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Parkinson's Disease Monitor & Commentary

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Practical Analysis on Today's Findings in Parkinson's Disease

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From the editor...

David J. Houghton, MD, MPH

It is with great pleasure that I accept the reigns of *PD Monitor & Commentary* from the outgoing editor Dr. Andrew Siderowf. As the founding editor, Dr. Siderowf set the tone with a mix of intriguing and informative articles that addressed both practical issues in patient management as well as new concepts in the pathophysiology of Parkinson's disease (PD). The challenge for every editor is not only to identify meaningful articles but match them with experts who can use their specific expertise to provide insight about how or even whether this new information is important for clinical practice or for understanding PD. Dr. Siderowf did an excellent job and I hope to follow in his footsteps.

As everyone who works in the field of PD is well aware, the amount of new information about the pathophysiological mechanisms of disease, the targets of therapy, and the importance of associated and related problems, such as cognitive loss, is overwhelming. Researchers who could once pursue a spectrum of clinical and basic science initiatives have increasingly had to narrow their focus to remain at the forefront of their areas of chief interest. For the clinician wishing to stay current with evolving concepts in the management of a disease that can encompass essentially every aspect of daily life, we hope this publication can make a modest but meaningful contribution.

In my first issue as editor, a broad array of topics is addressed—from white versus gray matter damage in PD to constipation treatment and tai chi to improve balance. Some have immediate clinical relevance. Others point the way to new directions in research. Our experts may not provide the final word on a given topic, but I think these commentaries provoke interest and allow our readers to hear a second opinion and perhaps gain more context for the area of interest. In addition, I have asked Drs. Elan Louis and Charles Adler to give their perspectives on whether essential tremor is predictive of PD (which they also, by the way, debated at June's Movement Disorders Society meeting held in Dublin, Ireland). And I myself tackle the issue of genetic testing for patients with PD in my first Q&A column.

I welcome your comments and suggestions, so please feel free to reach me at info@delmedgroup.com.

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PD Monitor & Commentary

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In This Issue

Commentaries

Q&A with David J. Houghton, MD, MPH

Controversies in PD

Clinicopathological correlations in corticobasal degeneration.

First Author and Institution:
Suzee E. Lee, MD, University of California, San Francisco.

Citation:
Annals of Neurology. 2011;70:327-340.

Objective:
Characterize clinical and morphological features of corticobasal degeneration (CBD).

Type of Study:
Single-center review of autopsy and clinical cases with known histopathology.

Result:
Patients with CBD typically present with cognitive or behavioral symptoms; less than half exhibit early motor deficits.

Conclusion:
No features were found specific to CBD, suggesting the diagnosis in living patients will remain challenging.

CBD, although first described more than 40 years ago, remains incompletely characterized and often confused with other neurodegenerative conditions. Other diagnoses included progressive supranuclear palsy (PSP), Alzheimer's disease (AD), dementia with Lewy bodies, frontotemporal lobar degeneration with TDP inclusions (FTLD-TDP), and Creutzfeldt-Jakob disease.

In this single-center study, cognitive problems were the most common initial manifestation in those with autopsy-confirmed CBD, occurring in 15 of the 18 subjects. The clinical syndromes associated with CBD in order of frequency were executive-motor disturbances (seven patients), progressive nonfluent aphasia (five patients), behavioral variant frontotemporal dementia (five patients), and posterior cortical atrophy (one patient). Although two of the autopsy patients had pathology other than CBD, none was related to α-synuclein.

This study suggests that CBD is driven by medial perirolandic dysfunction, but no specific underlying histopathology could be identified. Similarly, frontal lobe involvement is characteristic of CBD, which often presents with cognitive dysfunction, but the overlap of CBD with other disorders suggests the diagnosis may remain difficult without discovery of a biomarker.

Commentary:

Rachel Goldmann, MD
Assistant Professor of Neurology
University of Pennsylvania
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This study contributes data to the on-going effort to better characterize CBD. This article has two main parts: one that describes the characteristics of CBD, and the other that talks about the characteristics of CBD due to various pathologies. Overall, the study, which was relatively large and employed both neuropsychiatric and histopathological assessments, reconfirms other observations that CBD has a heterogeneous presentation and that misdiagnosis is common.

One of the reasons that there has been an intensification of interest in CBD is the progress that is being made toward the development of medications designed to target proteins implicated in the pathogenesis of neurodegenerative diseases. Anti-tau medications, which may be relevant for control of CBD, are one example. If this or other viable treatments are developed, it will be essential to determine which neurodegenerative processes are potential candidates for therapy.

