Lysosomal enzyme defects and Parkinson disease

The pathogenesis of Parkinson disease (PD) remains elusive. In the 1960s, the loss of dopamine neurons in the substantia nigra was linked to the etiology of PD. This finding paved the way for the development of dopaminergic therapy to alleviate some of the symptoms of PD. Despite intensive research, however, the cellular mechanisms that lead to degeneration of dopaminergic cells in PD remain poorly understood.

There is growing evidence that protein misfolding and deposition plays a role in the pathogenesis of PD, as well as other neurodegenerative disorders. The accumulation of damaged or misfolded proteins may perturb normal cell function and contribute to cell death. The cellular autophagy-lysosomal pathway (ALP), in which targeted abnormal proteins are contained within autophagosomes that fuse with lysosomes and are then degraded or recycled, plays an essential role in the proper removal of abnormal proteins. Thus, lysosomal enzymes play a crucial role in the ALP pathway, and defects in the ALP pathway of dopaminergic neurons may result in the excessive accumulation of aberrant proteins in the cytoplasm, ultimately resulting in cell loss and the clinical manifestations of PD. Heterozygous carriers of mutations in the glucocerebrosidase gene, a lysosomal enzyme that causes Gaucher disease when an individual carries 2 copies of mutations in its gene, have an increased risk of developing PD.

In this issue of Neurology, Gan-Or et al. have focused on 3 other autosomal recessive lysosomal storage disorders to determine whether heterozygote carriers of these mutations have an increased risk of developing PD. Tay-Sachs disease, Niemann-Pick type A, and mucolipidosis type IV are caused by mutations in different lysosomal enzymes. Deficiencies in any of these 3 enzymes result in the accumulation of their protein substrates within the cell. It thereby follows that heterozygote carriers of any of these gene mutations may have a defective ALP, resulting in the accumulation of abnormal proteins and rendering their dopaminergic neurons more susceptible to degradation.

Gan-Or et al. studied a well-characterized, genetically homogenous Ashkenazi Jewish population. They found that carriers of one of 3 mutations that cause Niemann-Pick type A (SMPD1), but not those who carried mutations that cause either Tay-Sachs disease or mucolipidosis type IV, were at a 9-fold higher risk of developing PD (p < 0.0001). It is possible that this risk is only clinically significant when expressed against a relatively homogeneous genetic background, such as that found in the Ashkenazi Jewish population that was analyzed. While PD remains a disorder that is diagnosed based on an individual’s history, examination, and response to levodopa, a family history of lysosomal storage disease in a given patient should alert one to a possible increased risk of PD in that individual.

While these data do not change the way in which patients with PD are diagnosed or treated, they do illustrate the utility of performing genetic studies in relatively ethnically homogeneous cohorts that have undergone careful clinical characterization. Data gleaned from such studies can identify pathogenic mechanisms that can then be studied further in the laboratory. The finding that a specific mutation in the SMPD1 enzyme is associated with an increased risk of PD gives further support to the hypothesis that defects in the ALP play a role in the pathogenesis of PD and identifies another cellular pathway as a target for drug development.

STUDY FUNDING
No targeted funding reported.

DISCLOSURE
N. Sharma receives research support from the NIH, the Bachmann Strauss Dystonia & Parkinson Foundation, and the Dystonia Medical Research Foundation. Dr. Sharma also serves on the Repligen Data Safety Monitoring Board for Phase 1 Double-Blind, Placebo Controlled, Ascending Multiple Dose Safety and Pharmacokinetic Study of RG3039 in Healthy Volunteers. Go to Neurology.org for full disclosures.

REFERENCES

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This Week’s Neurology® Podcast

Incidence of atrial fibrillation detected by implantable loop recorders in unexplained stroke (See p. 1546)

This podcast begins and closes with Dr. Robert Gross, Editor-in-Chief, briefly discussing highlighted articles from the April 23, 2013, issue of Neurology. In the second segment, Dr. Bryan Eckerle talks with Dr. Paul Cotter about his paper on incidence of atrial fibrillation and unexplained stroke. Dr. Adam Numis then reads the e-Pearl of the week about LGI-1 antibodies in limbic encephalitis. In the next part of the podcast, Dr. Brett Kissela focuses his interview with Drs. Ope Adeoye and Art Pancioli on the CLEAR-ER trial.

Disclosures can be found at www.neurology.org.

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