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Dysautonomia as a Prominent Manifestation of Dementia with Lewy Bodies: A Case Report

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ABSTRACT

BACKGROUND: Atypical Parkinsonism Syndromes or Parkinson plus Syndromes are degenerative disorders that are characterized by intracellular deposition of amyloidogenic proteins. In addition to parkinsonism, clinically they include disorders of other systems that are not commonly seen in Parkinson's disease [1].

CASE PRESENTATION: In this case we describe a 69-year-old male patient with a reported history of 7 years of fainting episodes and a history of declining cognitive function the last year.

Clinically, our patient showed mild asymmetrical extrapyramidal signs and a cognitive decline, but the most prominent clinical sign was severe autonomic dysfunction, that was notably seen since the first contact with the patient.

With the exclusion of prion diseases, scintigraphy scans were of great significance in order to distinguish the syndrome of our patient from other neurodegenerative dementias and parkinsonism syndromes. Finally, he was diagnosed with Dementia with Lewy Bodies after 123iodine-metaiodobenzylguanidine (MIBG) myocardial scintigraphy.

CONCLUSION: Dementia with Lewy Bodies is a neurodegenerative disease with progressive course leading ultimately to death. There is no disease specific treatment, while the symptomatic treatment aims the cognitive decline, the neuropsychiatric symptoms, REM sleep behavior disorder, parkinsonism and orthostatic hypotension.

KEYWORDS

Nutritional rickets; Genu varum; Serum alkaline phosphatase.

INTRODUCTION

Dementia with Lewy Bodies (DLB) is the second most common neurodegenerative dementia, after Alzheimer 's disease, and accounts for 10-25% of all dementias. Its prevalence among people older than 65 years is approximately 0.4%, whereas symptoms usually appear between the 50th and 80th year of life. Men are affected slightly more often than women [1,2]. Pathologically it is distinguished by intracellular inclusions with an eosinophilic core and peripheral halos, that is called Lewy Bodies [2] and were named because of German Neurologist Dr Friedrich Lewy, who described these lesions [3-5]. Lewy Bodies are found inside neurons not only in the substantia nigra and the brain stem nuclei, but in the limbic

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system, parahippocampal cortices, amygdala and cortex as well [2]. As a result of the key constituent of Lewy Bodies being a protein called α-synuclein, DLB is referred to as a synucleinopathy, alongside Multiple System Atrophy (MSA) and idiopathic Parkinson's Disease (PD) [2,3].

The diagnosis of DLB requires the presence of fluctuating cognition, in addition to 2 or more of the rest core clinical features including hallucinations, parkinsonism and REM sleep behavior disorder (RBD) [3,6]. The fourth consensus report of the DLB consortium in 2015 demonstrated the significance of biomarkers and their role in the diagnosis of the disease, also remarking the significance of 123iodine-metaiodobenzylguanidine (MIBG) myocardial scintigraphy [6].

Until the present day, there is no FDA approved specific DLB medication or disease-modifying agents. Treatment is symptomatic and targeted toward specific disease manifestations (cognitive deficits, neuropsychiatric symptoms and movement disorders), although there is no high level of evidence to support any forms of treatment [1,2,6].

CASE PRESENTATION

At 69-years- old Greek man presented to our outpatient clinic with a history of episodic faint and falls starting roughly 7 years ago. His wife also refers memory deficits and disorientation, a minor depressive disorder and agitation during night time, all being observed within the last year.

Regarding the fainting episodes, there are numerous hospitalizations throughout this 7 year period, with an extensive cardiological, neurological and lab test investigation up until that time, and no specific etiology was found. The episodes reportedly happen more frequently at the upright position, the loss of consciousness lasted less than 5 minutes and was followed by a short period of confusion as reported by his wife. There were no typical signs of epileptic activity (e.g., convulsions, loss of sphincter control or tongue biting), although there was a history of occasional urinary incontinence. The rest of his medical history includes hypertension, benign prostatic hyperplasia, chronic atrial fibrillation and an unspecified psychiatric condition, all treated accordingly. The aforementioned memory deficits and disorientation were of great concern for the patient's wife, as he used to be an employer in diplomacy and used to speak 4 languages fluently, thus these deficits interfered with his daily living.

The most recent investigation included cardiological (echocardiography, myocardial perfusion scintigraphy) and neurological examination (electroencephalography that showed generalized slow activity, brain MRI that demonstrated chronic small vessel angiopathy and brain atrophy more notably in the right hemisphere). Concerning the rest of the examination, there was a normal computer tomography (CT) of the abdomen, and a chest CT shows various rib fractures in healing stage (bony callus), that can be attributed to the multiple fainting / falling episodes.