For the clinician, this article may be useful for raising awareness about CBD, including identifying the specific challenges of making a definitive diagnosis.

For the clinician, this article may be useful for raising awareness about CBD, including identifying the specific challenges of making a definitive diagnosis. The effort of the authors to divide CBD into four clinical syndromes, progressive nonfluent aphasia (PNFA), posterior cortical atrophy (PCA), an executive motor (EM) dysfunction phenotype, and a behavioral variant frontotemporal dementia (bvFTD), may prove useful not only for improving the diagnosis of CBD but for pursuing the underlying pathophysiologic mechanisms. The description of the cognitive, behavioral, motor, and anatomical features within these syndromes did not produce unexpected findings, but the paper carefully evaluates a series of patients to substantiate previous descriptions. ■

Efficacy, safety, and tolerability of rasagiline as adjunctive therapy in elderly patients with Parkinson's disease.

First Author and Institution:
Eduardo Tolosa, MD, CIBERNED, University of Barcelona, Barcelona, Spain.

Citation:
European Journal of Neurology. 2012;19:258-264.

Objective:
Evaluate efficacy and safety of rasagiline as an adjunct to levodopa in elderly patients with Parkinson's disease (PD).

Type of Study:
Post-hoc analysis of data generated by two phase III trials.

Result:
When those 70 years or older were compared to those younger than 70 years, there was no difference in the efficacy or tolerability of adjunctive rasagiline.

Conclusion:
This evidence that rasagiline is effective and well tolerated in elderly patients is reassuring because of the frequency with which PD occurs in this age group.

Rasagiline, a second-generation and highly selective type-B monoamine oxidase inhibitor (MAOI-B) is approved for use as both a monotherapy and as an adjunct to levodopa for the treatment of PD on the basis of a series of phase III studies. Although these studies enrolled patients across broad age ranges, there are relatively few data looking explicitly at the efficacy and safety of this agent in older individuals.

In this study, data were pooled from the placebo-controlled PRESTO and LARGO phase III studies, which evaluated rasagiline as an adjunct to levodopa, in order to compare the relative efficacy and safety of rasagiline in those older and younger than age 70 years. The primary endpoint of total daily "off" time in this analysis was the same as in the initial studies.

The reduction in off time with rasagiline relative to placebo was highly significant in both age groups and comparable. The frequency of adverse events in the elderly was similar for total events and for most individual events, although rates of hallucinations, depression, constipation, pain, somnolence, and weight loss were slightly higher in the elderly. The risk of dopaminergic adverse events was not found to be related to age.

Rasagiline as an adjunct to levodopa appears to be as effective and well tolerated in individuals who are 70 years old or older with moderate to advanced PD relative to younger patients.

Commentary:

Irene Litvan, MD
Director, Movement Disorder Program
University of California, San Diego
La Jolla, California

Data on the efficacy and safety of rasagiline in the elderly are useful. Although a prospective study designed to address the questions of efficacy and safety specifically in the elderly is needed for definitive data, there are some strengths for this retrospective study. The two trials that supplied the data were well controlled and well conducted, the designs of the trials were similar, which helps with pooling of the data, and the trial data, which were published separately, are well known.

This study indicates rasagiline is efficacious in the elderly, but it also indicates that specific risks may differ modestly if importantly.

In these studies, a Mini-Mental Status Examination (MMSE) score of ≤24 points was an exclusion criterion, so it is important to recognize that the conclusions regarding safety and efficacy should be limited to the elderly with good cognitive function. On a statistical basis, there was no difference in the risk of adverse events, but I think that the data do point out a disparity in risk that deserves attention among clinicians. For example, hallucinations occurred in 1.7% and 1.9% of those on rasagiline and placebo, respectively, in the younger group, but 6.5% and 2.4%, respectively, in the older patients. Similar increases were seen for postural hypotension, somnolence, and weight loss. Although the absolute rates of these events remained low, it may be important to keep in mind the higher risk for a number of problems that are already more frequent in an elderly population.

Certainly, this study indicates rasagiline is efficacious in the elderly, but it also indicates that specific risks may differ modestly if importantly. ■

No correlation of substantia nigra echogenicity and nigrostriatal degeneration in Parkinson's disease.

First Author and Institution:
Elmar Lobsien, MD, University-Medicine, Berlin, Germany.

