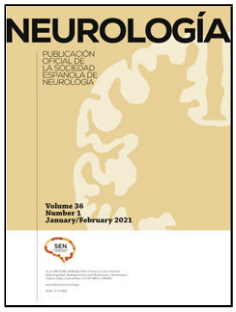

Motor band sign in ^{18}F-FDG PET/CT studies: a biomarker of degenerative upper motor neuron disease? A study of three cases and literature review

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Signo de la banda motora en el PET/TC ^{18}F-FDG cerebral: ¿un biomarcador de enfermedad degenerativa de primera motoneurona? A propósito de tres casos y revisión de la literatura

Motor band sign in ^{18}F-FDG PET/CT studies: a biomarker of degenerative upper motor neuron disease? A study of three cases and literature review

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Highlights

1. The lack of biomarkers represents an obstacle to the diagnosis of motor neuron diseases.
2. We present 3 cases of motor neuron disease showing hypometabolism around the Rolandic fissure in the brain ^{18}F-FDG PET study.
3. The literature suggests that the motor band sign is a biomarker of upper motor neuron degeneration.
4. Further studies are needed to confirm its clinical value and its possible inclusion as diagnostic criterion.

Resumen

Introducción. Las enfermedades de motoneurona (EMN) incluyen afecciones como la esclerosis lateral amiotrófica (ELA) y la esclerosis lateral primaria (ELP), caracterizadas por la degeneración progresiva de la primera y/o segunda motoneurona. La identificación de biomarcadores específicos es crucial para reducir los retrasos diagnósticos.

Métodos. Se presentan tres casos clínicos evaluados en el Hospital Universitario 12 de Octubre, donde el signo de la banda motora en PET/TC 18F-FDG cerebral contribuyó al diagnóstico de EMN. Los estudios se realizaron con un equipo SIEMENS Biograph True Point 6 y se revisó la literatura relevante.

Resultados. En los tres pacientes, el PET/TC mostró un hipometabolismo en la región prerrolándica, indicativo del signo de la banda motora, que ayudó a definir el diagnóstico de ELP o ELA en cada caso.

Discusión. El signo de la banda motora en PET/TC 18F-FDG cerebral emerge como un marcador potencial de afectación de primera motoneurona, si bien la heterogeneidad de las EMN y la variabilidad en los estudios requieren mayor investigación para definir su especificidad y sensibilidad.

Conclusión. El signo de la banda motora en PET/TC 18F-FDG cerebral es un biomarcador prometedor para las EMN, aunque se necesitan estudios adicionales para establecer su validez diagnóstica.

Palabras clave: Enfermedad de motoneurona, ELA, ELP, signo de la banda motora, biomarcador, PET-FDG

Abstract

Introduction. Motor neuron diseases (MND) encompass conditions like amyotrophic lateral sclerosis (ALS) and primary lateral sclerosis (PLS), marked by progressive degeneration of upper and/or lower motor neurons. The identification of specific biomarkers is crucial to reduce diagnostic delays.

Methods. This study presents three clinical cases evaluated at the Hospital Universitario 12 de Octubre, where the motor band sign on brain 18F-FDG PET/CT aided the diagnosis of MND. The studies were conducted using a SIEMENS Biograph True Point 6, with a review of relevant literature.

Results. In all three patients, PET/CT revealed hypometabolism in the prerolandic region, indicative of the motor band sign, contributing to the diagnosis of PLS or ALS.

Discussion. The motor band sign on 18F-FDG PET/CT emerges as a potential marker of upper motor neuron involvement, though the heterogeneity of MNDs and variability across studies call for further research to establish its specificity and sensitivity.

Conclusion. The motor band sign on 18F-FDG PET/CT is a promising biomarker for MNDs, although further studies are required to confirm its diagnostic validity.

