The Natural History of Cognitive Dysfunction in Late-Onset GM₂ Gangliosidosis

Lauren C. Frey, MD; Steven P. Ringel, MD; Christopher M. Filley, MD

Background: Late-onset GM₂ gangliosidosis (LGG) is a rare disease that is often considered in the differential diagnosis of adolescents and young adults who present with multiple realms of neurologic dysfunction. Cognitive disturbances are common but have not been systematically studied.

Objective: To determine the natural history of cognitive dysfunction in patients with LGG.

Design: Case series and literature review.

Setting: Urban tertiary referral clinic.

Patients: Individuals with hexosaminidase A deficiency as the origin of LGG.

Main Outcome Measures: Cognitive dysfunction, psychiatric symptoms, and cerebellar, upper motor neuron, lower motor neuron, or extrapyramidal symptoms and signs.

Results: Historical and examination data from 62 patients were found. Forty-four percent of LGG patients had some degree of cognitive dysfunction. Cognitive dysfunction was associated with a greater number of other elemental neurologic deficits. In 21 patients with acceptable longitudinal information, 8 (38%) had a static cognitive disorder, whereas progressive dementia was evident in 13 patients (62%), including 2 of our cases with serial neuropsychological testing. Neuroimaging often showed nonspecific cerebellar and/or cerebral atrophy.

Conclusions: Cognitive dysfunction is a frequent manifestation of LGG. Patients who experience cognitive dysfunction are more likely to have a greater number of other neurologic manifestations of the disease. Cognitive dysfunction may take the form of static encephalopathy, but progressive dementia is more often encountered. The pathogenesis of cognitive dysfunction in this disease is unknown, highlighting the need for further study.

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Late-onset GM₂ gangliosidosis (LGG), a rare genetic disease of adolescents and young adults, may produce cognitive dysfunction, psychiatric disturbances, cerebellar dysfunction, upper motor neuron (UMN) and lower motor neuron (LMN) involvement, and extrapyramidal dysfunction, either alone or in combination. Infantile GM₂ gangliosidosis, or Tay-Sachs disease, is a rare, devastating encephalopathy that largely affects people of Ashkenazi Jewish descent and results in rapidly progressive cognitive and elemental neurologic deterioration. Clinically, LGG is distinct from Tay-Sachs disease because of its prolonged disease course, its comparatively late onset of neurologic dysfunction, and the significant minority of affected people without Ashkenazi Jewish inheritance. Although the neuropsychological profile of LGG patients has recently been characterized as involving prominent executive and memory dysfunction, the long-term course of cognitive dysfunction is not known. We present 3 new cases and a critical literature review to elucidate the natural history of cognitive dysfunction in patients with LGG.
view of articles identified in the search. Case reports from relevant articles were included only if (1) deficiency of hexosaminidase A (Hex A) was clearly documented and (2) patients’ neurologic features were adequately described. Information about each patient’s clinical features was systematically abstracted from the case report and divided into 6 categories of neurologic dysfunction. These categories were consistent with prior reviews and included the following: (1) cognitive dysfunction, (2) psychiatric symptoms, (3) cerebellar symptoms and signs, (4) UMN symptoms and signs, (5) LMN symptoms and signs, and (6) extrapyramidal symptoms and signs.

Criteria for cognitive dysfunction included either overall cognitive dysfunction or more specific problems with language, attention, memory, visuospatial skills, or elements of executive function such as planning or calculations, as documented in a case report. Patients with psychiatric involvement included those with a previous diagnosis of psychosis with or without associated alteration of mood, aggression, hallucinations, paranoid ideation, delusions, mutism, inability to perform activities of daily living, anhedonia, or catatonia. Indications, paranoid ideation, delusions, mutism, inability to perform activities of daily living, anhedonia, or catatonia. Indications, paranoid ideation, delusions, mutism, inability to perform activities of daily living, anhedonia, or catatonia. Indications, paranoid ideation, delusions, mutism, inability to perform activities of daily living, anhedonia, or catatonia. Indications, paranoid ideation, delusions, mutism, inability to perform activities of daily living, anhedonia, or catatonia. Indications, paranoid ideation, delusions, mutism, inability to perform activities of daily living, anhedonia, or catatonia. Indications, paranoid ideation, delusions, mutism, inability to perform activities of daily living, anhedonia, or catatonia. Indications, paranoid ideation, delusions, mutism, inability to perform activities of daily living, anhedonia, or catatonia. Indications, paranoid ideation, delusions, mutism, inability to perform activities of daily living, anhedonia, or catatonia.

Differential data regarding specific features of cognitive dysfunction were also extracted from the case reports when available, including the temporal pattern and severity of the cognitive dysfunction and the profile of cognitive impairment within standard realms of cognitive function. Statistical analyses were performed using SPSS statistical software for Windows, version 9.0 (SPSS Inc, Chicago, Ill), analysis of variance (Bonferroni correction), and the t test for independent samples.

