Impulsive and compulsive parkin disease

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In this issue of *Neurology*®, Morgante et al.[1] present a nice genotype–phenotype study of *parkin*-associated Parkinson disease (PD). PD is a progressive neurodegenerative disorder that affects 4.1 to 4.6 million people worldwide[2] and results in motor dysfunction and nonmotor symptoms including psychiatric problems. Impulse control disorder (ICD) is one such psychiatric problem that may present in PD. These impulsive behaviors are diverse and include excessive shopping, hypersexuality, binge-eating behavior, and pathologic gambling.[3,4] The incidence of ICDs is higher in patients with PD who have been treated with long-term dopaminergic replacement therapy including dopamine agonists, levodopa, and amantadine. Increasing evidence suggests that higher levodopa equivalent daily dose, male sex, younger age at PD onset, history of alcoholism, history of smoking, family history of gambling problems, and novelty-seeking personality are risk factors of ICD.[4] In addition, imaging studies propose potential neural networks that may underlie impulsivity and ICDs in PD.[5] The prevalence of ICD in treated PD can be up to 35%.[6] However, in routine clinical practice, ICDs are often diagnosed late or remain undiagnosed and untreated.

The *PRKN* gene, which encodes a protein called Parkin, is the responsible gene for PARK2.[7] PARK2 is the most common autosomal recessive form of PD, accounting for 10% to 20% of early-onset (<40) "sporadic" PD and approximately 50% of early-onset autosomal recessive PD. Patients carrying *PRKN* mutations present with early-onset, slowly progressive, levodopa-responsive parkinsonism accompanied by foot dystonia that can predate the parkinsonism, sleep benefit (improvement of symptoms after sleep), leg tremor, normal olfaction, L-dopa sensitivity with early-onset dyskinesia especially affecting the feet ("Irish dancing" dyskinesia), and occasionally marked behavioral disturbance. The pathology differs markedly from idiopathic PD. There is a more restricted morphologic involvement predominantly affecting the ventral nigra with relative preservation of the dorsal nigral tier, i.e., a nigropathy reminiscent of the neuropathology in MPTP parkinsonism.[8] Lewy bodies are rare or absent. Psychiatric symptoms such as depression, anxiety, and obsessive compulsive symptoms occur[9]; However, no study has systematically investigated prevalence and severity of ICDs in patients with *parkin*-associated PD.

Morgante et al. conducted a multicenter, case-control study to evaluate prevalence and severity of ICDs in patients with PD carrying *PRKN* mutations. They evaluated the prevalence of ICDs in 22 patients carrying *PRKN* mutations (parkin-PD) and in 26 patients with early-onset PD without any mutations in the known genes for hereditary PD (PD-NM). They then compared the characteristics of ICD observed in 15 patients with parkin-PD to those observed in 13 patients with PD-NM. The Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease–Rating Scale score, a widely used rating scale that measures severity of ICDs, was greater in parkin-PD than in PD-NM. Of note, the presence of the *PRKN* mutation was associated with smoking status, already known to be associated with a decreased risk of developing PD. These are important findings that add additional evidence to the risk factor profile and the potential genetic associations of ICD in patients with PD.

Development of ICD can worsen motor function of patients with PD leading to a lower quality of life,[4] which in turn leads to increased economic and social burden. It is generally thought that parkin-PD has a relatively benign clinical course and a slower disease progression; however, the emergence of ICD in this patient group may substantially hamper quality of life. Therefore, knowledge about ICD in parkin-PD is important to guide appropriate management to improve patient quality of life.

The study by Morgante et al. highlights a broader phenotype of specific behavioral disturbances in the impulsive-compulsive spectrum in parkin-PD compared to PD without gene mutations related to PD. Of note, the most affected brain area in parkin-PD is the ventral nigra. This nigral region projects to the ventral striatum, which has a greater responsibility for goal-directed movement and executive behavior via connections with the dorsolateral prefrontal cortex.[10] The dorsolateral prefrontal cortex and ventral striatum have been strongly

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implicated in behavioral inhibition and reward physiology in both animal studies and imaging studies in patients with PD and ICD.[11] Impairments in executive function have also been demonstrated in patients with PD and ICD and these correlate with changes in the dorsolateral prefrontal cortex.[11] This raises some interesting questions: Does the topography of brain involvement in parkin-PD match its different clinical phenotype compared to idiopathic PD? Does this selective regional involvement explain why there is a more behavioral disturbance in parkin-PD? Finally, can the parkin/MPTP model provide an opportunity to study these functionally segregated corticobasal loops and their effect on behavior, cognitive function, and motor control?

As noted by the authors, the small number of study participants is a limitation of this study. Thus, prospective studies are warranted to confirm their findings in larger cohorts. Furthermore, the authors did not provide the specific mutations in *PRKN* (e.g., homozygous mutation or compound heterozygote mutations; deletion, duplication, or the common R275W missense point mutation). This is unfortunate because it would be of interest to map specific mutations onto the recently defined crystal structure of parkin in an effort to correlate with the clinical syndrome.[12] Do homozygous mutations with complete loss of parkin result in the same clinicopathologic syndrome as compared to compound heterozygote mutations with the common R275W mutation? Finally, the article by Morgante et al. highlights the urgent need for similar reports in the field of neurogenetics, which up to now have been hampered by inadequate clinical description in the genetic literature and inadequate molecular genetic information in the neurology literature. Clear genotype–phenotype descriptions and correlations could guide and steer the forthcoming tidal wave of precision medicine.

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