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Cognition and Lewy body disease

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Introduction. We're assisting in last years to an important change in clinical manifestations of Parkinson disease. Nowadays motor symptoms have best treatments if we compare with those existing some decades ago, which in last term, permits other manifestations being the main disabilities in an advanced Parkinson disease. Among these disabilities cognitives are the most severe due to it's prevalence and devastating consequences.

Clinical Case. We present the clinical case of a 72 aged woman who complains of cognitive and depressive symptoms, probably compatible with a depressive disorder, but finally diagnosed with Lewy body disease despite these cognitive manifestations are most common in advanced disease.

Conclusions. We're showing an interesting case of Lewy body disease due to it's incipient symptomatology in cognitive manifestations (which makes it interesting for psychiatric value), motor manifestations (interesting for neurological value) and organic manifestations as complementary tests demonstrate. Finally, we justify the usage of rivastigmine as the choice of treatment in these cases which onset is mainly composed by cognitive symptoms.

Key words:
Parkinson, Lewy Bodies, dementia, cognitive impairment, rivastigmine, dopamine.

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Cognición y enfermedad por cuerpos de Lewy

Introducción. Asistimos en los últimos años a un cambio importante en las manifestaciones clínicas de la Enfermedad de Parkinson (EP). Los problemas motores para los que hoy en día existen mejores tratamientos que hace unas décadas, han dado paso a manifestaciones no motoras como principal fuente de incapacidad en la EP

avanzada, siendo el deterioro cognitivo la más grave por su prevalencia y devastadoras consecuencias.

Caso Clínico. Presentamos el caso de una paciente mujer de 72 años que llega a nuestro servicio aludiendo quejas de tipo cognitivo y depresivas, posiblemente compatibles con un síndrome depresivo, y a la que finalmente se diagnostica de Enfermedad por Cuerpos de Lewy pese a ser dichas manifestaciones cognitivas más propias de los cuadros avanzados.

Conclusión. Mostrar un caso clínico de Enfermedad por Cuerpos de Lewy de interés por su sintomatología incipiente de tipo cognitivo (de interés para la valoración psiquiátrica), de tipo motor o parkinsonianos (de interés para la valoración neurológica) y de tipo orgánico, a la luz de las pruebas complementarias efectuadas. Asimismo, justificamos el uso de la rivastigmina como tratamiento de elección para este tipo de cuadros de Enfermedad por Cuerpos de Lewy que debutan con sintomatología cognitiva.

Palabras clave:
Parkinson, Cuerpos de Lewy, demencia, deterioro cognitivo, rivastigmina, dopamina.

INTRODUCTION

Parkinson's Disease (PD) is not only the consequence of lack of dopamine in different brain areas but also the result of a diffuse and slowly progressive neurodegenerative process that causes dysfunction of several neurotransmission systems (norepinephrine, serotonin, acetylcholine) as well as neuronal death of cortical and subcortical structures.¹

The clinical description of the non-motor disorders associated to PD has been supported, on the one hand, by clinical-pathological studies developed by Braak et al.² that show that the neurodegenerative process of PD seems to follow a progressive caudorostral course that initiates in the olfactory lobe and the dorsal motor nucleus of the vagus, on the level of the oblongata medulla (spinal bulb), and continues in an ascendant way, causing the degeneration of

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the *locus coeruleus*, formation of the reticular pontine, raphe nucleus and pedunculopontine nucleus before neuronal death and Lewy body (LB) deposit can be observed in the pars compacta of the substantia nigra (SNpc).

After, the neurodegenerative process and deposit of LB extends towards the hippocampus, anterior and posterior (precuneus) cingulate cortex and towards areas of neocortical association, such as the entorhinal cortex and neighboring structures of the medial temporal cortex, the insula and associative areas of the temporal, parietal and frontal lobes.