### Table 1. Serial Neuropsychological Test Results of Patient 1

<table>
<thead>
<tr>
<th>Test*</th>
<th>Patient Age, y</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10</td>
</tr>
<tr>
<td>Full-scale IQ</td>
<td>93</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>104</td>
</tr>
<tr>
<td>Performance IQ</td>
<td>82</td>
</tr>
</tbody>
</table>

*Wechsler Intelligence Scale for Children or Wechsler Adult Intelligence Scale.

### Patient 1

As a 46-year-old Ashkenazi Jewish woman required special tutoring and was often described as emotionally immature. A diagnosis of schizophrenia was given after multiple hospitalizations for emotional lability, aggressiveness, and visual hallucinations. Her symptoms were treated with carbamazepine.

Her latest neuropsychological evaluation revealed labile and often inappropriate affect, severe dysarthria, poor recall on memory testing, a supranuclear gaze palsy in all directions, oral dyskinesias, diffuse weakness, profound muscular atrophy and fasciculations, and marked appendicular ataxia with bilateral end-intention tremor and dysmetria. Reflexes were diffusely brisk with bilateral extensor plantar responses.

Both EMG and muscle biopsy performed at the age of 13 years suggested diffuse denervation. Her Hex A level at the age of 21 years showed a partial deficiency (20.3% residual white blood cell [WBC] Hex A activity). Computed tomography (CT) of the brain showed cerebellar atrophy.

The patient underwent neuropsychological testing at the ages of 10, 12, 17, and 20 years. The Wechsler Intelligence Scale for Children full-scale IQ was 93 at the age of 10 years compared with a Wechsler Adult Intelligence Scale full-scale IQ of 70 at the age of 20 years. Although the 2 test batteries are not identical, the results demonstrate a pronounced intellectual decline during the 10-year interval.

### Patient 2

This 42-year-old woman, the sister of patient 1, also had learning difficulties, weakness and ataxia, and multiple psychiatric hospitalizations for intermittent psychosis. She responded to phenothiazines and lithium carbonate. Her Hex A level at the age of 18 years revealed a partial deficiency (20% residual WBC Hex A activity).

Recent neurologic examination showed her to be mildly dystrophic, with normal fluency and good auditory comprehension. The remainder of the examination revealed supranuclear gaze palsy in all directions, tongue fasciculations, diffuse weakness, brisk reflexes, and flexor plantar responses. There was dysmetria on finger-to-nose testing and a wide-based, ataxic gait. A CT scan showed cerebellar atrophy.

Neuropsychological profiles were obtained at the ages of 19, 20, and 33 years. Table 2 gives the comparable test results from these evaluations. Despite some practice effect, the data indicate a significant decline in cognitive function, most notably in executive function, as determined by the Trail-Making Tests A and B, and memory, as measured by the Benton Story Memory Test.

### Table 2

<table>
<thead>
<tr>
<th>Test*</th>
<th>Patient Age, y</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>19</td>
</tr>
<tr>
<td>Full-scale IQ</td>
<td>93</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>104</td>
</tr>
<tr>
<td>Performance IQ</td>
<td>82</td>
</tr>
</tbody>
</table>

### Patient 3

This 30-year-old right-handed woman first came to neurologic attention in second grade when her schoolwork began to deteriorate. At the age of 25 years, she was hospitalized with a prolonged confusional state and profound abulia. The patient was prescribed multiple anticonvulsants with eventual recovery of her baseline cognition. Use of the anticonvulsants was later successfully discontinued.

On examination, a Mini-Mental State Examination score of 27 of 30 was recorded (3 points missed on recall). She had a limited fund of knowledge but was fully oriented with fluent speech and the ability to follow simple commands. The remainder of the examination revealed limited upgaze; mild neck flexor weakness; diffuse, moderate limb weakness; and mildly diminished vibratory sensation of the
distal extremities. Reflexes were diffusely brisk with bilateral extensor plantar responses. Rapid alternating movements were slow, but there was no dysmetria or other sign of cerebellar impairment.

Brain CT showed mild cortical atrophy, and EMG revealed widespread abnormal spontaneous activity and decreased motor unit amplitude. A muscle biopsy confirmed chronic denervation. Her Hex A level revealed a partial deficiency (14% residual WBC Hex A activity). The patient was not able to undergo formal neuropsychological testing.

RESULTS

Historical and examination data from 62 patients with a diagnosis of LGG, including the 3 presented herein, are included in this review. Descriptive statistics of reported neurologic features are provided in Table 3. There were 34 males, 25 females, and 3 for whom sex was not specified. Age at disease onset ranged from the first to the fourth decades of life, with onset within the first and second decades most common. Two thirds of the patients were of Ashkenazi Jewish ancestry. Lower motor neuron (82%) and cerebellar (69%) signs and symptoms were the most frequently reported noncognitive areas of neurologic dysfunction.

