a marker of damage in white matter lesions in multiple sclerosis due to the nonspecific uptake of these tracers in white matter.

**Method:** We present the case of a 59 year-old woman with a pathological-confirmed pseudotumoral multiple sclerosis, who was studied with the amyloid tracer <sup>18</sup>F-florbetaben. The patient had developed word-finding difficulties and right hemianopia twelve years ago. In that time, MRI showed a lesion on the left hemisphere with an infiltrating aspect in frontotemporal lobes. Brain biopsy showed demyelinating areas and inflammation. During the following years, two new clinical relapses occurred.

**Results:** <sup>18</sup>F-florbetaben PET showed lower uptake in the white matter lesion visualized in the CT and MRI images. Decreased tracer uptake was also observed in a larger area of the left hemisphere beyond the lesions observed on MRI or CT. White matter lesion volume on FLAIR was 44.2 mL, and tracer uptake change between damaged white matter and normal appearing white matter was – 40.5%. Standardized uptake value was inferior in the pseudotumoral lesion than in the other white matter lesions.

**Conclusion:** We report the findings of amyloid PET in a patient with pseudotumoral multiple sclerosis. This case provides further evidence on the role of amyloid PET in the assessment of white matter and demyelinating diseases.

## 1. Background

Pseudotumoral multiple sclerosis is a rare presentation of demyelinating disease of the central nervous system. Several subtypes (i.e. diffusely infiltrating, Balo-like, and megacystic) have been recognized that may assist in the differential diagnosis with other diseases (Mauri-Fábrega et al., 2014). However, the diagnosis is usually challenging and brain biopsy is often necessary.

Positron emission tomography (PET) with amyloid tracers is a useful tool in the diagnosis of cognitive impairment and dementia. It has also been suggested as a marker of damage in white matter lesions in multiple sclerosis due to the nonspecific uptake of these tracers in white matter (Matías-Guiu et al., 2015, 2016a). In fact, amyloid PET has been considered as an imaging marker for quantification of myelin

loss and its regeneration (Bodini et al., 2016; Matías-Guiu et al., 2016b). We present the case of a 59 year-old woman with a pathological-confirmed pseudotumoral presentation of multiple sclerosis. This case was studied with amyloid tracer <sup>18</sup>F-florbetaben. With this case report, we suggest the role of amyloid PET for evaluation of white matter diseases.

## 2. Methods

The patient was studied using brain MRI and <sup>18</sup>F-florbetaben PET. MRI imaging was performed using a 1.5 T scanner (Signa HDxt, GE Healthcare, Milwaukee, USA). T1-weighted 3D fast spoiled gradient-echo inversion recovery, T2-weighted fluid-attenuated inversion recovery, T2-weighted double-echo fast spin-echo and T1-weighted post-

**Abbreviations:** CT, computerized tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; SUV, standardized uptake value

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<http://dx.doi.org/10.1016/j.msard.2017.05.002>

Received 16 December 2016; Received in revised form 2 April 2017; Accepted 1 May 2017  
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contrast FSE sequences were acquired. PET was conducted using a Siemens Biograph™ TruePoint™ PET-CT platform with lutetium oxyorthosilicate crystals and 6-slice CT. The tracer  $^{18}\text{F}$ -florbetaben was administered at a dose of 300 MBq. Static images were taken 90 min after injection of the tracer, during a period of 15 min. Images were analyzed by two methods: firstly, using manual ROIs in the PET station to calculate the standardized uptake value (SUV); secondly, a semi-automatic analysis of the images. The entire procedure has been described in a previous study (Matías-Guiu et al., 2015). Briefly, T1-weighted MRI was co-registered with the PET image, using the T1-weighted image as the reference. T1-weighted MRI image was normalized to the T1 template provided by Statistical Parametric Mapping 8, and the same parameters were applied to normalize the co-registered PET images. T1-weighted images were filled using the lesion-filling step of the Lesion Segmentation Tool and segmented into grey matter, white matter, and cerebrospinal fluid probability maps. The Lesion Segmentation Tool was also used to segment the white matter lesions. The study was approved by the hospital ethics committee and meets the standards established by the Declaration of Helsinki.