Citation:
Movement Disorders. 2012;27:450-453.

Objective:
Evaluate extent of substantia nigra (SN) echogenicity as a marker of Parkinson's disease (PD) progression.

Type of Study:
Prospective study using imaging with computerized analysis.

Result:
Despite previous assertions of a correlation, no relationship was found between SN echogenicity and nigrostriatal degeneration as measured with transcranial sonography.

Conclusion:
While sonography has been shown to be a useful tool for the diagnosis of PD, it is not a substitute for FP-CIT-SPECT for quantifying pathologic degeneration.

While FP-CIT-SPECT has demonstrated utility for quantifying nigrostriatal dopaminergic deficits and correlates with PD severity, there have been conflicting reports about the correlation of SN hyperechogenicity on transcranial sonography and disease progression. This study attempted to resolve this controversy.

In this study, 92 patients with PD who demonstrated SN echogenicity were evaluated with ^{123}I-FP-CIT-SPECT to assess the relationship of the putaminal FP-CIT binding ratio and the SN echogenicity in the context of several clinical parameters, including the Hoehn and Yahr (H&R) stage and the Unified Parkinson's Disease Rating Scale (UPDRS). The FP-CIT-SPECT analysis of the binding ratio was investigator independent.

No correlation was observed between SN echogenicity and ipsilateral putaminal FP-CIT uptake on either the right or left hemispheres. There were also no differences in SN echogenicity across H&R stage, even though the putaminal FP-CIT binding ratios did show a strong correlation with this clinical staging system. Similarly, while there was an inverse correlation between FP-CIT binding ratios and UPDRS score, no correlation was found between the dominant side of SN echogenicity, the UPDRS score, and the L-DOPA equivalent.

This relatively large series was unable to find a previously reported correlation between SN echogenicity and the FP-CIT binding ratio, even though FP-CIT binding ratio was shown in this study, as well as previous studies, to correlate with clinical severity. SN echogenicity does not appear to be a marker of disease progression but a relatively stable disease trait. Overall, the results suggest that transcranial sonography is a useful tool for confirming the diagnosis of PD but is not a substitute for FP-CIT-SPECT in evaluating the severity of the brain pathology.

Commentary:

Jay M. Ferrara, MD
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A reliable biomarker of PD would be useful in assessing the efficacy of potential disease-modifying therapies. Ideally, such a test would not be affected by symptomatic therapies, would correlate with both pathological and clinical disease progression throughout all stages of the illness, and be noninvasive and cost effective.

As a candidate biomarker, transcranial sonography has a few potential assets: prior studies have demonstrated that nigral echogenicity is abnormal in early stages of PD, and transcranial sonography is safe, administrable at the bedside, and inexpensive. Also, unlike radiotracer-based functional imaging studies, there probably is no potential for levodopa and other symptomatic therapies to alter sonographic findings. There are, however, liabilities to ultrasound as a candidate biomarker: the cause of nigral hyperechogenicity is likely related to iron accumulation, which has not been shown to be either pathogenic or to correlate with the severity of α-synuclein pathology. Furthermore, prior work (cited by the authors) has shown that nigral hyperechogenicity does not evolve in a predictable manner over time. The current study bolsters evidence that nigral hyperechogenicity does not correlate with clinical disease stage or nigrostriatal degeneration, thereby limiting ultrasound's utility as a paraclinical surrogate in assessing putative neuroprotective agents.

Overall, the data suggest that nigral hyperechogenicity tracking in individual patients over time is not likely to be illuminating. ■

The topography of brain damage at different stages of Parkinson's disease.

First Author and Institution:
Federica Agosta, MD, San Raffaele Scientific Institute, Milan, Italy.

Citation:
Human Brain Mapping. 2012 [Epub ahead of print].

Objective:
Characterize damage to the brain at different stages of Parkinson's disease (PD).

Type of Study:
Prospective evaluation in 89 consecutive patients.

Result:
Unlike gray matter, which showed little damage even in patients with advanced PD, there was a correlation between white matter atrophy and PD severity and cognitive damage.

Conclusion:
The findings suggest that damage to the white matter in patients with PD is a major contributor to motor damage as well as to progression of nonmotor symptoms, such as cognitive deficits.

The development of diffusion tensor (DT) magnetic resonance imaging (MRI) is permitting brain abnormalities to be characterized in increasing detail. In PD, atrophy and other structural changes in the gray and white matter of the brain have been described, but there has been less definition of relative topographical changes in these regions relative to PD progression.

