Dementia-Like Presentation of Striatal Hypermetabolic State With Antistriatal Antibodies Responsive to Steroids

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Background: Hypermetabolic lesions of the striatum are rare. They usually involve autoimmunity and are associated with choreatic disorders such as Sydenham chorea, lupus, and the antiphospholipid antibody syndrome.

Patient: A 48-year-old woman was initially seen with a 1-year history of progressive changes in personality and attention. There were minor associated involuntary movements. Negative routine investigation results, including regular autoimmune serologies and magnetic resonance imaging, led to the diagnosis of a frontal dementia. Positron emission tomographic results demonstrated hypermetabolism in the left striatum. Western blot technique results demonstrated plasma antistriatal antibodies. Treatment with corticosteroids induced a resolution of her attentional deficits and a return of her personality to its premorbid state. The repeated positron emission tomographic scan results were near normal, and the titer of antistriatal antibodies was significantly reduced.

Conclusion: Autoimmune striatal dysfunction can initially appear with a clinical picture suggestive of a degenerative dementia. Recognition of the underlying etiology and treatment was possible because of abnormalities uncovered on positron emission tomographic images.

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DISEASES OF THE BASAL GANGLIA associated with regional hypermetabolism are uncommon. The initial appearance usually involves involuntary choreatic movements with occasional neuropsychiatric manifestations. They include putative autoimmune disorders such as Sydenham chorea, systemic lupus erythematosus, and the primary antiphospholipid syndrome. Investigation results often reveal elevated antistreptolysin O titers, abnormal sex hormonal profiles, or the presence of antiphospholipid antibodies. Striatal hypermetabolism, occasionally unilateral, may be detected by positron emission tomography (PET), whereas single-photon emission computed tomographic results can reveal alterations in blood flow.

We recently saw a patient with a clinical picture consistent with frontal lobe dementia. There were minimal involuntary movements of the right hand. The PET imaging results demonstrated unilateral striatal hypermetabolism, and a later search revealed antibodies to striatal epitopes. A short course of intravenous steroids produced definite improvement in cognitive function. This diagnosis and its treatment would not have been reached without PET imaging.

REPORT OF A CASE

A left-handed 48-year-old woman was initially seen with a 1-year history of progressive changes in personality and behavior without loss of memory or language. Declining performance and behavioral changes led her to stop her work as a teacher. In contrast to her premorbid state, she was described as more impulsive, obsessive, irritable, and abrasive.

A previous episode of neurological dysfunction occurred in her early 20s and involved flailing motions of her left limbs without cognitive deficits. Exhaustive investigations, including results of serologies, lumbar puncture, electroencephalography, 4-vessel angiography, and brain scan, were unrevealing. The episode lasted a few months and resolved spontaneously after discontinuation of her birth control pills.

Other medical history included repair of an ostium primum atrial septal defect at 6 years of age. There was no history of rheumatic fever. She had had mild migraines. Relevant family history included “St Vitus’ dance” in her grand-
The disease started at 17 years of age, lasted 1 year, resolved spontaneously, and did not recur.

Frustration and tearfulness were revealed during mental status examination. She was oriented but vague about current events. Concentration was poor. She could only generate 4 words starting with the letter A in 1 minute (average being 12). She had difficulties interpreting similarities, performed poorly on simple items of the Tower of London task (a test of reasoning), and committed errors of commission during a Go-NoGo paradigm (a test of disinhibition). There was no spatial neglect or aphasia. Memory was not significantly impaired as revealed by her knowledge of current events and full orientation.

On sensory-motor examination, few abnormalities could be demonstrated other than restlessness, with occasional twitching of the fingers of her right hand, and minor chorea-like movements around the face and neck, with slight hypomimia. Involuntary movements were more pronounced while engaged in cognitive tasks. Results of cranial nerve, sensory, cerebellar, and gait examination were otherwise unremarkable.

Neuropsychological testing results revealed that the most prominent deficits were in tasks requiring the integrity of the prefrontal networks (digit span, similarities, picture completion, digit symbol, lexical fluency, Trail-Making Test part B, California Verbal Learning Test II immediate recall, and Stroop interference test). Performance on the Judgment of Line Orientation task was also impaired. This was due to, at least in part, her impaired ability to make choices among the alternative possibilities and her impulsivity. Language and memory were relatively less impaired (Table).

