Characterization of the nigroestriatal system in a sample of patients with amyotrophic lateral sclerosis

Caracterização do sistema nigroestriatal em uma amostra de pacientes com esclerose lateral amiotrófica

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Abstract

Background The coexistence of amyotrophic lateral sclerosis (ALS) with clinical forms of Parkinson disease (PD), although uncommon, is found to a greater degree than one would expect by chance. The pathological mechanisms of ALS and PD are still not fully understood, and the coexistence of these two diseases suggests that they could share mechanisms in common.

Objective Here we present a sample of patients with clinically definitive or probable ALS who were evaluated with single-photon emission computed tomography SPECT/TRODAT and compared with non-ALS controls.

Methods Patients with clinically definite or probable ALS were assessed with the amyotrophic lateral sclerosis functional rating scale (ALSFRS) to define severity and had their demographic data collected. The TRODAT results of patients with ALS were compared with those of patients with a diagnosis of PD with less than 10 years of duration, and with patients with a diagnosis of others movement disorders not associated with neurodegenerative diseases.

Results A total of 75% of patients with ALS had TRODAT results below the levels considered normal; that was also true for 25% of the patients in the control group without neurodegenerative disease, and for 100% of the patients in the PD group. A

Keywords
- Amyotrophic Lateral Sclerosis
- Parkinson Disease
- Dopamine Plasma Membrane Transport Proteins
- Striatonigral Degeneration
- SPECT

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statistically significant difference was found between patients with ALS and the control group without neurodegenerative disease in the TRODAT values < 0.05.

Conclusions Our study fits with the neuropathological and functional evidence that demonstrates the existence of nigrostriatal dysfunction in patients with ALS. Further research to better understand the role of these changes in the pathophysiological process of ALS needs to be performed.

Resumo

Antecedentes A coexistência da esclerose lateral amiotrófica (ELA) com formas clínicas da doença de Parkinson (DP), embora incomum, é encontrada em um grau maior do que seria esperado ao acaso. Os mecanismos patológicos da ELA e da DP ainda não são totalmente compreendidos e a coexistência dessas duas doenças sugere que elas podem compartilhar mecanismos em comum.

Objetivo Apresentamos uma amostra de pacientes com ELA clinicamente definida ou provável que foram avaliados com tomografia computadorizada por emissão de fóton único (SPECT)/TRODAT e comparados com controles sem ELA.

Métodos Pacientes com ELA clinicamente definida ou provável foram avaliados com a escala funcional de esclerose lateral amiotrófica (ALSFRS) para definir a gravidade e foram coletados os seus dados demográficos. Os resultados do TRODAT de pacientes com ELA foram comparados com aqueles de pacientes com diagnóstico de DP com menos de 10 anos de duração e com pacientes com diagnóstico de outros distúrbios do movimento não associados a doenças neurodegenerativas.

Resultados Um total de 75% dos pacientes com ELA apresentou resultados de TRODAT abaixo dos níveis considerados normais; 25% no grupo controle sem doença neurodegenerativa e 100% no grupo DP. Uma diferença estatisticamente significativa foi encontrada entre os pacientes com ELA e o grupo controle sem doença neurodegenerativa nos valores de TRODAT $p < 0{,}05$.

Conclusões Nosso estudo está de acordo com as evidências neuropatológicas e funcionais que demonstram a existência de disfunção nigroestriatal em pacientes com ELA. Mais pesquisas para entender melhor o papel dessas mudanças no processo fisiopatológico da ELA precisam ser realizadas.

Palavras-chave

- Esclerose Amiotrófica Lateral
- Doença de Parkinson
- Proteínas da Membrana Plasmática de Transporte de Dopamina
- Degeneração Estriatonigral
- SPECT

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that affects the motor neurons.[1] It is relatively uncommon, with an annual incidence of 2 per 100,000 and a prevalence of 5 to 7 per 100,000 people. General practitioners may expect to see one or two cases throughout their careers.[2]

Amyotrophic lateral sclerosis is the most common acquired motor neuron disease. Currently, ALS is known to affect more than motor neurons and is often associated with cognitive abnormalities (frontotemporal dysfunction) and pseudobulbar affection.[3] About 5 to 10% of cases of ALS are familial, and the rest are sporadic. Interestingly, many familial ALS gene variants have been described in sporadic cases. Currently, the most common genes related to ALS are *C9orf72, SOD1, TARDBP*, and *FUS*.[4] Mutations in other genes associated with familial ALS, such as *alsin*, *senataxin*, *dynactin 1*, *angiogenin*, and *optineurin* are relatively uncommon.[5] Also, some of these gene variations may be associated with frontotemporal dementia and Parkinsonian features.[6]