The combined non-motor symptoms tend to worsen the course of the disease, so that they represent, in advanced phases, the symptoms having the greatest impact on quality of life.³ Specifically, the factors that condition a greater dependence and lack of satisfaction in PD, both for the patient and family, are the cognitive disorders, depression, sleep disorders and non-motor symptoms with poor response to dopaminergic therapy (dysphagia, dysarthria and postural reflex disorders).⁴

Among all the non-motor symptoms, cognitive deterioration leads to the most interest and has the greatest development. It is currently known that the presence of cognitive deterioration in PD is very frequent, it being possible for it to affect more than 60% of all the patients after 10 years of evolution,⁵ with risk of developing dementia of up to 6 times greater than in the general population.

Therefore, the clinical manifestations of the cognitive deterioration in Parkinson's Disease (PD) vary from subtle and focal deficits, basically demonstrable with neuropsychological test, to global dementia.

In the following, we present a case of Lewy body disease, which had an atypical onset with cognitive and behavioral type symptoms in absence of important extrapyramidal symptoms.

Our aim will be to demonstrate the diagnostic process made to be able to form a clinical opinion of a progressive Parkinson's disease and progressive dementia, associated in both cases to the presence of Lewy bodies.

CASE DESCRIPTION

M. is a 72-year old woman who was brought to our service due to affective deterioration and behavior disorder. She has been suffering from depressive type affective symptoms for the last 30 years, and has required several hospitalizations since then. During one of these hospitalizations, she received Electroconvulsive Therapy (ECT), with partial response.

On this occasion, the patient has a clinical picture characterized by apathy-abulic mood, presence of thematic delusions having weak structuration (she has developed delusional ideas of ruin, reporting being ruined by the large amounts of money her children have spent, without her knowledge, for her treatment in a private psychiatric clinic), sensorimotor disorders with hallucinations (mainly of human type, with unknown male figure) and alterations in the behavior subsequent to the delusional symptoms.

Recently, her mood state has seemed to worsen: she cries frequently and states she feels very alone in spite of the daily cares of her children and husband.

She reports having been a very active person, and that she currently has stopped doing most of the activities she did in the past.

The patient is correctly oriented spatially-temporally and autopsychic. No memory or recognition deficits or in fixation and evocation processes are observed. Only difficulties in focalized and maintained attention seem to be found.

RESULTS

In order to make a correct differential diagnosis between depressive episode with psychotic symptoms, depressive pseudodementia or cognitive deterioration, different complementary tests were made, finding the following results:

- Brain Magnetic Resonance: Senile lesions of the white matter on the frontal level. Mild corticosubcortical atrophy was also found.
- Brain SPECT: Frontotemporal and parietal hypoperfusion with cerebellar hypoperfusion, it being recommended to perform a second test to rule out "Lewy Body Disease."
- Brain SPECT with DAT-SCAN: Image consistent with basal ganglia involvement on level of right putamen.

For this reason, Neurology was able to observe the existence of mild-moderate cognitive deterioration with extrapyramidal symptoms. They reached the diagnosis of "Lewy body dementia."

During the entire hospitalization, the patient had an adequate attitude and both the sensorial-perceptive and affective symptoms which had motivated the consultation disappeared. Contact and functioning became marked by cognitive alterations, in absence of an affective-depressive background.

Due to the diagnosis made, the drug treatment of the patient was reviewed. Her treatment was changed to 20 mg

of Escitalopram, 100 mg of Trazodone and initiation of treatment with Rivastigmine as a solution, beginning with 3 mg which would subsequently be increased to 6 mg/day.

CONCLUSIONS

Lewy Body Dementia has recently been identified as its own entity, different from Alzheimer's disease and Parkinson's Disease (PD), with associated dementia. At times, it is very difficult to establish a differential diagnosis.⁶

In PD, the mild cognitive deficits mainly include abnormal use of memory storage and dysexecutive syndrome secondary to corticosubcortical circuits alterations that connect the dorso- and ventrolateral prefrontal cortex with the dorsal striate (putamen and dorsal caudate) and the mesencephalic ventral tegmental area.⁷

In the development of moderate and severe cognitive deterioration that leads to dementia, many regions such as the cortical and subcortical ones, and different neurochemical systems, are involved.⁸

Altered cognitive performance on neuropsychological tests can even be observed in non-medicated patients and in early stages of the disease⁹ in different cognitive domains, such as memory, visual-spatial processing, attention, forming of concepts and executive functions.