Keywords in English: motor neuron disease, ALS, PLS, motor band sign, biomarker, FDG PET

INTRODUCTION

The term motor neuron disease (MND) refers to a heterogeneous group of diseases characterised by progressive degeneration of the upper and/or lower motor neuron. This group includes amyotrophic lateral sclerosis (ALS) and primary lateral sclerosis (PLS).[1] Incidence increases with age, peaking between 60 and 79 years of age,[2] with an estimated lifetime risk of approximately 1 in 350.[3]

Diagnosis is fundamentally clinical and based on exclusion, with the problems inherent to this approach in non-evident cases. A significant delay in diagnosis currently persists, with a median of 11-12 months,[4] although in cases of spinal onset, the delay may be up to 22 months.[5] Therefore, there is a need for a specific biomarker, as is the case in such other neurodegenerative diseases as Alzheimer disease.[6]

Our study reports 3 patients presenting a characteristic alteration with a currently unclear but relevant role in the diagnostic work-up of the disease: the motor band sign in the brain ^{18}F-FDG PET/CT study.

METHODS

We present 3 patients attended at the neuromuscular diseases unit and the demyelinating diseases unit of Hospital Universitario 12 de Octubre, a public tertiary hospital in Spain. Clinical data are anonymised. Brain ^{18}F-FDG PET/CT studies were performed with a SIEMENS Biograph TruePoint 6 system, and images were analysed using the AW Server 3.2 (ext. 4.8) and CortexID software. We conducted a non-systematic review of the literature using the PubMed search engine and various combinations of the following search terms: ALS, PLS, motor neuron disease, FDG PET/CT, motor band sign, biomarkers. We selected those articles considered most relevant due to the number of study patients, impact factor, and the role of perirolandic hypometabolism in brain ^{18}F-FDG PET/CT studies. We excluded studies on general patterns of brain ^{18}F-FDG PET/CT in MNDs, which are more numerous in the literature and extend beyond the scope of our study, which is focused on the motor band sign. Table 1 summarises the characteristics of some of the most relevant studies reviewed.

RESULTS

Patient 1

Our first patient was a woman with history of smoking, dyslipidaemia, and seropositive rheumatoid arthritis with no disease-modifying treatment. At 52 years of age, she started to manifest progressive symptoms of dragging of the right foot with a tendency to fall, lack of coordination in the right hand, and difficulty speaking. She reported no sensory alterations, sphincter involvement, or cognitive complaints, but some emotional lability. Physical examination revealed mild dysarthria and spastic hypotonia in all 4 limbs, with no clear weakness in muscle group balance, amyotrophy, or fasciculations at any level. Gait was slow and spastic, with alterations predominantly affecting the right side. A brain MRI study performed at a different centre showed a subtle subcortical hyperintensity in prefrontal gyri and in the corticospinal tract (a nonspecific finding that may be observed in patients with MND). A neck MRI study ruled out compression of the cervical spinal cord. An electromyography (EMG) study performed one year after symptom onset revealed no relevant findings. An extensive blood analysis was performed, including routine serology studies, human T-lymphotropic virus 1 (HTLV-1) serology, and antineuronal antibody serology, and yielded no significant findings. We concluded that the patient presented progressive, asymmetric (predominantly on the right side) spastic paraparesis with signs of upper motor neuron involvement. Therefore, in the absence of other plausible alternative diagnoses, the patient was diagnosed with PLS-type MND (at the age of 53 years); treatment was started with riluzole.

The clinical course was characterised by slowly progressive impairment. By the age of 57 years, 5 years after symptom onset, she displayed anarthria, emotional lability, frontal release signs, bilateral facial weakness, tongue atrophy, general tetraparesis of 2/5 on the Medical Research Council (MRC) scale, proximal tetraparesis of 4–/5 in the upper limbs, neck flexor weakness of 4/5, hyperreflexia, and intense associated spasticity. A brain ^{18}F-FDG PET/CT study revealed marked hypometabolism in the bilateral prerolandic area (Fig. 1), compatible in this context with motor band sign. The patient's condition continued progressing and she began to display discreet signs of lower motor neuron involvement (hand amyotrophy); her diagnosis was revised to clinically definite ALS. The patient died 10 years after symptom onset, at the age of 62 years.

