Globular Gial Tauopathy Presenting as Semantic Variant Primary Progressive Aphasia

Semantic variant primary progressive aphasia (svPPA) most often is due to TAR DNA-binding protein 43 (TDP-43) pathology. Herein, we report a case of svPPA due to a globular gial tauopathy (GGT).

Report of a Case | The clinical, neuropsychometric, and imaging features of this case previously were reported in 2008. Briefly, a woman in her 60s was referred to the Behavioral Neurology Clinic for memory loss, characterized by difficulty remembering names. Longitudinal evaluations revealed progressive anoma with loss of word knowledge, prosopagnosia, and surface dyslexia. Her last completed neuropsychometric evaluation occurred at age 71 years (Figure 1). In her early 70s, her husband presented evidence of impaired object knowledge; for example, she frequently would use the incorrect silverware (eg, fork with soup) and was noted to have used toothpaste instead of hand lotion.

At age 73 years, disinhibition became more prominent. Her judgment continued to deteriorate as she would inappropriately pick up hot objects with her hands. In her mid-70s, she returned for follow-up and it was noted that despite her continued deterioration in most cognitive aspects, she had expanded her painting artistry. Later in her mid-70s, she was placed in a nursing home following a right hemispheric infarct. In the last few months of life, she developed significant echolalia. Three months after having a stroke, she died in her mid-70s. Neuropathologic evaluation revealed the pathologic substrate to be a GGT and not TDP-43. Gross findings included severe frontotemporal atrophy (temporal > frontal), with left hemibrain weight of 515 g. Histopathologic features are illustrated in Figure 2.

Figure 1. Neuropsychologic Testing and Magnetic Resonance Imaging

A, All raw scores were converted to scaled scores based on Mayo Older American Normative Studies (MOANS) norms (mean [SD], 10 [3]). AVLT delay indicates retention on the Auditory Verbal Learning Test; BNT, Boston Naming Test; Categ, category; DRS, Dementia Rating Scale; Flu, Fluency; JLO, Judgment of Line Orientation; Rey-O, Rey-Osterrieth Complex Figure Test; TMT, Trail Making Test; WAIS-BD, Block Design subtest of the Wechsler Adult Intelligence Scale-Revised; WMS-LM-R, Logical Memory of the Wechsler Memory Scale-Revised; Stroop CW, Stroop color-word test. B, Coronal T1-weighted magnetic resonance images of the patient in her early 70s showing continued disproportional left anterior temporal lobe atrophy.
Discussion

This is a rare case of svPPA due to a GGT. This variant of PPA is due to TDP-43 pathology in approximately 80% of cases.\(^1\) Frontotemporal lobar degeneration due to tau is the second most common cause of svPPA; however, the cases reported to date typically have been due to Pick disease,\(^1\) which is a 3R tauopathy. Mutations in the microtubule-associated protein tau gene have been associated with a semantic-like presentation, but many of these cases have a predominantly behavioral presentation with secondary semantic dysfunction.\(^3\) In the present case, the patient clearly met consensus criteria for svPPA for many years before behavioral symptoms evolved. She also developed increased artistic skill similar to other temporal predominant frontotemporal dementias.\(^4\)

Globular glial tauopathies (4R tauopathy) are subtypes of frontotemporal lobar degeneration due to tau characterized by globular tau-reactive oligodendrogial and astrocytic inclusions. Globular glial tauopathies are subdivided into 3 types based on the distribution of the inclusions.\(^5\) In this case, frontotemporal globular oligodendrogial inclusions dominated (type I).

The clinical presentations of GGTs are variable and include behavioral variant frontotemporal dementia, progressive supranuclear palsy, primary lateral sclerosis, corticobasal syndrome, and combinations of dementia, parkinsonism, and motor neuron disease.\(^5\) Prior cases of PPA with GGT pathology have been agragrammatic-nonnoun PPA.\(^5\)

These findings expand the pathologic substrate of svPPA to include GGTs.