In this study, 113 consecutive outpatients with PD were recruited for assessment with DT MRI. After a variety of exclusions, such as cerebrovascular disorders or a history of traumatic brain disorders, 89 patients were evaluated. Disease severity was characterized as early in 17, mild in 46, moderate in 14, and severe in 12. DT MRI examinations were also performed on 42 healthy controls with no history of neurologic or psychiatric disease. All groups were similar in age, gender distribution, and educational achievement.

Patients with PD had very little gray matter atrophy, even at advanced stages of the disease, compared with controls; the only significant difference between PD subgroups was modestly greater atrophy in the right thalamus among patients with moderate versus mild PD. Although there were no significant differences in white matter atrophy among early and mild subjects versus healthy controls, there were progressively greater white matter abnormalities in patients with moderate and severe disease relative to both healthy controls and to patients with early and mild PD. Abnormalities in the more advanced cases of PD were seen bilaterally and in most regions of white matter.

The authors note that the most striking change in white matter damage, which correlated with cognitive deficits, was observed between those with moderate disease when compared to those with mild disease. They conclude that the white matter damage may provide insight into the deficits associated with advancing PD.

Commentary:

Peter Hedera, MD
Assistant Professor of Neurology
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Nashville, Tennessee

Although this study is not the first to suggest that there is significant white matter damage associated with advancing PD, it does describe this damage in new detail through the use of DT MRI. Overall, the results make a very strong argument that it is important to think beyond dopamine in understanding the symptoms of advancing PD.

One of the strengths of this study is the correlation made between white matter damage and severity of PD symptoms. The study employed quite solid methodology in its analyses. While we have few therapeutic options for nondopamine targets in PD, it is important for clinicians to consider that nondopamine mechanisms are important to PD expression, particularly in advanced stages. In attempting to understand the mechanisms of PD-associated atrophy in the white matter, we are faced with a chicken-and-egg dilemma regarding whether the underlying pathophysiology is an independent and targetable primary phenomenon or a downstream complication of some mechanism we have yet to identify. In fact, I think it likely that there may be some surprises in the effort to better understand the involvement of areas of the brain other than the nigrostriatal pathway in the expression of symptoms in late-stage PD. ■

Placebo-controlled trial of lubiprostone for constipation associated with Parkinson disease.

First Author and Institution:
William Ondo, MD, University of Texas Health Science Center, Houston, Texas.

Citation:
Neurology. 2012;78:1650-1654.

Objective:
Evaluate efficacy and tolerability of lubiprostone to control Parkinson's disease (PD)-associated constipation.

Type of Study:
Double-blind, randomized, placebo-controlled trial.

Result:
A marked or very marked reduction in constipation was achieved in 64% of patients randomized to lubiprostone versus 18.5% (P=0.001) of those randomized to placebo. Side effects were mild.

Conclusion:
Lubiprostone was effective and well tolerated for the treatment of constipation in patients with PD over the 4 weeks of this trial. Further studies are needed to confirm a long-term benefit.

In patients with PD, constipation often precedes motor symptoms and is related to several changes in gastrointestinal (GI) function, including prolonged colon transit time and altered coordination of muscle relaxation and contraction in the rectum that is important to defecation. Although there is severe loss of both central and colonic dopaminergic neurons in PD, constipation does not respond well to dopaminergic treatment, thus implicating nondopaminergic mechanisms.

In this study, 54 patients with PD and clinically meaningful constipation were evaluated over a 2-week period before being randomized to lubiprostone, which activates CIC-2 chloride channels in GI epithelial cells, or placebo. The initial dose of lubiprostone was 24 µg day but upwards titration to a maximum of 48 µg per day was permitted. After 4 weeks, the two groups were compared on a variety of measures including constipation scales and global impressions.

A marked or very marked improvement in clinical global improvement was reported subjectively by 16 (64%) of the 25 patients randomized to lubiprostone versus five (18.5%) of the 27 placebo subjects (P=0.001). The advantage on the constipation rating scale and several secondary measures, such as stool frequency, also favored lubiprostone significantly. Mild episodes of intermittent loose stools were the most common lubiprostone-related adverse event.

According to the authors, only a small number of treatment trials for constipation have been conducted in patients with PD. This study associated lubiprostone with substantial efficacy for this indication. However, as PD-related constipation may require long-term or lifetime therapy, longer studies are needed to confirm safety and efficacy.