Patient 2

This patient was a man with history of smoking, moderate alcohol consumption, hypertension, revascularised ischaemic heart disease, and chronic bronchitis. At the age of 61 years, he displayed sensory alterations in both hands. A neck MRI study performed at another centre revealed compressive spondylotic myelopathy treated with surgery 2 years later. Subsequently, sensory symptoms improved but a gradual worsening persisted, manifesting as progressive weakness in all 4 limbs, gait instability, and urinary urgency. A brain MRI study revealed lesions of inflammatory-demyelinating appearance that met spatial

dissemination criteria for multiple sclerosis, visual evoked potentials revealed demyelination of both optic nerves (predominantly on the left), and CSF analysis showed absence of oligoclonal bands. With these results, a diagnosis of primary progressive multiple sclerosis (PPMS) was established.

The patient was referred to our centre 5 years after symptom onset (at the age of 66 years). The patient continued experiencing progressive worsening of sensory symptoms. The physical examination revealed no clear motor deficit in muscle group balance, although he presented generalised hyperreflexia with absent plantar reflex and increased spasticity in the right arm. Gait was slow with a slightly widened base of support. Sensitivity was normal.

We reviewed the case and observed that the patient did not meet the 2017 McDonald criteria for diagnosis of PPMS. The brain MRI study was then repeated, revealing non-specific white matter lesions (one larger lesion in the right subcortical region was interpreted as a residual ischaemic lesion). We completed the study with determination of vitamin B_{12}; serology tests for *Borrelia*, *Treponema pallidum*, and HTLV-1; and an autoimmunity study, which yielded no relevant findings. An EMG study showed no signs of lower motor neuron involvement, and a brain ^{18}F-FDG PET/CT study revealed bilateral perirolandic hypometabolism (motor band sign) (Fig. 2). Considering these findings, with seemingly progressive clinical signs during the 2 years of follow-up at our centre (at 68 years of age) that were not explained by the surgically treated neck myelopathy, and given the absence of other reasonable alternative diagnoses, we established a provisional diagnosis of PLS. Treatment was then started with riluzole.

Patient 3

The third patient was a woman with allergy to iodinated contrast agents, history of smoking, and no other relevant history. At the age of 61 years, she presented weakness with no sensory alterations in the left hand, with an insidious and slowly progressive course. An initial EMG study displayed signs of denervation in C6-C7 myotomes of the left side, and a neck MRI study showed spondyloarthritis with a certain degree of stenosis of the cervical spinal canal. Considering that there was no alternative explanation for the weakness, and cervical spondylotic myeloradiculopathy could not be ruled out based on the MRI findings, C3-C4, C4-C5, and C5-C6 cervical discectomies were performed. Despite surgical treatment, symptoms continued worsening and the patient developed weakness in the left leg and spastic dysarthria. A new EMG was performed, revealing signs of bilateral but predominantly left-sided metameric neck denervation. At 4 years after onset (age of 65 years), the patient underwent a brain ^{18}F-FDG PET/CT study, which showed the motor band sign in the right perirolandic region. At the age of 67 years, she presented symptoms affecting the contralateral hemibody, with signs of upper motor neuron disease in the physical examination (including spastic dysarthria that clearly surpassed that expected in any cervical spinal lesion); therefore, the patient was diagnosed with PLS and began treatment with riluzole.

Table 2 summarises the main characteristics of the 3 cases. Fig. 3 shows the brain ^{18}F-FDG PET/CT studies of all 3 patients, with graphical representations created using quantitative analysis software.

DISCUSSION

Diagnosis of MND continues to be based on the clinical and electrophysiological parameters summarised in the revised El Escorial diagnostic criteria[7] and adapted in such documents as the Awaji-shima consensus recommendations (Table 3).[8] According to these criteria, the remaining complementary tests are only useful for excluding alternative causes.

