On the reversibility of parkinsonian tremor. Brief review and hypothesis

Sobre la reversibilidad del temblor parkinsoniano. Breve revisión e hipótesis

Dear Editor:

Parkinson disease (PD) is clinically defined as the presence of the so-called cardinal motor symptoms such as bradykinesia, resting tremor, rigidity, and postural instability.[1] In addition, a plethora of non-motor symptoms can occur with the passage of time including cognitive decline and abnormal behavior.[1] PD is generally an irreversible and progressive condition as most symptoms such as bradykinesia and postural reflexes inexorably worsen. Occasionally, however, some symptoms may evolve in less predictable fashion. Tremor is the only cardinal parkinsonian symptom that can improve or even remit, although this fact has been only occasionally mentioned.[1–4] In this short review, we summarize what is known about the reversibility of parkinsonian tremor, and speculate on the mechanisms of this rare but fascinating phenomenon.

Tremor may be considered peculiar among classical motor symptoms, since its evolution is variable,[1–4] its response to levodopa unpredictable,[4] and its relationship with dopaminergic deficiency is rather weak.[5,6] Rest tremor is inversely correlated with serotonin transporter availability.[7] In addition, parkinsonian tremor is mediated by a distinct metabolic network involving cerebello-thalamocortical pathways.[8] In any case, the natural evolution of parkinsonian tremor is highly unpredictable, as it can become exacerbated over time, stabilize, improve, and, though rarely, even disappear.[1–4] The remission of parkinsonian tremor is not entirely exceptional however; Hughes et al., in their classic article observed that ''nine patients lost their tremor late in the disease''[1] and Toth et al. already noted the disappearance of rest tremor in 15 patients over an average of 7.1 years after onset.[3]

We identified a group of patients with evident and confirmed resting tremor (accompanied or not by positional tremor) at onset (minimum score of 2 points according to the tremor items of the UPDRS III) and confirmed remission of tremor on subsequent evaluations. We defined tremor remission as the objective and subjective disappearance of previous tremor (Score items: 0). This group of patients was extracted retrospectively from a series of patients followed at our institution over the last 30 years.[9,10] Table 1 summarizes the clinical characteristics of this group of patients. All our patients were treated with levodopa and at least one ancillary antiparkinsonian medication such as dopamine agonist and or IMAO. Due to the rarity of complete parkinsonian tremor remission (12 patients), comparison with patients not manifesting remission is obviously incomplete, but these patients were older compared to a control PD group with similar follow-up assembled from our general PD database (mean age at start: 67 ± 7.3 vs 58.5 ± 10.21 years; $P < 0.001$ *t* test). It is difficult to isolate a set of shared characteristics among this group of patients: some could be defined as advanced PD due to the presence of motor complications and/or cognitive decline (cases 1, 2, 6, 7, 8, 9, 11), but some other patients exhibited mild PD without relevant complications (case 12). The time period from the disease onset to tremor remission was variable, ranging from 3 to 12 years.

In essence, parkinsonian tremor remission is not an exceptional finding in PD, although this may be unnoticed by the patients, embarrassed by other, much more disabling symptoms (including motor, non-motor fluctuations, freezing of gait, loss of postural reflexes or cognitive decline)

There are several explanations for these intriguing observations. The mechanism by which parkinsonian tremor may occasionally improve or even disappear is unknown; but Tzoulis et al. proposed a very attractive explanation, pondering the reason why patients with polymerase gamma mutations did not develop significant parkinsonism in spite of severe nigral degeneration.[11] The authors suggested that concurrent lesions or dysfunction in other neuroanatomical structures and pathways (dysfunction of the cerebellum and/or its connections) can modulate the function of the basal ganglia and may compensate clinical parkinsonism in polymerase gamma mutation carriers.[11] Similarly, we could speculate that in some PD patients, dysfunction in several thalamic nuclei may explain the improvement or even remission of parkinsonian tremor. Thalamic median-parafascicular complex nuclei can also be affected in PD[12]; interestingly, deep-brain stimulation of the median-parafascicular complex has been suggested as treatment for tremor control in PD.[13]

Finally, in addition to parkinsonian tremor, several reports suggest that some other parkinsonian features such as REM behavior disorders and gait freezing may exceptionally improve spontaneously or even disappear.[14–17]

In any case we understand that the evidence of this topic is very limited, and our conjectures are highly speculative; and even we consider that some apparent remissions may result from limitations in the rating scales or tools used to assess patients. But after all, there are several reports suggesting that remission of parkinsonian tremor occasionally occur, and this rare but fascinating phenomenon may raise several aspect of neurodegeneration including the role of neuroplasticity and the existence of compensating lesions and dysfunction over time

Author roles

(1) *Research project*: (A) conception, (B) organization, (C) execution; (2) *statistical analysis*: (A) design, (B) execution, (C) review and critique; (3) *manuscript preparation*: (A) writing of the first draft, (B) review and critique.

P.J.G.R.: 1A, 1B, 1C, 2A, 2B, 2C, 3A; M.R.L.: 1C, 2C, 3B; C.F.: 1C, 2C, 3B.

Ethical compliance statement

The authors confirm the approval of our institutional review board written informed consent was not necessary.

Table 1 Tremor remission in Parkinson's disease.