Hexosaminidase A levels (percentage of residual activity in WBCs, standard heat inactivation method) were available for 46 of the 62 cases. These values, reported from multiple different laboratories, ranged from 0% to 48% (all below the reference range for respective laboratories), with a mean ± SD of 11% ± 9%. Mean Hex A levels were significantly associated with decade of disease onset (Table 3) (P = .04), with generally higher levels in patients with earlier disease onset. Hex A levels were not predictive of extent of neurologic disease or presence or degree of cognitive impairment.

Overall, 27 patients (44%) were described as having some degree of cognitive dysfunction. Because of the retrospective nature of the published case reports, it was difficult to pinpoint the onset of each patient’s cognitive dysfunction. However, in many of the previously published reports and in the 3 patients described herein, cognitive dysfunction, when present, was seen early.

The LGG patients with cognitive dysfunction had deficits in a mean ± SD of 3.37 ± 0.97 additional realms of neurologic function (psychiatric, cerebellar, UMN, LMN, or extrapyramidal). Patients without cognitive dysfunction had dysfunction in a mean ± SD of 2.66 ± 1.26 additional realms of neurologic function (P = .01). Sex, ethnicity, and age at disease onset were not significantly predictive of cognitive impairment.

A description of longitudinal changes in cognitive dysfunction was available for 21 of the 27 patients with cognitive deficits (Table 4). Patients could be classified into 2 categories: those with deficits that remained stable over time and those with progressive loss of cognitive function. Eight patients (38%) were classified as remaining stable, in some cases for more than 2 decades. The remaining 13 patients (62%) had progressive cognitive loss apparent in as few as 2 years.

Loss of general intellectual ability was the most common type of cognitive dysfunction (100% of patients), typically reflecting low scores on test batteries such as the Wechsler Intelligence Scale for Children30 and the Wechsler Adult Intelligence Scale.31 Deficits in attention, memory, and executive function were frequently re-
Patients with LGG may display florid neurobehavioral manifestations as a component of their disease. In addition to the neuropsychological profile of executive and memory dysfunction that has recently been reported, the psychiatric aspects of this disease have been reviewed. Our report, however, is the first to collect and analyze clinical information on the natural history of cognitive dysfunction in patients with LGG. We found that cognitively impaired individuals have more elemental neurologic dysfunction than those without cognitive loss and that most cognitively impaired individuals manifest a progressive dementia syndrome.

The frequency of cognitive dysfunction in patients with LGG described in previous reviews has ranged from 12% to 47%1,2; our results (44%) are consistent with the latter figure. The nature of this cognitive dysfunction has been controversial because the term dementia has been applied by some authors to certain cognitively impaired LGG patients3,8,35 whereas others have denied that dementia exists in this disease.1 In addressing this issue, it must first be acknowledged that the limitations of clinical data in reported cases often preclude secure classification using accepted criteria for dementia. In addition, the complexity of the clinical picture, typically including many elemental neurologic and psychiatric features that contribute to functional disability, makes it difficult to determine how much of the disability can be attributed to cognitive loss. Nevertheless, our data demonstrate that a substantial percentage of LGG patients develop progressive cognitive impairment during their disease that qualifies for the term dementia.36

Table 4. Longitudinal Cognitive Dysfunction in Patients With Late-Onset GM2 Gangliosidosis*