Whereas neurophysiological studies are available to complement the physical examination when detecting lower motor neuron signs, upper motor neuron involvement can only be identified through clinical assessment, which is sometimes not sufficiently sensitive or specific (as in patient 2, whose signs of upper motor neuron disease could also have been attributed to the surgically treated myelopathy or to the misdiagnosis of PPMS; patient 3 also underwent surgery for stenosis of the cervical spinal canal). Therefore, new diagnostic criteria have been proposed in recent years, such as the Gold Coast criteria, which introduce supportive evidence for upper motor neuron dysfunction from transcranial magnetic stimulation studies of the central motor nervous system, MRI, and neurofilament levels.[9] However, none of these is specific to the disease.

In the search for a reliable biomarker, corticospinal tract hyperintensity on T2/FLAIR sequences has been proposed as a sign of upper motor neuron degeneration, although it presents low sensitivity and specificity.[10,11] Presence of this hyperintensity in the prerolandic cortex constitutes the so-called motor band sign, which is detected with greater sensitivity on susceptibility-weighted imaging sequences (which show iron accumulation in siderophages after neuronal degeneration and death). A study using these sequences reported hyperintensities in up to 78% of patients with ALS,[12] although their specificity was not established with comparative studies including healthy controls. Another study performed a retrospective analysis of susceptibility-weighted imaging sequences of 30 patients with ALS, 5 with PLS, and 10 controls.[13] The motor band sign was observed in 69.2%, 80%, and 0% of subjects, respectively. The authors concluded with limited evidence that this sign may be a surrogate marker of upper motor neuron involvement.

We may wonder how the motor band sign is reflected in such functional neuroimaging studies as brain ^{18}F-FDG PET/CT. One study including 390 patients diagnosed with ALS reported that hypometabolism in the medial frontal gyrus and pre- and postcentral gyri (which we may interpret as the motor band sign) was inversely correlated with King staging (based on the dissemination of motor symptoms in 3 different parts of the body [brainstem, upper limbs, and lower limbs] and the need for non-invasive mechanical ventilation and enteral nutrition).[14] In this regard, one study analysed brain ^{18}F-FDG PET/CT patterns in patients

with ALS (194 cases and 40 controls), with hypometabolism in the primary motor cortex being a frequent finding (in addition to other locations in the frontal and occipital lobes, and hypermetabolism in the midbrain, temporal pole, and hippocampus).[15] Overall, the pattern of alterations in ^{18}F-FDG PET/CT studies showed a sensitivity of 95% and a specificity of 83% when separating patients from controls. Another interesting study, including presymptomatic *C9orf72* mutation carriers up to 10 years prior to symptom onset, found that the region showing the greatest hypometabolism was the perirolandic area (equivalent to the motor band sign).[16]

If we focus on patients diagnosed with PLS, the above-mentioned limitations when confirming the presence of upper motor neuron dysfunction increase, as by definition, this may be the only sign and symptom of the disease. Thus, PLS represents a diagnostic challenge with a typical delay of several years until a diagnosis is established. Turner et al.[17] propose consensus criteria that again include the need to rule out other processes by neuroimaging and laboratory studies, and consider the motor band sign in brain ^{18}F-FDG PET/CT studies to be a promising marker. Other studies report 3 patients and one patient, respectively, displaying hypometabolism in the primary motor cortex in brain ^{18}F-FDG PET/CT studies.[18,19] The hypometabolism pattern in brain ^{18}F-FDG PET/CT studies of patients with PLS and ALS seems not to significantly differ.[20]

However, one study showed a weak correlation between motor involvement and a specific pattern of metabolic alteration in the ^{18}F-FDG PET/CT study of 131 patients with ALS, other than general hypometabolism in the frontal lobe.[21] In another study including patients with ALS, mimics, PLS, and progressive muscular atrophy, brain ^{18}F-FDG PET/CT studies showed no specific differences between ALS/PLS and mimics, and spinal ^{18}F-FDG PET/CT was needed to differentiate them.[22] This apparent contradiction in the literature may be explained by such factors as: *1)* the inherent heterogeneity of MNDs; *2)* differences in the analysis techniques, devices, and software used; or *3)* differences in the study populations and the disease progression time at the time of the ^{18}F-FDG PET/CT study. In any case, and despite the current lack of studies establishing the sensitivity and specificity of the motor band sign in brain ^{18}F-FDG PET/CT, it seems reasonable to expect lower sensitivity in cases in which upper motor neuron involvement is not prominent, as has already been suggested by Claassen et al.[18] Regarding specificity, it would be reasonable to exercise caution when interpreting situations in which involvement is bilateral and mild.