The coexistence of ALS with clinical forms of Parkinsonism, although uncommon, is found to a greater degree than one would expect by mere chance. This suggests that patients with ALS could have subclinical lesions of the nigrostriatal system (NS).[7]

The relationship between ALS and Parkinsonism has been reported in medical literature for many years. Between 1962 and 1980, in the region of Papua (Indonesia), there were around 97 cases of ALS and Parkinsonism in the southern coastal region, among a population of 7,000 inhabitants. A distinct feature in these three regions was the greater number of patients with the ALS-Parkinsonism-dementia complex in Guam and Kii (Japan), a disease that has currently shown a significant decrease in its incidence due to the control over the neurotoxic factors that were related with the onset of symptoms.[8] There is pathophysiological evidence linking similar processes in the neurodegenerative phenomenon seen in patients with ALS, Parkinson disease (PD), and other forms of Parkinsonism.

Intracytoplasmic inclusions of the TDP43 protein, present in both familial ALS types associated with the *TARDBP* gene

mutation and in almost all cases of sporadic ALS, are not pathognomonic of ALS. These have also been observed in Alzheimer disease, Lewy corpuscle dementia, the Guam dementia-parkinsonism complex, and even in posttraumatic encephalopathy.[9] The pathological mechanisms of ALS and PD are still not fully understood, and the coexistence of these two diseases suggests that they could share mechanisms in common. Previous pathological and functional neuroimaging studies in patients with ALS without Parkinsonism have demonstrated dopaminergic neuronal loss in substantia nigra and presynaptic dopaminergic NS dysfunction.[10] Decreased dopamine D2 receptor binding has been demonstrated in vivo in ALS patients. A study to evaluate the mechanism of dopaminergic alteration in patients with ALS concluded that, probably, the D2 receptor deficit could be related to a down regulation phenomenon because of increased glutamate-related neurotoxicity.[11] Although used mainly in the differential diagnosis of Parkinson disease and similar disorders not associated with NS dysfunction, functional neuroimaging (SPECT-TRODAT) studies for the evaluation of dopamine transporter (DAT) have been of great help in the understanding of other neurodegenerative diseases.

To study the hypothesis that patients with ALS without clinical symptoms of Parkinsonism have dopaminergic dysfunction, we performed SPECT-TRODAT studies in a sample of patients diagnosed with ALS.

METHODS

Patients

Patients were selected from the service of neuromuscular diseases of Hospital Irmandade da Santa Casa de Misericórdia de Porto Alegre (ISCMPA), RS, Brazil. Up to December 2017, 26 patients with motor neuron disorders were followed up at the outpatient clinic, and a total of 16 patients met the criteria for probable or definite ALS, according to the Awaji-Shima recommendations (►**Figure 1**). To carry out the study, a convenience sample of 10 patients was defined. We reviewed the electrodiagnostic studies of the selected patients and performed a complete neurological exam to confirm the diagnosis of probable or definitive ALS, as well as to confirm the non-coexistence of Parkinsonian symptoms. All the included cases were sporadic. The ALSFRS functional assessment scale was applied, and data were collected, such as age of onset of symptoms, years of disease, pathological comorbidities, environmental risk factors, and family history. The project was approved by the ethics committee of ISCMPA. A signed informed consent was obtained from all patients.

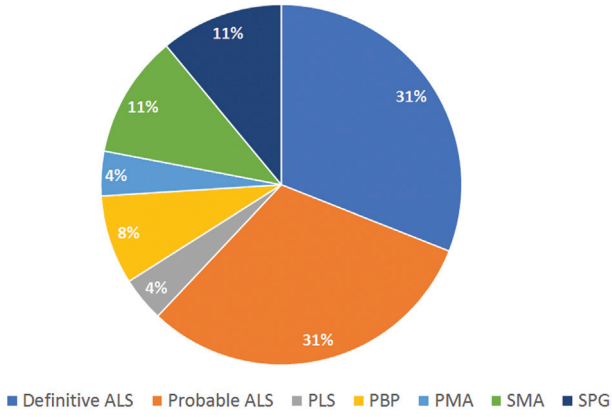

Figure 1 Distribution of patients with motor neuron disease from Hospital Irmandade da Santa Casa de Misericórdia de Porto Alegre. Abbreviations: ALS, amyotrophic lateral sclerosis; PLS, primary lateral sclerosis; PBP, pseudobulbar palsy; PMA, progressive muscular atrophy; SMA, spinal muscle atrophy; SPG, spastic paraplegia.