<table>
<thead>
<tr>
<th>Patient</th>
<th>Temporal Pattern</th>
<th>General Intellect</th>
<th>Other Areas of Cognitive Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>Progressive</td>
<td>FSIQ,† 93-70</td>
<td>NA</td>
</tr>
<tr>
<td>Patient 2</td>
<td>Progressive</td>
<td>FSIQ,† 78-72</td>
<td>Executive function, memory, language, visuospatial skills</td>
</tr>
<tr>
<td>Patient 3</td>
<td>Stable</td>
<td>MMSE score, 27</td>
<td>Memory</td>
</tr>
<tr>
<td>Patient 4</td>
<td>Stable</td>
<td>FSIQ,† 102-94</td>
<td>Visuospatial skills</td>
</tr>
<tr>
<td>Patient 5</td>
<td>Progressive</td>
<td>“Average” to “profoundly demented”</td>
<td>Memory, executive function</td>
</tr>
<tr>
<td>Patient 6</td>
<td>Progressive</td>
<td>“Deteriorating”</td>
<td>Memory, executive function</td>
</tr>
<tr>
<td>Patient 7</td>
<td>Progressive</td>
<td>FSIQ,† 70, to VIQ,† 70/PIQ,† 61</td>
<td>Attention, memory</td>
</tr>
<tr>
<td>Patient 8</td>
<td>Progressive</td>
<td>“Low-normal IQ” to “markedly impaired”</td>
<td>Attention, memory, language, visuospatial skills, executive function</td>
</tr>
<tr>
<td>Patient 9</td>
<td>Stable</td>
<td>NA</td>
<td>Executive function</td>
</tr>
<tr>
<td>Patient 10</td>
<td>Stable</td>
<td>FSIQ,† 69 (at 8 y)</td>
<td>Attention, memory, executive function</td>
</tr>
<tr>
<td>Patient 11</td>
<td>Stable</td>
<td>VIQ,† 82, PIQ,† 62</td>
<td>Memory, executive function</td>
</tr>
<tr>
<td>Patient 12</td>
<td>Progressive</td>
<td>“Declining” school performance</td>
<td>Memory, executive function</td>
</tr>
<tr>
<td>Patient 13</td>
<td>Progressive</td>
<td>“Deteriorating” school performance</td>
<td>Memory, executive function</td>
</tr>
<tr>
<td>Patient 14</td>
<td>Progressive</td>
<td>Historical decline in functioning</td>
<td>Memory</td>
</tr>
<tr>
<td>Patient 15</td>
<td>Progressive</td>
<td>Historical decline in functioning</td>
<td>Memory, language</td>
</tr>
<tr>
<td>Patient 16</td>
<td>Stable</td>
<td>VIQ,† 111 (at 50 y)</td>
<td>NA</td>
</tr>
<tr>
<td>Patient 17</td>
<td>Stable</td>
<td>VIQ,† 111 (at 45 y)</td>
<td>NA</td>
</tr>
<tr>
<td>Patient 18</td>
<td>Progressive</td>
<td>Historical decline in functioning</td>
<td>Attention, language, executive function</td>
</tr>
<tr>
<td>Patient 19</td>
<td>Progressive</td>
<td>“Deteriorating” school performance</td>
<td>Memory, visuospatial skills</td>
</tr>
<tr>
<td>Patient 20</td>
<td>Progressive</td>
<td>“Impaired”</td>
<td>Attention, visuospatial skills, executive function</td>
</tr>
<tr>
<td>Patient 21</td>
<td>Stable</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: FSIQ, full-scale IQ; MMSE, Mini-Mental State Examination; NA, not applicable; PIQ, performance IQ; VIQ, verbal IQ.

*In each case, the diagnosis of progressive cognitive decline was based on the information set in boldface type.
†Wechsler Intelligence Scale for Children or Wechsler Adult Intelligence Scale.
The presence of cognitive dysfunction in a patient with LGG can be considered a marker for more extensive non-cognitive neurologic dysfunction. This correlation has been reported anecdotally in previous reviews, but to our knowledge, ours is the first to offer data in support of this conclusion.

The limitations of this study relate mainly to the variability of clinical data in the reported cases of LGG. Thus, we could generate only estimates of the frequencies with which LGG affects various domains of neurologic function. Because the data were abstracted from case reports published throughout many years, diagnostic criteria varied widely, and observations of multiple domains, such as cognition and extrapyramidal function, were not always concurrently reported. We dealt with this variability by including only those reports in which some historical or examination data were offered to justify the presence of each area of reported dysfunction. To capture as much of the available clinical information as possible, we were occasionally obliged to assume that an individual patient was unaffected in a given category of neurologic function if no better information was offered. Although some degree of misclassification might have occurred if affected patients were coded incorrectly as unaffected, we made a strong effort to minimize such instances.

The presence of executive and memory dysfunction in the absence of aphasia, apraxia, and agnosia suggests that the GM1 gangliosidoses may be considered under the heading of subcortical dementia. Available neuropathologic studies support this classification because the abnormal neuronal storage and the degree of atrophy are both greater in subcortical structures, such as the cerebellum, substantia nigra, and spinal cord, than in the cerebral cortex. The cerebellum is of particular interest because our review found a high prevalence of cerebellar atrophy on neuroimaging studies, and cerebellar dysfunction has been speculated to account for cognitive impairment in LGG. However, cerebellar atrophy appeared to be frequent in LGG patients both with and without cognitive dysfunction. The data are thus insufficient to conclude that cerebellar neuropathologic features are associated with cognitive dysfunction, but study of this possibility may be useful in view of emerging information on the role of the cerebellum in both cognition and psychiatric function.

Our results are clearly retrospective and preliminary. Further observations of the neurobehavioral features of patients with LGG, including prospective clinical, neuropsychological, and neuroradiologic data, are needed to gain more complete understanding. Volumetric analysis of neuroimaging studies and detailed autopsy findings would enable correlations with clinical features that could further advance our knowledge.

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REFERENCES


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