

A clinical case of a patient affected by restless leg syndrome and “mixed tremor”: description of the diagnostic process and combined therapeutic outcome with regard to comorbidities.

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Abstract

The clinical case under study concerns a woman who came to the neurology outpatients' clinic for the 1st time in February 2016, at the age of 59 yrs for depressive syndrome and impairment in falling asleep due to imperious movements of the legs in the lying position in bed. She was treated for restless leg syndrome with dopaminergic therapy and antidepressant duloxetine with good outcome. Subsequently she developed a tremor of the head (type 'no') and slight postural of the hands, visible in holding objects or making fine movements, disappearing at rest. The patient was also suffering from diabetes, hypertension and chronic obstructive pulmonary disease treated with beta receptors-stimulant bronchodilators. A brain MRI performed in March 2016 resulted normal. A Datscan performed in June 2016 showed no anomalies. The first diagnosis was Essential Tremor associated with Restless Legs Syndrome (RLS). With the support of interdisciplinary cardiology and bronchopneumology consultancy, propranolol therapy was also instituted for tremor. The use of clonazepam, was interrupted due to interference with the diabetes affecting the patient. The tremor was subsequently successfully treated by adding other gabaergic therapy (gabapentin), because of suspension of propranolol. However, over time an efficacy of dopaminergic therapy was also found on tremor: in fact, attempts to reduce or interrupt the drug used for RLS due to symptom's remission gave as results a worsening of the tremor in the head, as well as of the mood disorder. However, the tremor benefited sustainably over time with the combination of gabaergic and dopaminergic therapy.

Keywords: essential tremor; mixed tremor; tremor; parkinson's disease; rls; gaba; dopaminergic therapy; propranolol

Introduction

Scientists know that tremor syndromes constitute a complex group of clinical entities in extrapyramidal diseases whose treatment can be difficult to define at an initial approach. In some cases, the expectancy about the outcome of therapeutic approach is not fulfilled despite a relative initial certainty in the diagnosis. This happens because of the response to drug therapy as well as the evolution along time of the clinical characteristics and drug sensitivity; there are many examples of this frames, like for example in Parkinson's Disease (PD), in which neurologists experience reduction of efficacy in advanced stages of prolonged dopaminergic therapy. The clinical case in description showed a neurological comorbidity consisting in depressive syndrome, tremor, restless leg syndrome (RLS) with concomitant internal comorbidity consisting in diabetes, cardiac and respiratory diseases, treated over time with combinations of dopaminergic and gabaergic drugs selected in a way compatible with the concomitant clinical conditions, comorbidities and contraindications of medications.

Case description:

A 59 years old woman came to observation in February 2016 complaining impairment in falling asleep due to the compulsion to move the lower limbs when getting into bed. Moreover, she was affected by low mood, pulmonary impairment with chronic obstructive pulmonary disease (COPD) with sleep apnea and use of cPAP, diabetes treated with oral hypoglycemic agents (metformin), hypothyroidism treated with levothyroxine 100mg. Firstly she did not report the trembling in her head or was not aware of it. At physical examination she showed normal muscle tone, moderate tremor of the head type “no”, slight tremor of limbs, in dynamic phase or sustained position, normal gait; the UPDRS score resulted 16, the cognitive test MMSE corrected was 28. FT3, FT4 and TSH values resulted within normal limits (2.21-1.26-046, in 2018, October, with successive controls in the subsequent years) the electromyography examination performed in 2016 and in subsequent control (2021) was within normal limits, i.e., it did not show diabetic neuropathy or radiculopathy. The patient reported in subsequent follow-ups that family members had noticed the head tremor, which she could not assess if it disappeared or not by leaning on the pillow. The EEG performed in 2016, February was normal. Blood analysis showed normal

levels of sodium, potassium, calcium, the serum iron value was 74 (range 50-170), transferrin 294, ferritin 15.6. Brain MRI (2016, March) and cerebral [(123) I] β -CIT SPECT (Datscan, 2016, June) resulted normal. In 2020 she suffered from pericarditis with recovery. The previous ECGs with 24-hour dynamic Holter (2018, December) had shown atrioventricular conduction delay (first degree block), intraventricular block with sporadic extrasystoles, with contraindication for use of beta-blockers, so that the initial proposed propranolol resulted contraindicated. Dopamine therapy was instituted with rotigotine patch for RLS with dosage increases up to 8 mg, initially at night, then extended over 24 hours, as the lower limb disorder begun to occur even during the day, associated with duloxetine 60 mg and subsequently adding

gabapentin 100mg bis daily, due to the presence of electric discharge-type paresthesias, and simultaneously to support therapy for the tremor. There was a complete resolution of the RLS, an improving of depressive syndrome and of head tremor. The improvement of head tremor was attributed to the use of gabapentin, on the assumption (also based on the Datscan outcome) that the diagnosis was Essential Tremor (ET). However, with the remission of RLS symptoms, a reduction in dopaminergic therapy was attempted in the following years at the patient's wish. However, this was associated with a concomitant worsening of head tremor, so that the previous dosages were taken back.

