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

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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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tion about each patient's clinical features was systematically ab-
standard realms of cognitive function.29 Statistical analyses were
able, including the temporal pattern and severity of the cogni-
function were also extracted from the case reports when avail-
athetosis, blepharospasm, and tics.
Indicators of extrapyramidal dysfunction included buccofacial
phy or electromyographic (EMG) evidence of denervation.
LMN involvement included fasciculations and/or muscle atro-
postural maintenance, a wide-based gait, and limb or truncal
dysdiadochokinesia, dysmetria, past pointing on finger-to-
tors of cerebellar dysfunction included end-intention tremors,
form activities of daily living, anhedonia, or catatonia. Indica-
tions, paranoid ideation, delusions, mutism, inability to per-
mented in a case report. Patients with psychiatric involvement
included those with a previous diagnosis of psychosis with or
without associated alteration of mood, aggression, hallucina-
tions, paranoid ideation, delusions, mutism, inability to per-
perform activities of daily living, anhedonia, or catatonia. Indic-
tors of cerebellar dysfunction included end-intention tremors,
dysdiadochokinesia, dysmetria, past pointing on finger-to-
tose testing, “lack of check” or increased rebound on tests of
postural maintenance, a wide-based gait, and limb or truncal
ataxia. Indicators of UMN involvement included spasticity,
brisk reflexes, and/or extensor plantar responses. Indicators of
LMN involvement included fasciculations and/or muscle atro-
phy or electromyographic (EMG) evidence of denervation.
Indicators of extrapyramidal dysfunction included buccofacial
dyskinesia, parkinsonism, axial or appendicular dystonias,
athetosis, blepharospasm, and tics.
Detailed data regarding specific features of cognitive dys-
function were also extracted from the case reports when avail-
including the temporal pattern and severity of the cogni-
tive dysfunction and the profile of cognitive impairment within
standard realms of cognitive function.29 Statistical analyses were
performed using SPSS statistical software for Windows, ver-
version 9.0 (SPSS Inc, Chicago, Ill), analysis of variance (Bonfer-
roni correction), and the t test for independent samples.

REPORT OF CASES

PATIENT 1

As a child, this 46-year-old Ashkenazi Jewish woman required
special tutoring and was often described as emotionally imma-
ture. A diagnosis of schizophrenia was given after multiple hospi-
talizations for emotional lability, aggressiveness, and visual hal-
 lucinations. Her symptoms were treated with carbamazepine.

Her latest neurologic evaluation revealed labile and often
inappropriate affect, severe dystarthis, poor recall on memory
testing, a supranuclear gaze palsy in all directions, oral dyski-
nesias, diffuse weakness, profound muscular atrophy and fas-
ciculations, 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 (Table 1). The Wechsler Intelli-
gence Scale for Children30 full-scale IQ was 93 at the age of 10
years compared with a Wechsler Adult Intelligence Scale31 full-
scale IQ of 70 at the age of 20 years. Although the 2 test bat-
tries 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 learn-
ing 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 dys-
arthric, with normal fluency and good auditory comprehen-
sion. The remainder of the examination revealed supranu-
clear 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 no-
tably in executive function, as determined by the Trail-
Making Tests A and B,32 and memory, as measured by the Hea-
ton Story Memory Test.33

PATIENT 3

This 30-year-old right-handed woman first came to neuro-
logic 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 recov-
ery of her baseline cognition. Use of the anticonvulsants was
later successfully discontinued.

On examination, a Mini-Mental State Examination34 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 com-
mands. The remainder of the examination revealed limited
upgaze; mild neck flexor weakness; diffuse, moderate limb
weakness; and mildly diminished vibratory sensation of the

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Table 1. Serial Neuropsychological Test Results of Patient 1

<table>
<thead>
<tr>
<th>Test*</th>
<th>10</th>
<th>12</th>
<th>17</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full-scale IQ</td>
<td>93</td>
<td>80</td>
<td>77</td>
<td>70</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>104</td>
<td>86</td>
<td>86</td>
<td>77</td>
</tr>
<tr>
<td>Performance IQ</td>
<td>82</td>
<td>78</td>
<td>69</td>
<td>64</td>
</tr>
</tbody>
</table>