Routine investigation findings were negative, including serologies, electroencephalography, and magnetic resonance imaging (Figure 1A and B). The PET with 18fluorodeoxyglucose results demonstrated striking hypermetabolism in the left basal ganglia (Figure 1C), contralateral to the side of the movements. The left to right caudate activity ratio was 1:7. No abnormal movements were noted either during or after tracer administration. Anti-streptolysin, antinuclear, and antiphospholipid antibody titers were within normal limits with the exception of an anticardiolipin IgM antibody titer 50% higher than normal. Results of a previously described Western blot technique demonstrated plasma antistriatal antibodies typical of those found in Sydenham chorea (Figure 2).

Treatment with intravenous methylprednisolone sodium succinate (1 g/d) for 3 days, followed by a 2-week prednisone taper produced an observable improvement in most of her cognitive deficits and a return of her personality to its premorbid state (Figure 3) (Table). In addition, the ratio of right to left finger taps in 10 seconds increased from 0.69 to 0.75. Repeated PET scan results showed reduction of the striatal asymmetry (Figure 1D). The right to left ratio of activity in the caudate nucleus dropped from 1.7 to 1:1. Although the level of plasma anticardiolipin antibody remained unchanged, the titer of antistriatal antibodies as demonstrated by results of Western blot technique was reduced significantly (from 1:2000 to 1:500) (Figure 2). At 6 months posttreatment, she remained stable.

**Neuropsychological Test Scores**

<table>
<thead>
<tr>
<th>Time, z Score</th>
<th>Baseline</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal lobe functions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit span</td>
<td>−2.00</td>
<td>−3.33</td>
</tr>
<tr>
<td>Similarities</td>
<td>−2.00</td>
<td>−2.67</td>
</tr>
<tr>
<td>Picture completion</td>
<td>−1.33</td>
<td>0.67</td>
</tr>
<tr>
<td>Digit symbol</td>
<td>−0.67</td>
<td>0.67</td>
</tr>
<tr>
<td>Lexical fluency (total)</td>
<td>−1.21</td>
<td>−0.15</td>
</tr>
<tr>
<td>Trail-Making Test part B</td>
<td>−5.33</td>
<td>−1.88</td>
</tr>
<tr>
<td>CVLT-II immediate recall</td>
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<td>−0.50</td>
</tr>
<tr>
<td>Stroop interference test (T score)</td>
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<td>0.19</td>
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<tr>
<td>Language</td>
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<tr>
<td>Boston Naming Test</td>
<td>−0.44</td>
<td>0.78</td>
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<tr>
<td>Visuospatial</td>
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<td></td>
</tr>
<tr>
<td>Judgment of line orientation</td>
<td>−3.18</td>
<td>−3.18</td>
</tr>
<tr>
<td>Memory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVLT-II long delay recall</td>
<td>−0.50</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Abbreviation: CVLT, California Verbal Learning Test.
*Scores are expressed as standard deviations lower or higher than age-matched population averaged scores.

Sydenham chorea and the chorea associated with the primary antiphospholipid syndrome are putative autoim-
mune disorders associated with abnormal involuntary movements, occasional neuropsychiatric manifestations, and evidence of autoimmunity, usually directed to the striatum. Sydenham chorea occurs in children as a complication of infection with groups A-hemolytic streptococcus and β-hemolytic streptococcus. Initial appearance is one of chorea accompanied by other motor signs such as facial grimacing, hypotonia, and loss of fine motor control. Alterations in behavior and neuropsychiatric changes are often present, including mood changes and obsessive-compulsive behaviors. Elevated antistreptolysin O titers are usually present. Antibodies to epitopes of the streptococcal M protein have been demonstrated to cross-react with epitopes in striatum. Magnetic resonance images may show reversible focal striatal enlargement and T2-weighted hyperintensities, with more permanent T1-weighted signal changes. Rare pathologic studies have shown relatively isolated striatal cellular infiltration and neuronal loss. The course is usually self-limited, resolving spontaneously within 6 months. Abnormal movements may be present beyond 2 years in up to 50% of cases. Case reports suggest that immunomodulation may be useful.