By the time he was admitted to out clinic, on examination, he had a mild resting tremor, asymmetrical extrapyramidal stiffness in his left extremities, especially the upper limb, and cogwheel sign in his left hand, and also a barely noticeable dysmetria in his left upper limb. Also, there were fasciculations especially in the upper limbs, and oral automatism. On the other hand, there were no motor or sensory loss, the deep tendon and plantar reflexes were normal and the cranial nerves were also normal.

During the course of the hospitalization, the patient had a number of fainting episodes that were noticed to happen due to excessive dysautonomia (severe orthostatic hypotension, with a decrease in systolic blood pressure of about 70mmHg), and so he was administered Midodrine, with moderate results. Complex visual hallucinations and night time myoclonic activity were reported to have reappeared in hospital, after a period of absence. This myoclonic activity was present 1 year ago, for which he was treated with Lamotrigine. There was also a fluctuation of psychomotor agitation.

Initial neuropsychological assessment showed a progressive decline in cognition over a period of 3 years and especially in word registration and recall, disorientation to time (MMSE 20/30 in 2019, compared to a similar assessment in 2017 with a MMSE 23/30), and also a decline in executive function, as measured with the Functional cognitive assessment scale (FUCAS).

The patient underwent an extensive series of exams:

a) Lumbar puncture yielded normal results concerning cells, protein and glucose levels and virology testing. Immunoenzymatic analysis of the CSF (beta-amyloid proteins, total tau protein and p-tau) ruled out the possibility of Alzheimer's Dementia. Testing for Creutzfeldt-Jakob disease (CJD) was also negative (no 14-3-3 protein detected, normal Real-Time Quaking Induced Conversion, or RT-QuIC).
b) New echocardiography, 24-hour heart-rate monitoring and 99m-Tc scintigraphy were also normal ruling out myocardial damage and cardiac Amyloidosis, that could possibly explain episodes of fainting.
c) EEG and brain MRI were similar with the prior exams.

Taking into consideration the various clinical findings, including a progressive cognitive decline, visual hallucinations, myoclonic activity, dysautonomia and parkinsonism, differential diagnosis were focused on an atypical parkinsonism syndrome. Of greater significance were the scans at our hospital's Nuclear Medicine Department:

Ioflupane-123 SPECT (I^{123}-DaTSCAN)

The results showed decreased uptake of the radiotracer in the striatum in both sides and especially in the caudate. This is indicative of disorder of the presynaptic dopaminergic enervation, and thus of the integrity of the striatonigral system.

123I-Metaiodobenzylguanidine scintigraphy (I^{123}-MIBG SPECT)

Results indicative of decreased uptake of the radiotracer in the myocardium, as indicated by the reduced density of the a1 postsynaptic adrenergic receptor in the left ventricle of the heart. MIBG SPECT here was helpful distinguishing DLB from MSA, as in the latter the SPECT would be normal [7].

The patient meets the recommended criteria, as proposed by the Fourth consensus report of the DLB consortium in 2015. The day he was discharged, he was examined had a profound cognitive decline and psychomotor agitation, as where as more intense extrapyramidal signs compared to the day he was admitted.Lamotrigine was replaced with Levetiracetam and he was started on Rivastigmine and Midodrin. His prior antihypertensive medication was discontinued. He or his wife did not schedule an appointment in our outpatient clinic for re-evaluation, because they returned to their city 600 km far away from our Hospital, but informed us that he was better, 8 months after he was discharged.

DISCUSSION

Our case highlights the importance of the use of biomarkers as a tool in diagnosing atypical parkinsonism syndromes, and more specifically the spectrum of Lewy Body Dementias.

The spectrum of Lewy Body Dementias (LBDs) is an umbrella term that encompasses Dementia with Lewy Bodies (DLB) and Parkinson's disease with Dementia (PDD) [3]. They have many overlapping symptoms and in later disease stages, it can be really challenging to distinguish between these two, or even other forms of dementia [3]. As stated before, they are characterized by the intraneuronal aggregation of α-synuclein within the so-called Lewy Bodies [2]. The differential diagnosis between them relies on the different cognitive decline, the fluctuations and deficits in motor functioning [3].

Apart from the fact that it is the second most common form of neurodegenerative dementia, DLB is still greatly underdiagnosed, as there is a high percentage of overlapping symptoms between DLB and other synucleinopathies, or even Alzheimer's Dementia (AD) [3].

The need for better diagnosing DLB led to the refinement of the criteria for the clinical and pathological diagnosis of it, as proposed by the Fourth consensus report of the DLB Consortium in 2015. Increased weighing was given to REM sleep behavior disorders and MIBG SPECT, as was conducted on our patient.