Commentary:

Pratap Chand, MD, FRCP
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St. Louis, Missouri

Constipation is a major premotor and nonmotor symptom in PD, affecting about 70% of patients with PD. The constipation does not respond well in all patients to current therapeutic options and there is an unmet need for newer treatment strategies.

The clinical significance of this study is that it has identified a new medication for constipation in PD that appears to offer substantial efficacy with minimal side effects. The double-blind, placebo-controlled design is a standard for medication trials. Overall, the majority of patients responded well, although 24% had only mild subjective improvement and 12% had no subjective improvement. It would be useful to study nonresponders further to determine if there were identifiable differences in the cause of the constipation. Specifically, studies of colon transit time and anal sphincter dysfunction, although time consuming, would be a useful adjunct to this study to correlate the benefit with causal mechanisms such as slow colon transit time or anal sphincter dysfunction.

As the authors acknowledge, there is also a need for long-term follow-up in these patients to see if the therapeutic benefit persists. However this is a very useful initial study of the potential use of lubiprostone for constipation in PD. The study has practical relevance in identifying a potentially useful treatment for constipation in patients with PD. ■

Tai chi and postural stability in patients with Parkinson's disease.

First Author and Institution:
Fuzhong Li, MD, Oregon Research Institute, Eugene, Oregon.

Citation:
New England Journal of Medicine. 2012;366:511-519.

Objective:
Evaluate whether tai chi training can improve postural control in patients with idiopathic Parkinson's disease (PD).

Type of Study:
Randomized, controlled trial.

Result:
When compared to those randomized to resistance training or stretching, those who received instruction in tai chi had significantly greater improvements in measures of postural control.

Conclusion:
The effects of tai chi, which include relative advantages across multiple measures of gait, strength, and directional control, are consistent with an expectation of functional improvements.

One of the functional limitations of PD is progressive loss of postural stability leading to decreased mobility and increased risk of falls. Parkinsonian treatments have limited effects on these symptoms. Some benefits have been associated with resistance-based exercises, but tai chi, a discipline that emphasizes balance and postural control, is an attractive behavioral intervention.

In this study, 195 patients with PD and disability ranging from 1 to 4 on the Hoehn and Yahr scale were randomized to tai chi, resistance training, or stretching. In all three groups, the patients participated in 60-minute exercise sessions twice a week for 24 weeks. The primary outcome was a change in baseline in maximum excursion and directional control as measured by computerized dynamic posturography. Secondary outcomes included quantification of gait dynamics, also evaluated with a computer-aided system, and an up-and-go test that measured time taken to rise from a chair and walk 10 feet.

For maximum postural excursion, the improvement from baseline at 6 months was significantly better for those randomized to tai chi than either resistance exercise (P=0.01) and stretching (P<0.001). The relative advantage of tai chi was also significant against resistance exercise (P=0.002) and stretching (P<0.001) for directional control. Of the secondary measures, tai chi had a statistically significant advantage over stretching for all outcomes. Relative to resistance exercises, tai chi offered a significant advantage for some outcomes, such as stride length, but not others, such as gait velocity. Relative to stretching but not to resistance exercises, falls occurred significantly less often among patients doing tai chi.

The authors conclude that tai chi improves postural stability and functional ability in patients with PD.

Commentary:

Tiffini Voss, MD
Assistant Professor of Neurology
University of Virginia
Charlottesville, Virginia

There is a critical need for treatments for postural instability and falls, which are one of the most common reasons for patients with PD to enter a long-term care facility. This well-conducted study suggests behavioral interventions such as tai chi may be useful in improving functional balance and reducing instability. The major limitation is that it was not double-blind, but the investigators did take reasonable steps to minimize this limitation, including conducting the baseline and end-of-study evaluations with blinded assessors. Although a potential placebo effect may still impact the results, the size of the treatment effect was encouraging. Not least important, the study demonstrated that balance-specific behavioral interventions are safe even among patients with significant impairment in postural reflexes (individuals with Hoehn and Yahr stages 3 and 4 disease were included).

The data would be even more compelling if the study had evaluated and demonstrated an improvement in quality of life or had demonstrated a reduced risk of traumatic falls leading to injury, but I think it should encourage clinicians to consider this type of strategy. It is not clear that tai chi, specifically, is uniquely effective for improving balance, but the results of the study do suggest that balance training can provide practical benefit with little risk. ■

Q&A WITH EDITOR David J. Houghton, MD, MPH

Question: Should I consider genetic testing for patients with Parkinson's disease (PD)?