CONCLUSIONS

In conclusion, there is still a significant delay in the diagnosis of MNDs due to the current lack of reliable biomarkers. As suggested in our study, by unifying the findings of structural and functional neuroimaging studies, the motor band sign is identified as a promising

biomarker of upper motor neuron degeneration. Further studies are needed on its sensitivity and specificity parameters before we can consider its inclusion in future diagnostic criteria for MND.

Declaration of authorship

All authors have significantly contributed to the performance of this study, in agreement with the recommendations from the ICMJE.

Conflicts of interest

Dr Mariano Ruiz-Ortiz (mariano.ruiz.ortiz@gmail.com) has no conflicts of interest.

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differentiation between ALS and ALS mimics. Eur J Nucl Med Mol Imaging. 2020 Oct;47(11):2681-2690. doi: 10.1007/s00259-020-04786-y. Epub 2020 Apr 20. PMID: 32314027.

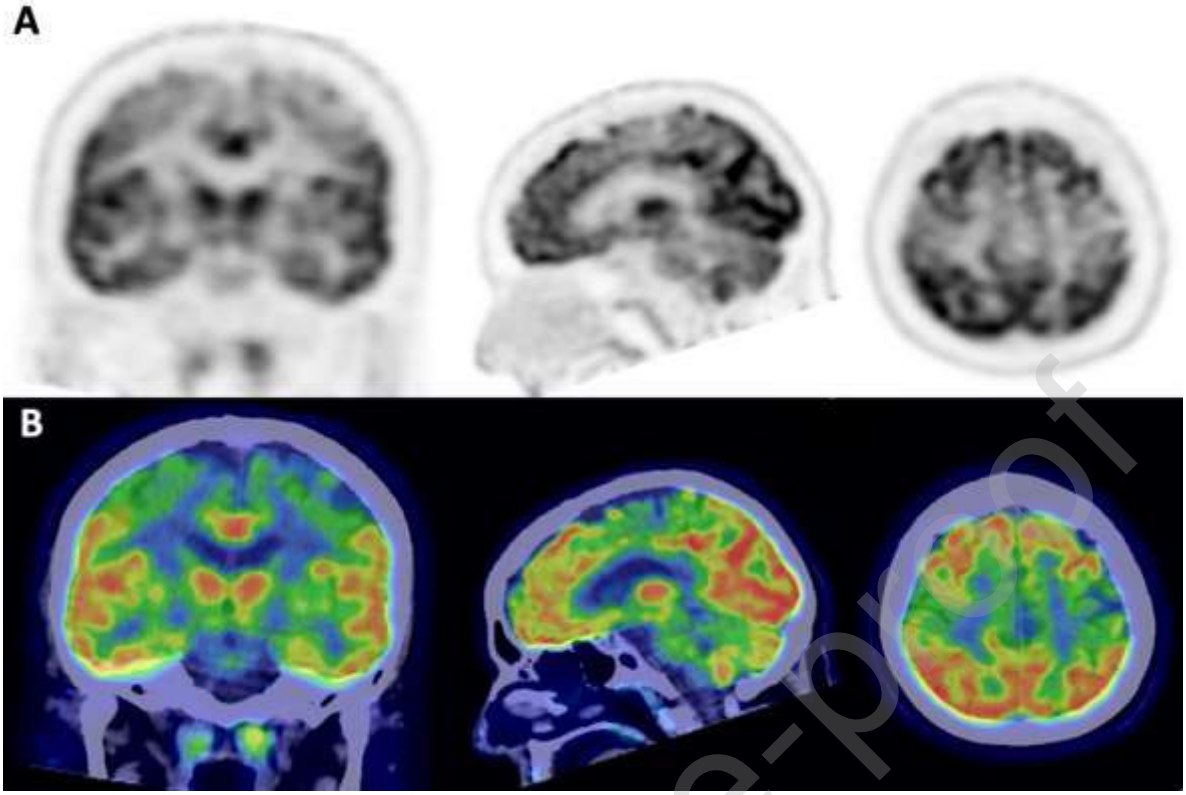
FIGURES

Figura 1 Caso 1. Imagen de PET 18F-FDG cerebral (A) y PET/TC 18F-FDG cerebral (B) en cortes coronal, sagital y axial (de izquierda a derecha) que muestran un marcado hipometabolismo en área perirrolándica.