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**Figure 2. Histopathology Demonstrating Globular Glial Tauopathy**

| A | Hematoxylin-eosin | B | Phospho-tau | C | Phospho-tau |
| D | Gallyas | E | 4R tau | F | Gallyas |

Globular glial tauopathy, type I, with 4R tau-positive globular glial inclusions, predominantly oligodendrogial and to a lesser extent astrocytic. The Gallyas stain was positive in oligodendrogial and negative in astrocytic lesions, as is typical of globular glial tauopathy. There were no TAR DNA-binding protein 43-positive inclusions. A, Temporal white matter (hematoxylin-eosin; original magnification ×200; inset ×750); B, temporal white matter (phospho-tau [AT8]; original magnification ×200); C, temporal gray matter (phospho-tau [AT8]; original magnification ×200; inset: 4R tau ×400); D, temporal white matter (Gallyas; original magnification ×200; inset ×750); E, temporal white matter (4R tau; original magnification ×200); and F, temporal gray matter (Gallyas; original magnification ×200).
Genetic Correlation Between Schizophrenia and Epilepsy

Neuropathological, clinical, and epidemiological data suggest that schizophrenia and epilepsy are associated.\(^1\) Reported estimates of the prevalence of schizophrenia among people with epilepsy vary, depending on phenotypic definition, but may be around 7%.\(^2\) One hypothesis to account for people with epilepsy varies, depending on phenotypic definition.

Methods

The International League Against Epilepsy meta-analysis of GWAS included data on 8696 people with epilepsy of all types and 26 157 control individuals. Data were also included on the subtypes of genetic generalized (n = 2606) and focal (n = 5310) epilepsy. The Psychiatric Genetics Consortium meta-analysis of schizophrenia GWAS included 13 833 cases and 18 310 control individuals. The LDSC regression provides an estimation of \(r_G\) between 2 diseases based on the effect size of each single-nucleotide polymorphism shared by the 2 traits and incorporates the appropriately weighted effect size of all other single-nucleotide polymorphisms with which it is in LD. The calculation also includes the sample size for each study and the degree of sample overlap between the studies, which in this case was zero. Because sample overlap can impair the ability of this method to detect genetic correlation, we did not use the most recent Psychiatric Genetics Consortium meta-analysis of schizophrenia GWAS because this study shared some control individuals with those of the epilepsy GWAS.

Results

Results are shown in the Table. There was a positive genetic correlation between schizophrenia and epilepsy (all subtypes) of 0.22 (SE, 0.07; \(P = 0.001\)). The heritability for schizophrenia was 0.30 (SE, 0.02). All heritability estimates are presented on the liability scale.

Discussion

In this study, the LDSC regression has revealed a statistically significant positive association between schizophrenia and epilepsy (all subtypes). The individual significant positive \(r_G\) for schizophrenia with focal epilepsy, although it does not survive Bonferroni correction for multiple comparisons, could be taken to suggest that it is this subtype of epilepsy driving the overall significant positive correlation.

The value for epilepsy heritability of 0.05 calculated by LDSC here is significantly lower than values calculated previously using alternative methods.\(^6\) This is likely attributable in part to the genomic control correction applied to each constituent study of the epilepsy meta-analysis data. This biases estimates of heritability downwards without affecting the value for genetic correlation.\(^3\) The schizophrenia data set did not undergo genomic control correction and accordingly the heritability reported here is more in keeping with previously published estimates. We would also note that the complete epilepsy data set included both genetic generalized epilepsy and focal epilepsy, and the low heritability estimate could potentially be explained by heterogeneity among these cases. However, neither of these limitations is likely to produce a falsely significant positive result for genetic correlation.

The power of LDSC lies in the fact that it only requires summary statistics, rather than individual-level genotype data, to estimate trait heritability and genetic correlation. Estimations of correlation can provide insights into shared biology at the molecular level and are especially useful where environmental confounders might otherwise be thought to link 2 diseases. A link between schizophrenia and epilepsy has been the subject of interest and controversy since it was noted early in the 20th century that there was some apparent phenotypic overlap between them. However, whether this link represents a shared etiology has not previously been clarified. Here, we have provided an initial demonstration of a significant shared liability to schizophrenia and epilepsy.

Table. Heritability of Epilepsy and Subtypes and Genetic Correlation With Schizophrenia

<table>
<thead>
<tr>
<th>Disease Type</th>
<th>Heritability (SE)</th>
<th>Correlation With Schizophrenia</th>
</tr>
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<tbody>
<tr>
<td>All epilepsy (n = 8696)</td>
<td>0.05 (0.01)</td>
<td>0.22 (0.07)</td>
</tr>
<tr>
<td>Genetic generalized epilepsy</td>
<td>0.32 (0.05)</td>
<td>0.02 (0.04)</td>
</tr>
<tr>
<td>Focal epilepsy(n = 5310)</td>
<td>0.04 (0.03)</td>
<td>0.31 (0.15)</td>
</tr>
</tbody>
</table>

Abbreviation: \(r_G\), genetic correlation.

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Letters

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