Answer: To describe the issue of genetic testing in PD as "complicated" is quite an understatement, with scientific, financial, legal, and emotional ramifications to consider. Genetic PD from recognized genes still likely makes up a relatively low prevalence of all patients with PD (10%-15%), although these identified genes certainly do not account for all genetic cases of PD.[1] Genome-wide association studies (GWAS) are becoming a powerful technique for screening large populations of patients for associated genes and dozens of such relationships have already been discovered, perhaps accounting for up to 25% of all cases of presumed sporadic PD.[2] Penetrance of the phenotype is often variable with genetic PD, implying a mixed susceptibility and clinical picture that may highlight the genetic-environmental interaction of this disease.

Genetic testing can be quite costly upfront with inconsistent coverage by health care plans, although a web-based service now will test symptomatic patients with PD for several genes for no charge. In addition, federal passage of the Genetic Information Non-discrimination Act (GINA) of 2008 legislates some medical and employment protection for gene-positive asymptomatic individuals, but problems with other insurances (life, disability, long-term care) and social stigmatization are always possible.[3]

For patients with clinical features that meet the UK Brain Bank criteria for PD, genetic testing is usually unnecessary for diagnosis of the disease, and the arrival of functional dopamine transporter imaging may make genetic testing even less helpful in some cases. However, young-onset patients and those with complicated parkinsonism may benefit from diagnostic testing. Recessive cases may not have a clear family history, and other heterozygous susceptibility genes should be considered (i.e., GBA1 in Gaucher's disease carriers or late-onset PRKN heterozygotes). As an example, in a young patient with dystonia and parkinsonism, genetic testing for a PRKN gene (or even PINK1, DJ-1, or GCH1) mutation prior to testing for DYT dystonia genes may be diagnostically helpful.

In addition, patients often present with a clear family history of PD or a more nebulous description of a relative with parkinsonian or tremorous features. In these cases, patients may be interested in testing to support their own diagnosis and offer predictive information for their family. Asymptomatic individuals may also attempt to quantify their risk. Here, the patient and family must be clear about the lack of scientific discovery and commercially available testing to cover all of the potential genetic variability that may be contributing to the prevalence of PD in their family.

To help navigate the potential minefield of genetic testing, it is recommended that patients and families undergo genetic counseling prior to any testing, even that offered by the newly established online community of web-based databases. Ideally, this counseling is part of an interdisciplinary clinic associated with a neurology practice group. Alternatively, most academic and some private institutions offer these counseling services independently. Risks and benefits of testing should be mutually discussed and understood.

Asymptomatic, predictive testing for any genetic disease is most useful when it is accompanied by a treatment to prevent or reverse pathology. Definitive protection from the neurodegeneration of genetic PD remains elusive. A genetic diagnosis will also not routinely change PD management. However, in the research arena, early knowledge of genetic susceptibility may provide a unique patient population for testing of neuroprotective therapies prior to the onset of motor PD. The research setting may also afford greater protection of genetic results, and patients may even opt to remain uninformed.

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Controversies in PD

PRO Opinion

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The possible link between ET and PD has been a subject of interest and debate for some time. Dating back to the first comprehensive clinical review of ET in 1949, there has been discussion regarding the possibility of a relationship between these two tremor disorders, with clinicians observing that patients with ET have a tendency over time to develop PD.[1-3] Interestingly, the converse does not seem to occur (i.e., patients with PD developing ET).[2,3] The co-occurrence of the two tremor disorders within the same families is also well-documented.[4]

Three epidemiological studies, including two case-control studies and one population-based prospective study, each provide measures of association that support the notion that there is a link between ET and PD and, furthermore, that the presence of baseline ET increases the risk of developing incident PD during follow-up.[5,6] The magnitude of the increased odds/risk reported in the three epidemiological studies is on the order of 3 to 13.[5] Most important of these was the 2010 prospective, population-based study that was conducted to estimate the incidence of PD in patients with ET versus normal controls.[6] The study sample was comprised of 3,813 elderly persons (age ≥65 years) residing in three communities in central Spain. The baseline evaluation consisted of an initial screening questionnaire followed by an in-person neurological examination; a follow-up examination was performed after a median interval of 3.3 years. During that time interval, six of 201 (3.0%) ET cases versus 24 of 3,574 (0.7%) controls developed incident PD (adjusted relative risk [RR]=4.27, 95% confidence interval [CI]=1.72-10.61, P=0.002).[5,6] Presently, there are no contrary data, either from case-control or prospective studies, to refute the model that ET is a risk factor for PD.[5]