Figura 2 Caso 2. A la izquierda se presenta un corte axial de un 18F-FDG cerebral cerebral donde puede observarse un hipometabolismo perirrolándico bilateral (signo de la banda motora), que se corresponde con una zona de mayor atrofia en la RM cerebral a la derecha.

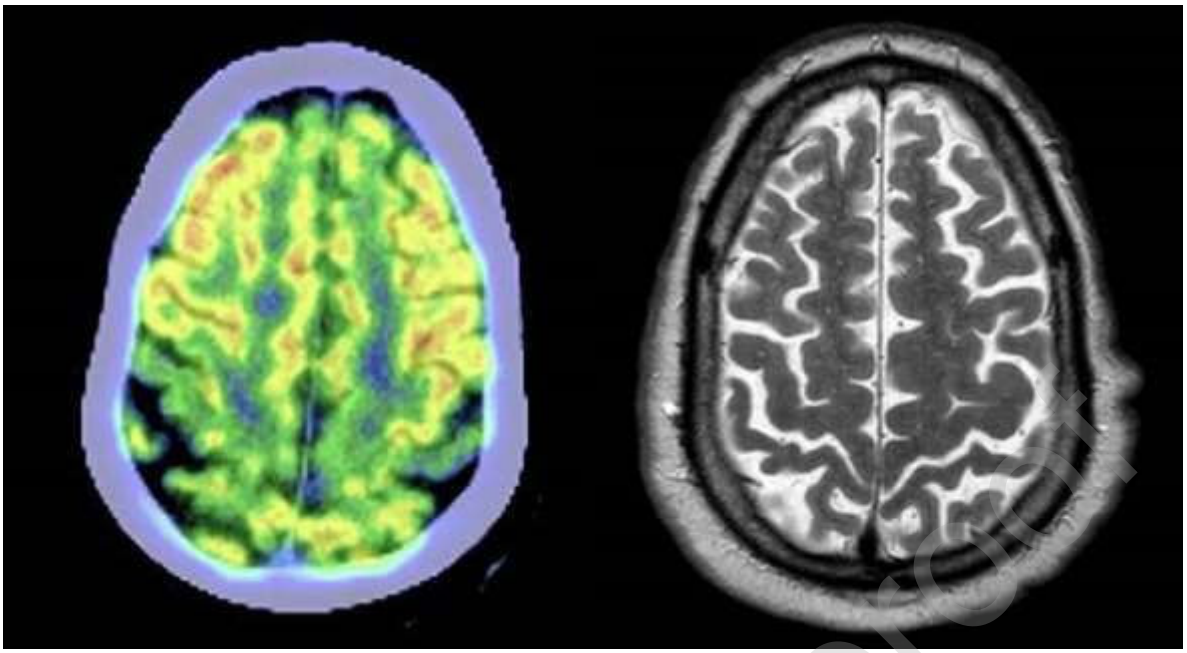
Figura 3 Se muestran arriba los cortex axiales de fusión de los estudios PET/TC 18F-FDG en cada caso (fila superior). En la fila inferior se muestra el análisis semicuantitativo mediante software CortexID con reconstrucción tridimensional cerebral, con valores de z-score. El caso 1 es el más claro de los tres, con una afectación en rango muy patológico y bilateral. En el caso 2 la afectación es asimétrica, cuantitativamente menos llamativa pero patológica especialmente en el lado derecho (esta afectación más leve se corresponde con el paciente con menor grado de certidumbre en el diagnóstico). En el caso 3 la afectación es claramente asimétrica, peor derecha, concordante con la clínica del paciente (mayor afectación hemicorporal izquierda).