Controls

The database of the movement disorder service of Hospital ISCMPA was searched for patients with diagnoses of non-neurodegenerative diseases (drug-induced Parkinsonism, exacerbated physiological tremor, psychogenic tremor, and essential tremor) who had performed SPECT-TRODAT studies to evaluate the NS in the period from 2000 to 2018. A total of two controls per patient was defined. Another search for patients with Parkinson disease (PD), according to the London Brain Bank Criteria, with 10 years or less of disease duration and having performed SPECT-TRODAT was performed. In these patients, data such as age of onset of symptoms and time of disease evolution were collected. A total of two PD cases per patient were selected.

SPECT-TRODAT

All patients selected with probable or definitive ALS according to the Awaji-Shima recommendations were referred to the nuclear medicine service of Hospital Santa Rita, part of the ISCMPA hospital complex. A total of eight patients underwent the study. Due to the lack of radiopharmaceuticals in the last months of 2017 until May 2018 in Brazil, it was not possible to reach the defined sample of 10 patients. TRODAT is labeled with 99 mTc (technetium). The vial containing the saline solution ("cold" kit) is marked with 50 mCi of pertechnetate. Chemical quality control tests are performed prior to the administration of the radiopharmaceutical in the subjects. No preparation is required prior to the injection of the radiopharmaceutical. The dose administered is 20 mCi of (99mTc) TRODAT. After release of the dose by radiopharmacy, the material is administered by peripheral vein. The time required between dose administration and the onset of imaging is $\sim$ 4 hours. The acquisition is performed on Siemens SPECT/CT (Symbia T2) equipment with high resolution, low energy collimators; the matrix used is 128×128, circular orbit, 120 stops, 30 seconds per image. The low-dose tomographic image is performed for co-recording and attenuation correction. Regions of interest (ROI) identified in the transaxial cut referring to striatum, caudate, and putamen (anterior and posterior) are generated from the anatomical image of each patient, using the structural limit as a reference. Activity per pixel in each region is used to calculate the radiopharmaceutical binding index through the formula: binding index or density of the active dopamine transporter (DAT) in the caudate = (caudate activity - activity in the reference region [occipital lobe]) activity

Table 1 Clinical data on amyotrophic lateral sclerosis, non-neurodegenerative disease, and Parkinson disease groups

	ALS	NNDD	PD	Statistics
Definitive diagnosis	4	16	16	
Probable diagnosis	4			
Age (years - SD)	57.8 ± 16.1	64.1 ± 12.5	61.0 ± 11.0	$p = 0.518$
Sex (F/M)	2/6	6/10	4/12	$\chi^2 = 0.7$
Years of diseases duration	4.3 ± 3		6.3 ± 2.4	$p = 0.7$
Smoking	4/8			
Exposure to agrochemicals	4/8			
TRODAT abnormal	75%	25%	100%	$\chi^2 < 0.001$
TRODAT normal	25%	75%	0%	

Abbreviaions: ALS, amyotrophic lateral sclerosis; F/M, female/male; NNDD, non-neurodegenerative diseases; PD, Parkinson disease; SD, standard deviation.

in the reference region. The same is done for the anterior putamen, posterior putamen, and striatum (putamen and caudate together). A value greater than 1.1 was considered normal for the SPECT/TRODAT study.

Statistical analysis

Data was entered in a Microsoft Excel spreadsheet (Microsoft Corp., Redmond, WA, USA) and later exported to the IBM SPSS Statistics for Windows, version 24.0 software (IBM Corp., Armonk, NY, USA) for statistical analysis. The categorical variables were described by frequencies and percentages and were associated with the chi-squared test of the trend or the chi-squared test of association. The quantitative variables were evaluated in relation to their symmetry by the Kolmogorov Smirnov test. The variables with symmetrical distribution were described by mean and standard deviation and compared between the groups by the analysis of variance (ANOVA) test. To compare the variables with asymmetric distribution between two levels of a qualitative factor, the Mann-Whitney test was used. A significance level of 5% was considered.