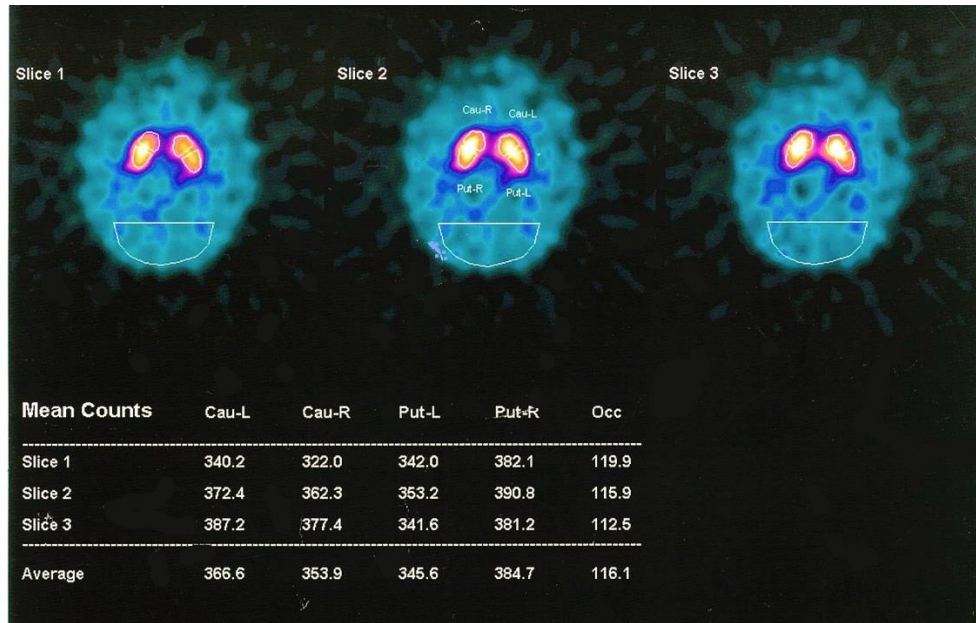


Figure 1: [(123) I] β -CIT SPECT (Datscan, 2016, June) resulting with normal values, despite the patient's was responder to dopaminergic therapy both to RLS and head tremor; she reported also a mood improvement.

Discussion

According to broad specialists' experience, tremor is not only a symptom, but a complex disorder with a high impact with patients' quality of life. Moreover, the coexistence of multiple diseases in the domain of the extrapyramidal system within individual clinical cases has been widely described in the literature (1,2,3,4); it is therefore often useful in the practice to subdivide the patients' case diagnosis in order to construct a therapy that can produce a satisfactory improvement of the clinical conditions in which tremor is the main discomfort complained. In several cases this symptom is not undoubtedly superimposable with typical features, but uncertainty with diagnosis of ET or PD is generated by intermediate or coexisting characteristics, especially when the general clinical picture does not indicate other clear extrapyramidal signs; it is not only the case of the "trembling hand" during walking or drinking a cup of coffee commonly observed in PD patients. This fact produces initial uncertainty about the first therapeutic approach, or may cause unexpected results to medications. In many cases, it has been proven useful a diagnostic-therapeutic approach free of prejudices due to both the rigid classification of the symptomatic characteristics and the results of instrumental tests, such as the MRI scan and the Datscan. Furthermore, the localization of the symptom can lead the specialist to draw hasty conclusions in the diagnosis, as happens with head tremor, frequently attributed in the first hypothesis to ET (5, 6). Besides, varied coexistences of RLS, PD and vascular parkinsonism (VP) have been described in the literature (7, 8, 9, 10, 11); these diseases share a positive response to dopaminergic therapy, despite being distinct entities, for which the eventual common pathophysiology is under debate (12, 13). The relevance of the described clinical case is both in the presentation of symptoms of uncertain attribution (head tremor 'ET-like', which began after RLS and responsive to the same dopaminergic therapy, despite the normal Datscan) and in the comorbidity with cardiac, pulmonary and diabetic disease, which

conditioned the choice of drug therapy (alternative use of the gabaergic drug to propranolol contraindicated in COPD and heart dysrhythmia, exclusion of clonazepam for diabetic contraindication). Furthermore, patient's mood disorders and depressive syndrome deserve special mention: in fact, she was always reporting the mood changes in the clinical follow-up both in correlation with the drugs taken and as a response to improvement in symptoms, since depressive syndrome has always been the most relevant element focused by the patient. On the other hand, she showed a good response to antidepressant therapy, but the combination of gabaergic and dopaminergic therapy for tremor treatment showed a notable influence on the mood disorder too. This effect was not only due to the positive psychological reaction to the motor symptom's improvement but can probably be attributed to the stabilizing effect of gabapentin together with the well-known effect of dopaminergic therapy on the limbic 'reward' circuit.

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