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 glial 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 amnesia 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 (e.g., 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. Histo-pathologic features are illustrated in Figure 2.

Figure 1. Neuropsychologic Testing and Magnetic Resonance Imaging

A. Neropsychologic testing

<table>
<thead>
<tr>
<th>Cognitive Measures and Domains</th>
<th>DRS-2</th>
<th>WMS-LM-R %</th>
<th>AVLT Delay</th>
<th>BNT</th>
<th>Letter Flu</th>
<th>Categ Flu</th>
<th>TMT A</th>
<th>TMT B</th>
<th>Stroop CW</th>
<th>Rey-O</th>
<th>WAIS-BD</th>
<th>JLO</th>
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<tbody>
<tr>
<td>Global</td>
<td>0</td>
<td>16</td>
<td>14</td>
<td>12</td>
<td>10</td>
<td>8</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>1</td>
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<td>Memory</td>
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<td>14</td>
<td>12</td>
<td>10</td>
<td>8</td>
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<tr>
<td>Language</td>
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<td>14</td>
<td>12</td>
<td>10</td>
<td>8</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>10</td>
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<tr>
<td>Attention/Executive</td>
<td>0</td>
<td>16</td>
<td>14</td>
<td>12</td>
<td>10</td>
<td>8</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>10</td>
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<tr>
<td>Visuospatial</td>
<td>0</td>
<td>16</td>
<td>14</td>
<td>12</td>
<td>10</td>
<td>8</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>0</td>
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</table>

B. Coronal 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. 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, 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. 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.

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. 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. Prior cases of PPA with GGT pathology have been agrammatic-nonfluent PPA.

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

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Author Contributions: Dr Graff-Radford had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors reviewed the manuscript and were in agreement with its content and provided final approval of the version to be published.

Study concept and design: Graff-Radford, Josephs, Parisi, Boeve. Acquisition, analysis, or interpretation of data: Graff-Radford, Parisi, Dickson, Giannini, Boeve. Drafting of the manuscript: Graff-Radford. Critical revision of the manuscript for important intellectual content: All authors. Administrative, technical, or material support: Parisi, Giannini, Boeve. Study supervision: Josephs, Parisi, Giannini, Boeve.
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schizophrenia4 and epilepsy.5 In this retrospective case-
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relationship is that the 2 diseases share a common etiol-
testimony of linkage disequilibrium (LD) score regression (known as
control analysis, we used a technique called linkage disequi-
LDSC regression

1. Josephs KA, Hodges JR, Snowden JS, et al. Neuropathological background of

temporal lobe atrophy: an 8-year longitudinal study. Arch Neurol


Genetic Correlation Between Schizophrenia and Epilepsy

Neuropathological, clinical, and epidemiological data sug-
ggest that schizophrenia and epilepsy are associated.1 Re-
ports estimated the prevalence of schizophrenia among
people with epilepsy vary, depending on phenotypic defini-
tion, but may be around 7%.5 One hypothesis to account for the relationship is that the 2 diseases share a common etiology. Methodological advances now make it possible to test the extent to which genetic predisposition is common to the 2 conditions based on molecular genetic data.3 We sought to do so using publically available genome-wide association study (GWAS) summary statistics from large meta-analyses of schizophrenia4 and epilepsy.5 In this retrospective case-control analysis, we used a technique called linkage disequi-

Methods | The International League Against Epilepsy meta-
analysis of GWAS included data on 8696 people with epi-
lysis 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 Consort-

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 = .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 rG 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 pre-
vious using alternative methods.6 This is likely attribut-
able 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 schizophre-

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>
</thead>
<tbody>
<tr>
<td></td>
<td>rG (SE)</td>
<td>P Value</td>
</tr>
<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 (n = 2606)</td>
<td>0.32 (0.05)</td>
<td>0.02 (0.04)</td>
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<tr>
<td>Focal epilepsy (n = 5310)</td>
<td>0.04 (0.03)</td>
<td>0.31 (0.15)</td>
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</table>

Abbreviation: rG, genetic correlation.