RESULTS

A total of 8 patients with sporadic ALS were evaluated (ages between 29–75 years [SD = 16.09, mean 57.9]) All patients met the criteria for definite or probable ALS according to the recommendations of Awaji-Shima (4 probable and 4 definite). None of the patients showed signs of Parkinsonism or dementia on physical examination. Disease duration among patients ranged from 1 to 11 years, with an average time of 4.3 years and SD = 2.9.

The distribution between the groups ALS, controls (non-neurodegenerative diseases), and PD did not show differences between sex and age of the patients (for sex, the Pearson chi squared test showed $p = 0.7$, and for age, the ANOVA showed a p value of 0.518).

Demographic data such as education, smoking, and exposure to agrochemicals were collected in the group of patients with ALS. In this group, family history of ALS and Parkinsonism was negative. In the case of the control and PD groups, the data that were available in the electronic medical record were collected (►**Table 1**).

In the group of patients with ALS, 6\8 TRODAT showed some degree of NS dysfunction (below the levels accepted as normal [1.1]), which represents a total of 75%, compared with 25% in the control group (none-neurodegenerative disease) and 100% in the PD group ($p < 0.001$) (►**Figure 2**). The main factor that contributed to this difference was the significantly low values in the NS of patients with PD, which has mean values of radiopharmaceutical uptake far below the patients and controls (►**Table 2**). To determine if there was a real NS dysfunction in patients with ALS, a comparison was made with the control group (none-neurodegenerative disease), and a statistically significant difference was found ($p = 0.019$) (►**Table 2**). In this study, it was not possible to evaluate if there was a greater correlation between the presence of nigrostriatal dysfunction and a specific ALS subtype in our study, due to the small sample of patients.

To assess the severity of ALS, the ALSFRS was used. Subsequently, we compared the number of abnormal TRODATs against the ALSFRS results. Through this evaluation, we observed that, for our sample of patients with ALS, there was no difference between the severity of the disease and the presence of functional alteration of the NS evaluated by TRODAT (►**Table 3**). In our sample of patients, it was not possible to establish a relationship between NS degeneration in patients with ALS and disease duration (►**Table 4**) or severity according to the functional scale.

DISCUSSION

Amyotrophic lateral sclerosis is classically considered to be a disease of the motor neurons. However, several imaging studies have demonstrated diffuse neuronal degeneration in subcortical structures in a patient with ALS, including the thalamus, substantia nigra, basal ganglia, subthalamic nucleus, and cerebellum. Studies using techniques such as PET, functional magnetic resonance imaging (MRI), and diffusion tensor imaging (DTI) have demonstrated the pathological findings of the involvement of these structures.[12]

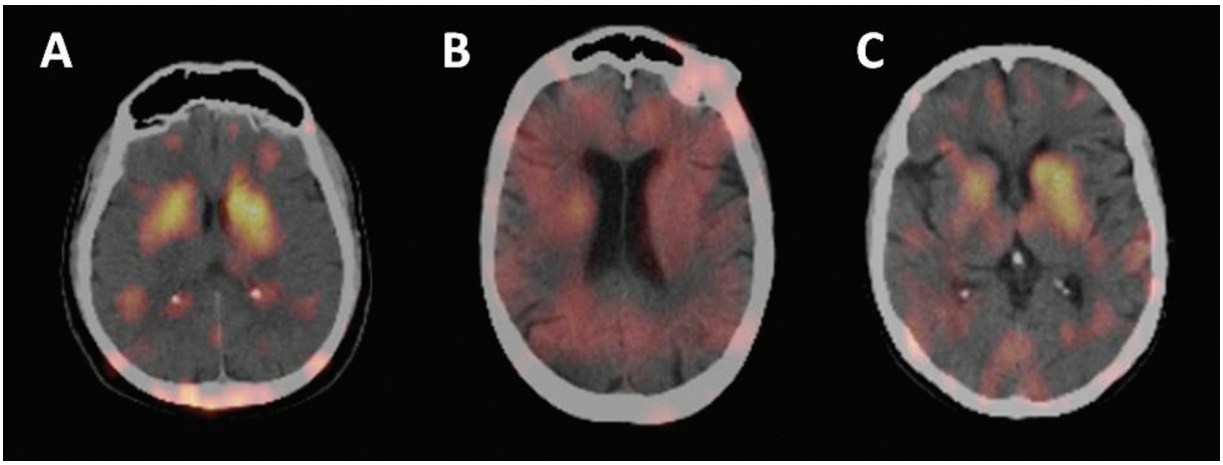

Figure 2 TRODAT-SPECT imaging in normal control, PD, and ALS. **(A)** TRODAT in a normal control showing normal tracer uptake; **(B)** TRODAT in a PD patient showing diffuse and bilaterally severe reduction in tracer uptake**; (C)** TRODAT in an ALS patient showing a preserved tracer uptake in the left striatum and reduced in the right (light degree in the caudate and more severely in the putamen). Abbreviations: ALS, amyotrophic lateral sclerosis; PD, Parkinson disease.