Figure 1



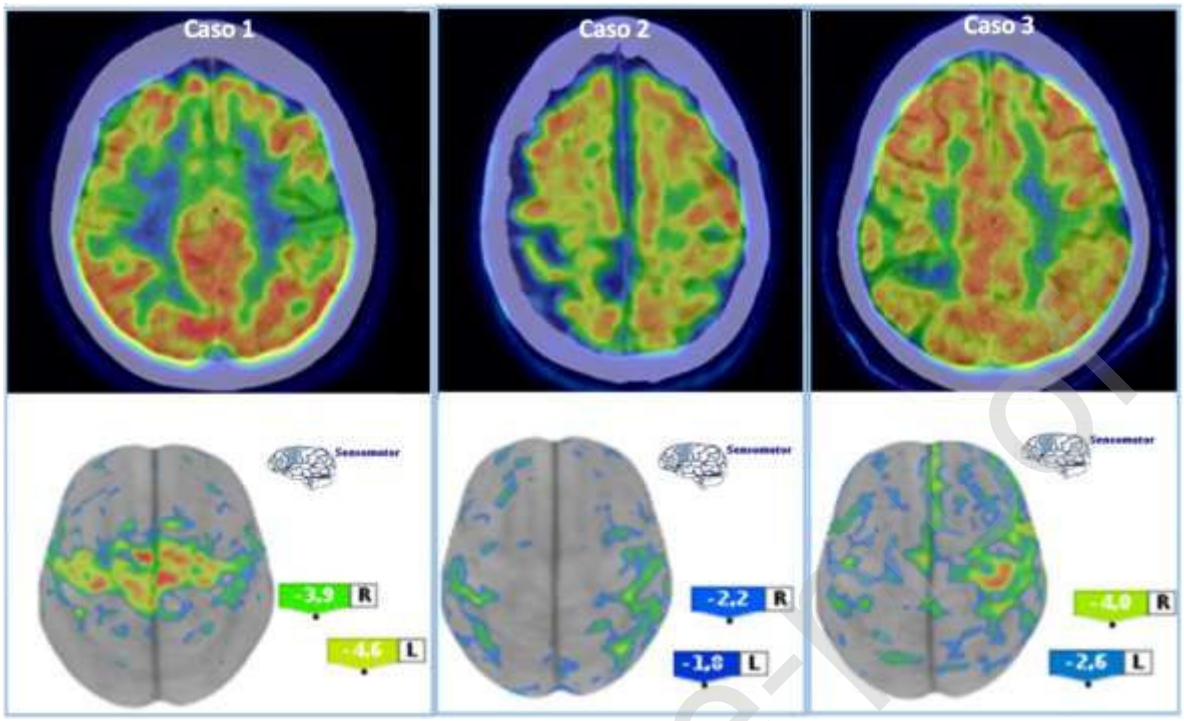
Patient 1. Coronal, sagittal, and axial slices (from left to right) from brain ^{18}F-FDG PET (A) and brain ^{18}F-FDG PET/CT (B) studies, showing pronounced hypometabolism in the perirolandic area.

Figure 2



Patient 2. Left: axial slice from a brain ^{18}F-FDG PET study, revealing bilateral perirolandic hypometabolism (motor band sign). Right: brain MRI showing an area of greater atrophy, coinciding with the area of hypometabolism in the left image.

Figure 3



Caso 1	Patient 1
Caso 2	Patient 2
Caso 3	Patient 3

Above: axial slices from brain ^{18}F-FDG PET studies of the 3 patients. Below: semi-quantitative analysis using the CortexID software, which uses z-score to generate a three-dimensional reconstruction of the brain. Patient 1 is the most obvious case, with bilateral involvement within very pathological ranges. In patient 2, involvement is asymmetrical and quantitatively less pronounced, but especially pathological on the right side (this milder involvement corresponds to the patient with lower diagnostic certainty). In patient 3, involvement is clearly asymmetrical and predominantly affects the right side, which is consistent with the patient's symptoms (the left hemibody was more affected).