The acronym PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections) identifies the more long-term obsessive-compulsive and tic disorders that rarely develop from streptococcal autoimmunity. They may also respond to immunomodulation. Antistriatal antibodies have been implicated in a variety of neurobehavioral syndromes including Gilles de la Tourette and anorexia nervosa.

Primary antiphospholipid syndrome, defined by the presence of elevated titers of antiphospholipid antibodies, can occasionally initially appear as an otherwise isolated and reversible chorea. A chorea associated with systemic lupus erythematosus has similar features but initially appears with multiple additional manifestations specific to systemic lupus erythematosus. Treatment depends on symptom severity and involves immune suppression. If antiphospholipid antibody titers were elevated, treatment usually produces normalization.

In Sydenham chorea, metabolic imaging results using PET frequently demonstrate focal increases in striatal uptake, which can be unilateral and reversible. Perfusion imaging using single-photon emission computed tomography has been less consistent, with results demonstrating either no change, increases, or decreases in blood flow. When chorea is present in systemic lupus erythematosus or the primary antiphospholipid syndrome, PET imaging results demonstrate striatal hypermetabolism, which can be unilateral and reversible, recurrent, and even alternating.

The striatal asymmetry of 70% greater glucose use on the right (left-right ratio of 1:7) demonstrated in our patient was striking and resolved almost entirely with treatment. Left-right caudate ratios for the general population are essentially unitary. There is less than 6% variability and test-retest reliability has been clearly demonstrated. The exact process leading to hypermetabolism is not known. The presence of inflammatory infiltrates may represent the most likely source of increased metabolism. Cellular infiltrates have been shown in Sydenham chorea. Limbic encephalitis (also considered a form of cerebral autoimmunity) is associated with mesiotemporal hypermetabolism, antineuronal antibodies, and cellular infiltrates. Nonconvulsive seizures are unlikely since her electroencephalographic results were entirely normal and seizures isolated to the basal ganglia have never been reported. Potential direct activation of striatal neurons by antibodies in a way similar to the activation of thyroid tissue by thyroid-stimulating immunoglobulins is possible. There is no natural precedent for direct immunoglobulin-mediated activation of
neurons, but antibodies able to stimulate glutamate receptors have been created in experimental models.\textsuperscript{33} Finally, immunoglobulin interference in the synthesis of inhibitory neurotransmitters as present in stiff-person syndrome\textsuperscript{34} also represents a potential mechanism.

Our case has some unique features. Previous cases of unilateral striatal hypermetabolism with antistriatal antibodies have been associated with clearly diagnosed Sydenham chorea, primary antiphospholipid syndrome, or systemic lupus erythematosus. Our patient did not meet the criteria for the diagnosis of any of these disorders. Nonetheless, the presence of demonstrable antistriatal antibodies and a steroid response of both her behavioral syndrome and the PET hypermetabolic lesion support the notion of an autoimmune etiology to her illness. The presence of St Vitus’ dance in her grandmother also suggests the existence of a genetic component, as is observed in many autoimmune disorders.

Our patient’s main complaints and findings on examination involved a neurobehavioral syndrome that we initially diagnosed clinically as a frontal dementia. Although there was no metabolic or structural evidence of frontal lobe dysfunction on the findings of magnetic resonance imaging, electroencephalography, and PET, the clinical picture is consistent with the notion that frontal lobe functions are subserved by a large-scale distributed network that involves striatal components.\textsuperscript{33}

Rare as our patient’s syndrome must be, its diagnosis and subsequent treatment as an autoimmune disorder would not have been possible without PET imaging.

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\textbf{Author contributions:} Study concept and design (Drs Léger and Mesulam); acquisition of data (Drs Léger, Johnson, Horowitz, Dale, and Mesulam and Mr Church); analysis and interpretation of data (Drs Léger, Horowitz, Dale, and Mesulam and Mr Church); drafting of the manuscript (Drs Léger, Johnson, Dale, and Mesulam and Mr Church); critical revision of the manuscript for important intellectual content (Drs Léger, Johnson, Horowitz, and Mesulam); statistical expertise (Drs Léger and Johnson); administrative, technical, and material support (Drs Léger, Horowitz, and Dale and Mr Church); study supervision (Drs Horowitz and Mesulam).

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\textbf{REFERENCES}