In spite of the cognitive heterogeneity, the dysexecutive syndrome is constituted as the core component of the cognitive deterioration in PD and as one that conditions greater alteration of the functionality in the daily life activities.

In our case, given the early detection of the picture, our patient has still not developed all of the above-mentioned symptoms, so that main objective has been to detain their appearance as much as possible.

At present, having better neurological and neurochemical knowledge of PD has made it possible to detect a cognitive heterogeneity, observable from the first phase of the disease in consequence of a cholinergic deficit associated to the dopaminergic deficit.

However, dopaminergic replacement does not compensate all the cognitive deficits (incomplete improvement of the cognitive function with central dopaminergic replacement), suggesting the intervention of other neurotransmission systems.

One of the explanations why dopaminergic replacement does not compensate all of the cognitive deficits is that other

neurotransmission systems intervene in their deterioration. In PD, there is loss of noradrenergic neurons in the *locus coeruleus*, serotonergic neurons of the pontine raphe neurons and of cholinergic neurons both in the basal nucleus of Meynert and of the pedunculopontine nucleus, in absence of concomitant Alzheimer type disease. Among these deficient neurotransmission systems of PD, the alterations of the cholinergic projection pathways are those that have been most consistently related with the cognitive deterioration of the patients.¹⁰

In summary, cholinergic deficit is associated to the cognitive deterioration of PD from the first phases of the disease. It seems to play a more relevant role than dopamine in the progression of mild cognitive deterioration to dementia.

Given the clinical characteristics of our patient, who began with a Lewy body disease picture with predominance of cognitive symptoms with mild motor alterations, it is legitimate to propose a cholinergic action potentiating treatment against the dopaminergic as a therapeutic option.

We can see the confirmation of this hypothesis in the literature after the "EXPRESS Study" (*Exelon in Parkinson's disease dementia study*). This study constitutes the first multicenter, double blind and placebo-controlled study that has analyzed the effects of rivastigmine, a dual AChE (acetylcholinesterase and butyrylcholinesterase) on cognition, behavior and functionality in the daily life activities in patients with dementia associated with PD (DEP).¹¹

Rivastigmine has demonstrated, thanks to the EXPRESS study, a statistically significant improvement of the cognitive function, of behavior symptoms and of the functional state after 24 weeks of treatment. This suggests a clinically relevant impact on the quality of life of these patients.

Recently, in 2010, the British Association for Psychopharmacology (BAP) gathered a series of experts on the material in a scientific committee in order to revise the guide already-published in 2006 "Clinical practice with anti-dementia drugs." A consensus was reached in this meeting based on the available clinical evidence to indicate the use of cholinergic inhibitors (among those rivastigmine together with donepezil or galantamine) for the treatment of Lewy Body Dementia, especially for the neuropsychiatric symptoms, which could even produce cognitive improvement for this type of dementia. However, they pointed out that the use of cholinergic inhibitors does not currently have preventive properties against the appearance of this disease.¹²

All of this would justify the early onset of treatment with 3 ml daily of rivastigmine in this patient, which has a preventive action against progression to dementia.

PD is also characterized by an almost inevitable progression towards dementia after 10-15 years of evolution. Abundant data

from both neuropathological and structural neuroimaging studies (by voxel-based morphometry) have demonstrated that progression to dementia is principally the consequence of the extension of neurodegenerative process to multiple neocortical areas. Among all of them, neuronal death and density of the Lewy body deposit on the level of the limbic-paralimbic system (in the pars compacta of the substantia nigra), together with the degeneration of the *precuneus* and other areas of temporal-parietal-occipital association, make up the most consistent and independently related factor of the progression to dementia of PD.

Thus, performing an early diagnosis of "Lewy Body Disease," as occurs in our case, would allow for the initiation of appropriate preventive measures in order to avoid an inevitable progression to dementia and also to contain the wide spectrum of symptoms, which beyond that of the motor one, have a tremendous impact both on the patient and his/her family, producing an important reduction in their quality of life.

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