### 3. Case presentation

The patient had developed word-finding difficulties and right hemianopia twelve years ago. In that time, MRI showed a lesion on the left hemisphere with an infiltrating aspect in frontotemporal lobes. At that moment, brain biopsy showed demyelinating areas and inflammation, with macrophages and reactive astrocytes, as well as B and T lymphocytes in the brain parenchyma and perivascular spaces. Staining for myelin and axons proved severe myelin loss and relative axonal sparing. Oligoclonal bands of IgG were positive in cerebrospinal fluid. The patient was treated with steroids, with partial improvement of both the lesion and symptoms. During the following years, the patient presented partial seizures and residual aphasia. Moreover, two new clinical relapses with visual impairment occurred. These relapses were probably related to the development of two lesions in the left and right occipital lobes. In the last evaluation at the time of PET, neurological and cognitive assessment showed mild nominal aphasia, and visual scanning impairment. In the Fig. 1, CT,  $^{18}\text{F}$ -florbetaben PET and MRI images are shown. CT and MRI (T2-weighted fluid-attenuated inversion recovery sequence) showed a white matter lesion in the left frontal and temporal lobes, with atrophy in the perisylvian region. Amyloid PET showed lower uptake in the white matter lesion visualized in the CT and MRI images. However, decreased tracer uptake was also observed in a larger area of the left hemisphere beyond the lesions observed on MRI or CT. Standardized uptake value (SUV) was 0.50 in the left frontal lesion, and 1.57 in the same region in the right frontal lobe. In the left temporal lesion, SUV was 0.63, and 1.48 in the homologous corresponding region of the right hemisphere. In the occipital lesions, SUV was 1.05 in the lesion of the left hemisphere, 1.09 in the lesion of the right hemisphere, and 1.55 in the normal appearing white matter in the occipital lobe. We conducted also a semiautomatic analysis following the procedure previously described (Matías-Guiu et al., 2015). Using this procedure, white matter lesion volume on FLAIR was 44.2 mL, and tracer uptake change between damaged white matter and normal appearing white matter was -40.5%.

### 4. Discussion

We report the findings of amyloid PET in a patient with pseudotumoral presentation of multiple sclerosis. To our knowledge, this is the first case reported in the literature regarding the use of amyloid PET in this form of demyelinating disease in the literature. The lower uptake observed in the white matter lesion confirms the findings previously reported in case series with multiple sclerosis (Matías-Guiu et al., 2015; Bodini et al., 2016). Moreover, the lower uptake also observed in the