The revised clinical criteria incorporate 4 core clinical characteristics [7] and a number of supportive ones, as well as indicative and supportive biomarkers. They are all summarized in Table 1 [6]. In our case, the patient showed all 4 core clinical features, 5 out of 10 supportive clinical criteria, and met the criteria for 2 indicative biomarkers (DaTSCAN and MIBG SPECT) (probable Lewy Body Case). As there is no standardized way to assess many of the cognitive of behavioral symptoms, a clinical tool named Lewy Body Composite Risk Score (LBCRS) was developed. This was developed to increase the ability to detect the spectrum of the Lewy Body dementias in clinic, and enhances the ability to determine whether Lewy Bodies are the cause of the cognitive decline. The score

incorporates 10 yes/no questions, 4 of which cover motor symptoms and the remaining 6 cover non-motor symptoms [8]. In our case, the patient scored 7/10 (probable Lewy Body Case).

Core Clinical Features	Fluctuating cognition with pronounced variations in attention and alertness	
	Recurrent visual hallucinations that are typically well formed and detailed	
	REM sleep behavior disorder, which may precede cognitive decline	
	One or more spontaneous cardinal features of parkinsonism (bradykinesia, rest tremor, rigidity)	
Supportive Clinical Features	Severe sensitivity to antipsychotic agents	Hypersomnia
	Postural instability	Hyposmia
	Repeated falls	Hallucinations in other modalities
	Syncope or other transient episodes of unresponsiveness	Systematized delusions
	Severe autonomic dysfunction (eg, constipation, orthostatic hypotension, urinary incontinence)	Apathy, anxiety, and depression
Indicative Biomarkers	Reduced dopamine transporter uptake in basal ganglia by SPECT or PET	
	Abnormal (low-uptake) 123iodine-MIBG myocardial scintigraphy	
	Polysomnographic confirmation of REM sleep without atonia	
Supportive Biomarkers	Relative preservation of medial temporal lobe structures on CT/MRI scan	
	Generalized low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity ± cingulate island sign on FDG-PET imaging	
	Prominent posterior slow-wave activity on EEG with periodic fluctuations in the pre-alpha/theta range	

Table 1: Revised criteria for the clinical diagnosis of Dementia with Lewy Bodies (DLB).

As stated earlier, there is no FDA approved specific DLB medication or disease-modifying agents. The present focus is on alleviating symptoms, something that is also challenging, considering that certain medications, while improving one symptom may worsen another [3]. Medication is directed towards the three categories of cardinal clinical manifestations: cognitive deficits, neuropsychiatric symptoms and movement disorder.

Cholinesterase inhibitors (ChEIs) are used to treat cognitive and psychiatric symptoms of the LBD spectrum. Among them, only Rivastigmine was approved for treating LBD, while the rest is used off label. Our patient received when he was discharged Rivastigmine. A 10% of the patients experienced worsening of the tremor, while nausea, vomiting and somnolence were also noted [2,12]. Our patient had no side effects.

Dopaminergic agents such as Levodopa and the combination Levodopa / Carvidopa are administered to improve motor function, but not all patients are in need of anti-Parkinson treatment, as the parkinsonism signs may be subtle at first. These patients are also vulnerable to the development of medication- induced behavioral or antipsychotic symptoms. Our patient did not have parkinsonism as his cardinal symptoms and also had profound psychomotor agitation, and so was discharged without anti-parkinsonism medication [2,12].

Regarding behavioral changes, if hallucinations are not frightening or not considered to be bothersome, antipsychotic agents may not be necessary. Delusions, on the contrary, tend to be socially disruptive and should be treated. Typical or traditional antipsychotics should be avoided [6].Clonazepam is the preferred agent to treat REM sleep behavior disorders [2,12].

CONCLUSION

This was a case of a male patient with remarked dysautonomia and episodic faints as his symptoms, rather than parkinsonism, who met the criteria as proposed by the Fourth consensus report of the DLB Consortium in 2015. The diagnosis of DLB is still challenging, but the symptoms should raise suspicion to the clinician. Although the consensus criteria have excellent specificity (79-100%) [8], the most sensitive biomarkers such as the SPECTs are not readily available outside of academic institutions, thus limiting diagnosis capabilities. This should affect patients' prognosis, as the median survival is 4.7 years in those with DLB and 3.8 in those with PDD after the time of diagnosis, both of which are considerably lower than patients with AD [10]. DLB tends to have a higher economic burden of a healthcare system than AD, as implied by the higher admission rate among patients with DLB compared to AD ones, due to falls, delirium and pneumonia [13,14].

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