TABLES

Table 1. Articles on brain ^{18}F-FDG PET studies in motor neuron disease.

Authors	Date	Journal	Type of study	No. patients	Results/conclusions
Canosa et al.[14]	2020	*Eur J Nucl Med Mol Imaging*	Case-control study	390 cases 40 controls	Brain hypometabolism in ^{18}F-FDG PET/CT studies affected the bilateral medial frontal gyri, right precentral gyrus, and right postcentral gyrus, which was inversely correlated with King stage of ALS.
Van Laere et al.[20]	2014	*JAMA Neurol*	Case-control study	81 cases 81 controls	^{18}F-FDG PET/CT studies were able to correctly classify 95% of cases of ALS and 71% of cases of PLS
Pagani et al.[15]	2014	*Neurology*	Case-control study	195 cases 40 controls	The study identified a 95% sensitivity and 83% specificity rate for separating patients from controls using brain ^{18}F-FDG PET/CT studies.
Claassen et al.[18]	2010	*Arch Neurol*	Case series	3 cases	All 3 patients presented the motor band sign in the brain ^{18}F-FDG PET/CT studies.

ALS: amyotrophic lateral sclerosis; PLS: primary lateral sclerosis.

Table 2. Characteristics of our study patients.

Patient	**Age**	**Progression time**	**Affected body parts[1]**	**Motor band sign in the ^{18}F-FDG PET study**	**Working/alternative diagnoses**
Patient 1	62 years	5 years	Signs of UMN degeneration at the bulbar, cervical, thoracic, and lumbosacral levels	Bilateral	Strong suspicion of PLS Progressed to clinically definite ALS during follow-up

Patient 2	68 years	7 years	Signs of UMN degeneration at the cervical and lumbosacral levels	Bilateral	Moderate suspicion of PLS Alternative diagnosis: cervical spondylotic myelopathy with incomplete recovery after neurosurgery
Patient 3	67 years	4 years	Signs of UMN degeneration at the bulbar, cervical, and lumbosacral levels. Signs of LMN degeneration at the cervical level	Unilateral	Strong suspicion of PLS Signs of LMN degeneration at the cervical level, attributed to cervical polyradiculopathy

[1]At the time of performance of the brain ^{18}F-FDG PET/CT study.
ALS: amyotrophic lateral sclerosis; LMN: lower motor neuron; PLS: primary lateral sclerosis; UMN: upper motor neuron.

Table 3. El Escorial criteria with Awaji-shima consensus recommendations.[1]

Principles

Diagnosis of ALS requires (A) *the presence of:*

(1) *evidence of lower motor neuron (LMN) degeneration* by clinical, electrophysiological or neuropathological examination; and

(2) *evidence of upper motor neuron (UMN) degeneration* by clinical examination; and

(3) *progressive spread of symptoms or signs* within a region or to other regions, as determined by history, physical examination, or electrophysiological tests

(B) *in absence of*:

(1) *electrophysiological or pathological evidence of other disease* processes that might explain the signs of LMN and/or UMN degeneration, and

(2) *neuroimaging evidence of other disease processes* that might explain the observed clinical and electrophysiological signs.

Diagnostic categories

Clinically definite ALS is defined by clinical or electrophysiological evidence by the presence of LMN as well as UMN signs in the bulbar region and at least 2 spinal regions[2] or the presence of LMN and UMN signs in 3 spinal regions.

Clinically probable ALS is defined on clinical or electrophysiological evidence by LMN and UMN signs in at least 2 regions with some UMN signs necessarily rostral to (above) the LMN sign.

Clinically possible ALS is defined when clinical or electrophysiological signs of UMN and LMN dysfunction are found in only one region; or UMN signs are found alone in 2 or more regions; or LMN signs are found rostral to UMN signs. Neuroimaging and clinical laboratory studies will have been performed and other diagnoses must have been excluded.

ALS: amyotrophic lateral sclerosis.[1]Adapted from de Carvalho et al.[8]
[2] Body regions are defined as bulbar, cervical, thoracic, and lumbosacral.