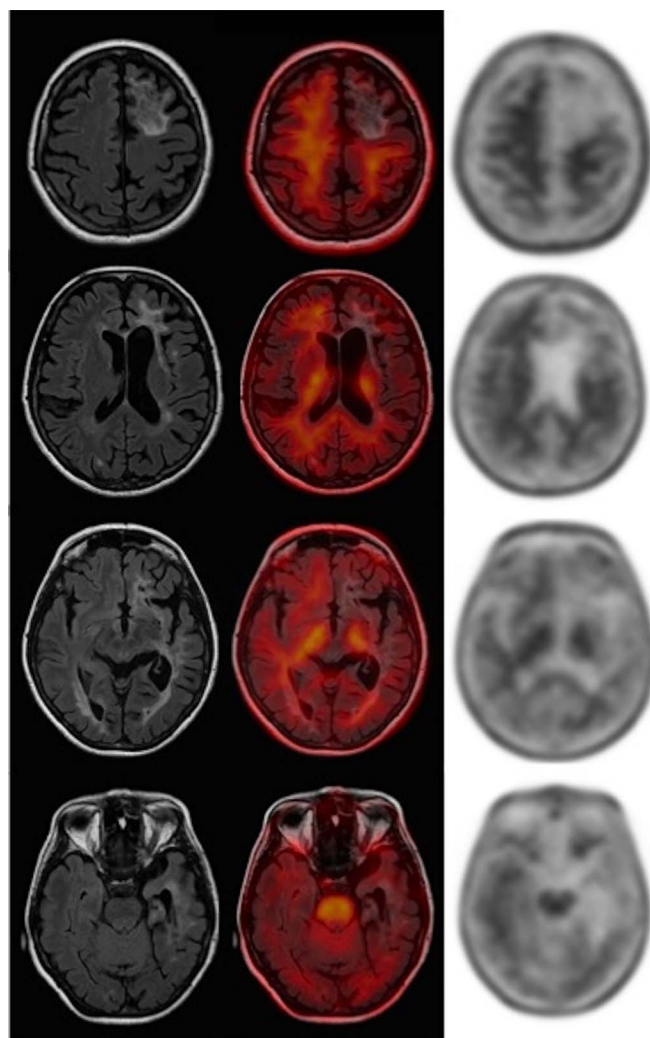


Fig. 1. MRI (left), co-registered  $^{18}\text{F}$ -florbetaben PET-MRI (center), and  $^{18}\text{F}$ -florbetaben PET (right). A large left frontal and temporal hyperintense lesion is shown in MRI. Uptake of the tracer is lower in the white matter lesion, but it is extended beyond the lesions observed in MRI. Periventricular white matter lesions may also be seen.

white matter without noticeable lesion on MRI T2-weighted suggests the possibility to detect abnormalities in the normal appearing white matter. The degree of impairment in multiple sclerosis of these white matter regions without visible lesions in conventional MRI is currently under debate, and PET imaging with amyloid or other tracers could be useful (Matías-Guiu et al., 2016b). Furthermore, we observed lower SUVs in the pseudotumoral lesion than in the other white matter lesions, and in this case in comparison to the relapsing-remitting and progressive forms of multiple sclerosis previously reported (Matías-Guiu et al., 2015). This difference may suggest a lower remyelination in the pseudotumoral lesion. The greater distance from the boundaries in this large lesion might explain the lower migration of the oligodendrocyte progenitor cells and, thus, failure of the remyelination. Interestingly, available evidence indicates that a subset of patients with pseudotumoral lesions may have an even more benign outcome (Lucchinetti et al., 2008; Hardy and Chataway, 2013), so the use of biomarkers of myelin loss and remyelination, such as amyloid PET tracers, could be useful to clarify whether outcome differences in individual patients are related to the degree of demyelination and subsequent remyelination, or if other factors are also involved. Another open question in the literature is the role of beta-amyloid in MS. Recently, lower levels of beta-amyloid in cerebrospinal fluid has been related to a worse prognosis in MS (Pietroboni et al., 2016), although

the exact mechanism of this association is unknown. Specific studies designed to evaluate the relationship between the beta-amyloid cascade and remyelination, and between beta-amyloid CSF levels and brain uptake of amyloid tracers are necessary (Matías-Guiu et al., 2016a).

Another interesting issue is the use of amyloid PET in the differential diagnosis of tumoral lesions in the central nervous system. In our study, PET imaging was performed several years after the onset of the disease, so we are not able to fully describe the tracer's behaviour during the acute phase of the disease. In this regard, our study has some limitations. First, PET imaging was performed several years after the onset, so a potential use in the acute phase is only hypothetical. Second, the uptake in the pseudotumoral lesion may be influenced by the fact that a brain biopsy was performed on this lesion some years earlier. However, brain biopsy was performed on one of the impaired lobes but, in contrast, tracer uptake values were similar in both.

In summary, this case report provides evidence on the role of amyloid PET in the assessment of white matter and demyelinating diseases. Further studies are necessary to explore the findings in the acute phase of pseudotumoral lesions, as well as the usefulness of amyloid imaging in the differential diagnosis with brain tumors.

### Ethics

The hospital ethics committee approved this study.

### Conflict of interest statement

The authors declare that they have no competing interests.

### Acknowledgments

None

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