Subject	Age at onset/sex	Evolution years	MOTOR COMPL.	CD	Baseline	
					Total UPDRS	UPDRS III
1	70/F	4	D, GF	0	50	37
2	73/F	6	—	+	37	30
3	60/M	4	—	0	31	22
4	72/M	3	—	0	29	21
5	64/F	5	—	0	39	27
6	78/F	4	—	+	69	48
7	68/M	3	F	0	36	22
8	54/M	11	F, D, GF	0	27	17
9	66/M	12	F, D, GF	+	26	17
10	77/M	5	—	0	42	25
11	72/F	9	D, GF	0	34	26
12	59/F	12	—	0	19	11

MOTOR COMPL.: motor complications; F: fluctuations; GF: gait freezing; D: dyskinesias; CD: cognitive decline.

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Conflicts of interest

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P.J. Garcia Ruiz*, M. Ruiz Lopez, C.E. Feliz

Movement Disorders Unit, Department of Neurology, Fundacion Jimenez Diaz, Madrid, Spain

* Corresponding author.
E-mail address: PGarcia@fjd.es (P.J. Garcia Ruiz).

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Acute porphyric polyneuropathy in a pregnant patient with systemic lupus erythematosus

Polineuropatía porfírica aguda en una paciente embarazada con lupus eritematoso sistémico

Dear Editor:

Guillain-Barré syndrome (GBS) is a heterogenous condition and may be mimicked by other acute polyneuropathies. Both acute porphyria and systemic lupus erythematosus (SLE) are included in this differential diagnosis. We report an instance of acute polyneuropathy in a pregnant patient with known SLE, whose neurological picture occurred during a flare of SLE but was found to be due to a previously undiagnosed hereditary coproporphyria (HCP).

We present the case of a 25-year-old Asian female with SLE with severe multisystemic involvement, diagnosed during a life-threatening flare in her first pregnancy. There was no other relevant personal or family history. Medication included prednisolone 5 mg, azathioprine 100 mg, and hydroxychloroquine 400 mg. She was admitted for abdominal pain, vomiting, and constipation, followed by dark urine; she also described other self-limiting abdominal pain episodes over the previous 2 years. On examination, persistent tachycardia was noted. Laboratory studies were significant for hypocomplementemia, elevated erythrocyte sedimentation rate and elevated β-Human chorionic gonadotropin compatible with a 1—2-week pregnancy. There was no laboratory evidence of hematuria. Abdominal and obstetric ultrasound, and abdominal MRI were unremarkable. A provisional diagnosis of SLE-associated autonomic neuropathy was made and she was treated with IV methylprednisolone pulse plus an increase in prednisolone to 1 mg/kg/day. A rapidly progressive quadriparesis developed the first week after admission. On day 7 the patient was unable to independently walk, had a generalized areflexia, and patchy hypoesthesia. Electrodiagnostic studies showed increased F wave latency and absent H reflexes, suggesting GBS. CSF studies were normal. Despite treatment with intravenous immunoglobulin, followed by plasma exchange, her neurological condition continued to deteriorate, with facial diplegia, worsening of quadriparesis (grade 2 MRC in the proximal segments and grade 0 distally), marked hypopalesthesia and proprioceptive errors up to the knees and elbows, and periods of severe dysautonomia. Repeat nerve conduction studies showed an acute sensory-motor axonal neuropathy (AMSAN). Meanwhile, the patient developed thrombocytopenia, prolonged clotting times, hypoproliferative anemia and elevated hepatic transaminases, and a provisional diagnosis of SLE flare with SLE-related acute polyneuropathy was made. The patient agreed to an interruption of the pregnancy, followed by treatment with cyclophosphamide. Systemic manifestations resolved, without any improvement of neurological symptoms. Additional investigations for GBS mimics were ordered, and urinary porphobilinogen and porphyrins were markedly elevated (Table 1). After withdrawal of potentially porphyrinogenic drugs and administration of IV hemin, the patient showed dramatic improvement, with resolution of sensory manifestations and plateauing of muscle strength. She was discharged to a rehabilitation center. At 20 months after onset, full recovery had occurred except for bilateral grade 4 MRCankle dorsiflexion. Genetic testing revealed a previously unreported *CPOX* gene variant (NM_000097.5:c.245T>C [p.Leu82Pro]).

The present case illustrates a challenging differential diagnosis of acute polyneuropathy. Our patient had both an established diagnosis of SLE and laboratory evidence of increased disease activity. Still, she defied Occam's razor and final diagnosis was of a second chronic disease, hereditary coproporphyria (HCP), as the cause of the neurological symptoms.

Clinical reasoning favors acute porphyric neuropathy against SLE-associated neuropathy: there had been self-limiting abdominal pain episodes accompanied by dark urine, abdominal pain and dysautonomia occurred before the acute neuropathy, and response to immunosuppression was absent while there was a response to hemin treatment and withdrawal of porphyrinogenic drugs. The lack of cutaneous manifestations is not unexpected, since they are far less frequent than neurovisceral manifestations in patients with HCP, occurring only in 5—30% of patients.[1] The main limitations of the present report include limited biochemical testing (unavailable fecal and plasma porphyrin testing; urinary porphyrins and PBG unadjusted for creatinine) and incomplete genetic testing, namely of unaffected

Table 1 Urinary porphobilinogen (PBG) and urinary porphyrins before treatment with hemin. ALA: delta-aminolevulinic acid.

PBG (<1.5 mg/L)	12.10
PBG (24 h) (<2.0 mg/24 h)	18.15
ALA (<0.6 mg/dL)	32.50
ALA (24 h) (<8.0 mg/24 h)	42.25
Coproporphyrin (<150 μg/L)	3097
Uroporphyrin (5—30 μg/L)	4410