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Case Report

A rare cause of axial worsening in Parkinson's disease: A case of myasthenic pseudo-parkinsonism

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1. Introduction

Movement impairment, fatigue and ophthalmoparesis could feature neurodegenerative and neuromuscular disorders, with distinctive qualities. Myasthenia Gravis (MG) is a rare but treatable autoimmune disorder of the neuromuscular junction (NMJ). Parkinson's disease (PD) is a neurodegenerative disorder which involves roughly 1–2% of the population over 60 years of age. Hence, in a highly prevalent degenerative disease such as PD, the chance of diagnosing an overlapping condition such as MG is a target to strike down.

2. Case report

A 73-years-old man has been diagnosed with PD for 8 years (2010–2018). He reported typical non-motor symptoms since the prodromal stage and, at onset, he presented left sided resting tremor, bradykinesia and rigidity. Signs showed a typical bilateral diffusion, a linear progression and a sustained levodopa response until 2016 (Fig. 1). At that point, he manifested a subtle onset and worsening of PD axial symptoms with camptocormia and anterocollis. Symptoms fluctuated during the day, with a correlation with the levodopa-carbidopa intake (1000–250 mg, plus safinamide 100 mg daily). From 2016 to 2018, symptoms became disabling, due to drug resistant postural deformities and falls. The presence of dysphagia, fatigue and hyporexia caused a severe weight loss. Occasional diplopia was reported, as less disabling. On early 2018, he presented a bilateral asymmetric parkinsonism, prevalent on the left, mildly altered postural reflexes, festination, freezing of gait, marked camptocormia, Pisa syndrome and anterocollis. Cranial exploration showed hypomimia, reduced blinking rate and fixed postures of the lower face, parted lips and bilateral mild ptosis. There were no square-waved jerks. Saccades were mildly slow but hypometric, smooth pursues were mildly fragmented. There was a severe bilateral vertical gaze palsy, with persistence of the upward limitation also at oculocephalic maneuvers. Noteworthy, the cognitive status was normal (MoCA, 28). The patient underwent a levodopa-carbidopa challenge (250 + 25 mg), which showed a Unified Parkinson's Disease Rating Scale (UPDRS) improvement of 22% (47 to 37) (Video-1), mild dyskinesias and subsequent wearing-off. All symptoms improved out of neck, and cranial findings.

Interestingly, the aforementioned signs were influenced by fatiguing maneuvers, revealing exhaustion of neck and shoulder girdle muscles. Simpson's test elicited the appearance of diplopia with bilateral asymmetric impairment of right eye abduction and adduction/intra-rotation, bilateral ptosis and marked left lower facial hyposthenia (Video-2).

Ice-pack test (Supplementary materials) and administration of intrastigmine were performed, both with improvement. Repetitive axillary nerve stimulation (RNS, 3 Hz) showed a decremental response (up to 20%) in the fourth compound muscle action potential (CMAP) recorded from deltoid muscle (Supplementary materials). Moreover, needle electromyography (EMG) on neck and limb-girdles finally ruled