Moreover, evidence from three genetic epidemiological studies suggests that ET and PD seem to co-occur in families to an extent greater than expected by chance alone, with patients with PD being more likely than controls to have first-degree relatives with ET.[5]

The epidemiological and genetic epidemiological data are consistent with biological evidence, which further supports the possibility of common disease mechanisms and pathogenesis.[7] Thus, several imaging studies have suggested that there may be some degree of overlap between ET and PD.[5] These findings are further supported by genetic studies, which demonstrate that some of the same genetic variants are associated with both ET and PD.[5,8] More recently, large post-mortem series have demonstrated the presence of more brainstem Lewy bodies in ET cases than in similarly-aged controls, suggesting that there is the presence of Lewy body variant of ET, and raising the possibility that these cases might be at increased risk for developing a more complete Lewy body syndrome (i.e., PD).[9]

The composite data are difficult to ignore. Indeed, a recent editorial on the putative relationship between ET and PD remarked as follows: "Perhaps there are not enough studies to completely end the discussion, but the consistency of the results and the biological plausibility of the association are very strong."[10]

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The Question: Is essential tremor (ET) predictive of Parkinson's disease (PD)?

CON Opinion

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Whether ET is a risk factor for PD or whether they occur coincidentally remains unclear. Both likely have multiple etiologies, so finding a link is difficult. Clinically, both ET and PD may have rest, postural, and kinetic tremor as well as bradykinesia and rigidity. Yet these clinical signs are not diagnostic for PD as evidenced by normal dopaminergic imaging (so called Scans Without Evidence of Dopamine Deficiency or SWEDDs) and no evidence of Lewy bodies neuropathologically. Two ways to approach the issue are: 1) Is there an increased occurrence of α-synuclein staining or Lewy bodies in cases of ET, and 2) Is there an increase in ET in subjects with Lewy body pathology?

Initial autopsy reports in ET found no Lewy body pathology.[1,2] One group initially reported an increased occurrence of Lewy bodies in ET versus controls, but their prospective data now show there is no difference in Lewy body occurrence (ET 2/32, 6.3%; controls 2/21, 9.5%).[3-5] Their initial conclusion that ET has a "Lewy body variant" is now not supported. Our series of prospectively ascertained and examined ET cases found no difference in Lewy body occurrence between ET cases (3/24, 12.5%) and controls (2/21, 9.5%).[6]

Up to 30% of autopsied individuals over age 65 have incidental Lewy body disease (ILBD), so both ET and ILBD are extremely common. We reported no difference in the occurrence of ET in ILBD cases (6/13, 46%) compared with controls (22/55, 40%) and no difference in the occurrence of ≥2+ postural or kinetic tremor of the hands: 4/13 (31%) ILBD and 14/55 (25%) controls.[7]

Neurochemical studies show that striatal tyrosine hydroxylase (TH) levels are low in PD and ILBD but this was not found in ET, not even in a subgroup of ET cases.[8,9]

Epidemiologic studies have many flaws. The retrospective study showing more ET in PD cases compared to Parkinson-plus cases had no control group, so no link was established.[10] The study finding a 4x higher incidence of PD in ET cases ≥65 years of age found very few incident PD cases (6/201 ET and 24/3,574 controls) and produced an absolute increased risk of only 2.3%; furthermore, the diagnosis of PD can be questioned in this study as they did not require dopaminergic response for the diagnosis of PD, nor was there imaging or pathology to support the diagnosis of PD.[11] There is no definitive evidence that genes associated with PD (LRRK2, SNCA variants, glucocerebrosidase, LINGO1, or LINGO2) have an association with ET. There is also no definitive neuroimaging data or therapeutic evidence linking ET to PD.

In conclusion, the overwhelming evidence supports a lack of ET being a risk factor for PD. ET is very common and its occurrence in PD may well be coincidental. We need clear diagnostic markers for both disorders along with prospective, controlled studies utilizing longitudinal, standardized assessments for tremor and parkinsonism in subjects with and without ET along with either neuroimaging (a surrogate marker) or autopsy, the only gold-standard marker, for PD to answer this debate.

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