Table 2 99 mTc-TRODAT-1 SPECT/CT scan in amyotrophic lateral sclerosis and control (NNDD) groups

TRODAT\Group	ALS	NNDD	Statistics
Abnormal	6	4	$p = 0.019$
Normal	2	12	

Abbreviations: ALS, amyotrophic lateral sclerosis; NNDD, non-neurodegenerative diseases.

Nigrostriatal system dysfunction in patients with ALS has been previously demonstrated in other studies through SPECT-TRODAT as well as pathologic evaluation methods. However, in some of these reports, the patients presented with atypical symptoms associated with the diagnosis of ALS, such as Parkinsonism or ophthalmoplegia.[7]

Previous studies (►**Table 5**)[10,11,13–16] have evaluated NS function in patients with sporadic ALS with and without associated Parkinsonian symptoms. In our study, we observed dysfunction of the NS in 6 of 8 patients, which was significant when compared with controls with non-neurodegenerative diseases. Due to the small sample size, it was not possible in our study to correlate the alterations in the functioning of the NS with other data, such as disease progression time, severity assessed by functional scale, or clinical subtype (bulbar or limb onset). Another previous study has correlated the loss of dopaminergic nigrostriatal neurons with the occurrence of motivational and affective disorders in PD.[17] Perhaps, a similar pathophysiological mechanism might be related to the genesis of these symptoms also in patients with ALS.

In summary, we know that an altered TRODAT study suggests dysfunction of the nigrostriatal system, which is known to be present in PD, but also in forms of atypical Parkinsonism. This article broadens the understanding of the pathophysiology of ALS, suggesting that, in addition to involvement of the motor neurons, there is involvement of the nigrostriatal pathways. In fact, there is increasing evidence that ALS, although recognized as a predominant motor neuron disease, presents subclinical diffuse neurological changes in different subcortical structures. This could modify not only our understanding of the neurodegenerative disease process but also the future diagnostic and therapeutic approach.

As future perspectives, studies with a larger sample of patients, evaluating different clinical stages of the disease

Table 3 Abnormal TRODAT and amyotrophic lateral sclerosis functional rating scaleresults

	TRODAT	N	Mean	SD
ALS-FRS TOTAL	Abnormal	6	23.33	6.47
	Normal	2	21.5	4.95

Abbreviations: ALS, amyotrophic lateral sclerosis; ALS-FRS, ALS functional rating scale; SD, standard deviation.

Table 4 Relationship between amyotrophic lateral sclerosis disease duration and TRODAT

	TRODAT	N	Mean	SD	Statistics
ALS years of diseases duration	Abnormal	6	4.8	3.31	$p = 0.49$
	Normal	2	3.0	1.41	

Abbreviations: ALS, amyotrophic lateral sclerosis; SD, standard deviation.

Table 5 Medical literature on sporadic amyotrophic lateral sclerosis and NS function

Autor	Year	Country	Diagnostic criteria	N	Nigrostriatal dysfunction prevalence
Takuto Hideyama[13]	2006	Japan	Definitive ALS	5	0%
OJM Vogels[11]	2000	Holland	Definitive ALS	30	Significative reduction (% not referred)
Hirohide Takahashi[15]	1993	Canada	Definitive ALS	16	18.75%
Hee Kyung Park[10]	2011	Korea	ALS (criteria not referred)	2	100%
GD Borasio[14]	1998	Germany	Definitive or probable ALS	18	66.6%
Marcello Deriu[16]	2011	Italy	ALS	1	100%

Abbreviation: ALS, amyotrophic lateral sclerosis.

and including the assessment of genetic forms of ALS could add more information about the involvement of the nigrostriatal system in this context. Furthermore, it would be possible to assess whether there are differences in the involvement of this system in the sporadic and familial forms.

Authors' Contributions

CAJM, LHTF, NSJ, DTN, EGCN: acquisition of data, literature review; FTR, CRMR: critical revision of manuscript for intellectual content, study supervision.

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Conflict of Interest

The authors have no conflict of interests to declare.

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