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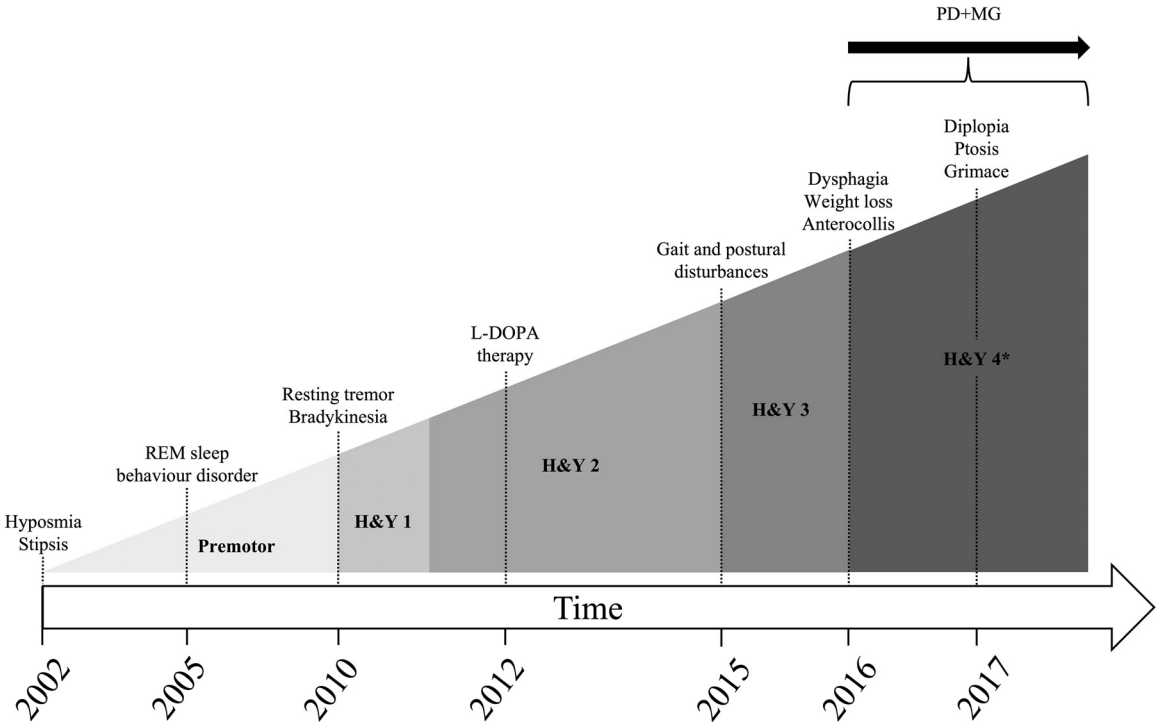

Fig. 1. Myasthenia gravis pseudo-parkinsonism in Parkinson's Disease.
Legend. The progression of Parkinson's disease symptoms placed in a timeline, together with the Hoehn & Yahr stage (H&Y, grey scale) worsening throughout years. The black thick line represents the period of time marked by myasthenia symptoms overlap (PD + MG). * The H&Y stage 4 was not only caused by Parkinson's disease.

out signs of myopathy. Findings raised the suspect of MG and the serum assay detected anti-AChR antibodies (6.01 mMol/l; limit < 0.5) supporting the clinical and neurophysiological diagnosis. Hence, the specific therapy was gradually introduced (pyridostigmine, prednisolone and azathioprine) and PD therapy was optimized accordingly to the new overlapping diagnosis, with a striking global improvement of symptoms including posture (Video-1) and oculomotion. Also the bilateral upward gaze paresis significantly improved (Video-2; Supplementary-materials).

3. Discussion

The clinical picture was challenging, and included the chance that the degenerative process (parkinsonism) involved axial functions, leading to posture, gait, swallowing and ocular movement deterioration, refractory to levodopa. Supranuclear gaze palsy (SGP) is the hallmark of progressive supranuclear palsy (PSP). Although the early selective downgaze impairment is often thought to be representative, the upward gaze palsy is the most reported PSP oculomotion sign (see Supplementary references). In early stages, oculocephalic maneuvers are able to overcome eye impairment. However, in advanced PSP, all volitional and activated movements are abolished (ophthalmoplegia). Parkinson's disease patients frequently show saccade hypometria, while slowing of vertical saccades presents in advanced stages. Ocular dysconjugacy, especially convergence impairment, is a main cause of subtle diplopia in PD. Ptosis is not reported in PD, on the other hand parkinsonian syndromes could present lid lag, as observed in PSP. In such patients, eyelid apraxia or blepharospasm could cause eyelid opening difficulties.

Also posture deteriorates in PD and atypical parkinsonisms: camptocormia and Pisa syndrome are the most representative PD skeletal deformities, while anterocollis (or dropped head, a marked neck flexion that lead to the patient unavailability to lift the head against gravity while sitting or standing, without a loss of strength) has been more frequently reported in multiple system atrophy (MSA) than PD or PSP (see Supplementary references).

Bradykinesia is a cardinal PD sign and is characterized by slowness and progressive reduction of movement amplitude. This is clinically tested asking the patient to perform rapid alternating motor tasks (e.g. finger tapping) in order to study movement pace, rhythm and amplitude. Indeed, bradykinesia manifests in absence of weakness or fatigability. Muscular exhaustion featured patient examination, raising the suspect of NMJ disorder. To this extent, neck extensor myopathy, already described in PD/MG [1] (see also Supplementary references), has been ruled due to the location of clinical findings (bulbar and cranial district) and by needle EMG. Thus, biopsy was not performed. Neurophysiology supported the clinical diagnosis at each step. Indeed, RNS was able to corroborate the suspect of MG, and a single fiber EMG (SFEMG), although more sensitive than RNS for MG diagnosis (i.e. 50–70% vs 99% respectively, depending on muscles and MG subtype), was not necessary (see Supplementary references).

However, in PD, iatrogenic disturbances of neuromuscular transmission should be ruled out before making the final diagnosis. Indeed, anticholinergics (trihexyphenidyl) could inhibit post-synaptic acetylcholine binding at the muscarinic receptor, causing NMJ disturbances. However, no intake of anticholinergics was reported. Levodopa-carbidopa and monoamine-oxidase-type-B (MAO-B) inhibitors (selegiline, rasagiline) (both widely prescribed in PD) have never been associated to NMJ failure, except for an anecdotal "myasthenia" reported in a recent selegiline trial (Supplementary-materials for further references). Safinamide (MAO-B/glutamate release inhibitor) has never been associated to myasthenia, although glutamatergic transmission plays a putative role in NMJ.

Chance of coming across a PD/MG "double trouble" is remote, with a cumulative incidence of roughly 0.5–40/10^9, with a second peak of incidence in males during their sixth-seventh decade (see Supplementary references). According to the available literature, ocular symptoms (60%), dropped head (53%) and bulbar symptoms (40%) are

the most common presentation of MG in PD patients. In 69% of cases, serum presented anti-AChR antibodies [1]. Deteriorating posture, swallowing and ocular movements were initially misleading, compatible with the presence of progressive unresponsive PD axial symptoms or even atypical parkinsonism (PSP, MSA) overlap. Fatigability was the key to reach the diagnosis, but it was intriguingly embedded with PD motor fluctuations. Eye movement examination provides unique hints in parkinsonism diagnosis, nevertheless it has not yet been included in the UPDRS (the functional PD scale). Here eyelid and extraocular muscle exhaustion manifested in absence of any other remarkable saccadic or smooth pursue impairment. Bilateral SGP palsy was an unexpected and misleading finding, that had to be put in the context of the global eye movement examination.

Preserved cognitive status and the absence of prominent dysautonomia were also clues that suggested the presence of a “non-degenerative” overlapping condition.

Before this paper, there were seventeen cases of comorbidity between PD and MG reported in literature [2], including a co-occurrence of these two conditions with rheumatoid arthritis [3]. Several studies indicate that PD pathogenesis is associated with neuroinflammation and autoimmunity. For instance, plasma antibodies isolated from PD patients were shown to recognize dopaminergic cells or antigens related to PD pathogenesis, such as melanin, α-synuclein, and GM1 ganglioside. In addition, neuromelanin appeared to activate dendritic cells and microglia, which in turn may trigger a proliferative T and B response [4].

Interestingly, a recent study also proposed a role of α-synuclein in the development of immune tolerance [5].

4. Conclusions

Parkinson’s disease is a slowly progressive disease, which could last over than 20 years of a patient life. Signs are heterogeneous and strictly connected with the pharmacological history. The disease progression through stages (Hoehn and Yahr scale) is also determined by the accumulation of levodopa unresponsive axial symptoms. Our patient presented a MG pseudo-parkinsonism on a typical longstanding PD (Fig. 1). Symptoms that in healthy subjects would immediately alert the clinician of MG (diplopia, head-drop, fatigue, and ptosis) became blurred in the wider picture of pre-existing PD, being merely included in the extrapyramidal spectrum of disease and leading to MG misdiagnosis (Supplementary materials). Also cases reported in literature [1] suggest, in hindsight, that it could be hard escaping the mind-set of a firm diagnosis such as PD.

Although we acknowledge that this association may be casual, this case may be added to the growing evidence of an involvement of immune system in PD pathogenesis.

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Appendix A. Supplementary data

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