*Wechsler Intelligence Scale for Children or Wechsler Adult Intelligence Scale.
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 = .01). Sex, ethnicity, and age at disease onset were not significantly predictive 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 Children and the Wechsler Adult Intelligence Scale. Deficits in attention, memory, and executive function were frequently re-

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**Table 2. Serial Neuropsychological Test Results of Patient 2**

<table>
<thead>
<tr>
<th>Test</th>
<th>Patient Age, y</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>19</td>
</tr>
<tr>
<td>General intellectual ability†</td>
<td>78</td>
</tr>
<tr>
<td>Full-scale IQ</td>
<td>78</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>80</td>
</tr>
<tr>
<td>Performance IQ</td>
<td>25</td>
</tr>
<tr>
<td>Executive function, s</td>
<td>76</td>
</tr>
<tr>
<td>Trail-Making Test A</td>
<td>4.5</td>
</tr>
<tr>
<td>Trail 2</td>
<td>7.0</td>
</tr>
<tr>
<td>Trial 3</td>
<td>10.0</td>
</tr>
<tr>
<td>Trial 4</td>
<td>11.6</td>
</tr>
<tr>
<td>Trial 5</td>
<td>13.8</td>
</tr>
<tr>
<td>4-h Delayed recall</td>
<td>13.0</td>
</tr>
</tbody>
</table>

*The patient’s progressive cognitive decline was most evident in memory and executive functioning testing.
†Wechsler Adult Intelligence Scale or revised version. Subtest scores available on request from the authors.

**Table 3. Neurologic Features of 62 Patients With Late-Onset GM2 Gangliosidosis**

<table>
<thead>
<tr>
<th>Feature</th>
<th>No. (%) of Patients</th>
<th>Hexosaminidase A Level, Mean ± SD*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>34 (55)</td>
<td>14 ± 2</td>
</tr>
<tr>
<td>10-20</td>
<td>19 (31)</td>
<td>6 ± 1</td>
</tr>
<tr>
<td>21-30</td>
<td>9 (14)</td>
<td>7 ± 3</td>
</tr>
<tr>
<td>31-40</td>
<td>3 (5)</td>
<td>3 ± 1</td>
</tr>
<tr>
<td>Unclear</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Cognitive dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>27 (44)</td>
<td>11 ± 9</td>
</tr>
<tr>
<td>No</td>
<td>35 (56)</td>
<td>10 ± 10</td>
</tr>
<tr>
<td>Psychiatric involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>30 (48)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>32 (52)</td>
<td></td>
</tr>
<tr>
<td>Cerebellar dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>43 (69)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>19 (31)</td>
<td></td>
</tr>
<tr>
<td>Upper motor neuron involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>40 (64)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>22 (35)</td>
<td></td>
</tr>
<tr>
<td>Lower motor neuron involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>51 (82)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>11 (18)</td>
<td></td>
</tr>
<tr>
<td>Extrapyramidal dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>20 (32)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>42 (68)</td>
<td></td>
</tr>
</tbody>
</table>

*Hexosaminidase A levels are the percentage of residual activity in white blood cells.

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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%; 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 patients, whereas others have denied that dementia exists in this disease. 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.

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

<table>
<thead>
<tr>
<th>Current study</th>
<th>Patient 1</th>
<th>Progressive</th>
<th>FSIQ,† 93-70</th>
<th>NA</th>
<th>Executive function, memory, language, visuospatial skills</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 2</td>
<td>Progressive</td>
<td>FSIQ,† 78-72</td>
<td>NA</td>
<td>Executive function, memory, language, visuospatial skills</td>
<td></td>
</tr>
<tr>
<td>Patient 3</td>
<td>Stable</td>
<td>MMSE score, 27</td>
<td>NA</td>
<td>Memory</td>
<td></td>
</tr>
</tbody>
</table>

| Reviewed literature | Patient 4     | Progressive | FSIQ,† 102-94 | NA | Visuospatial skills |
|                    | Patient 5     | Progressive | FSIQ,† 71-58 | NA | Memory, executive function |
|                    | Patient 6     | Progressive | “Average” to “profoundly demented” | NA | NA |
|                    | Patient 7     | Progressive | “Average” to “profoundly demented” | NA | NA |

Additional information on neuroimaging was collected when available. Thirty-two patients (52%) had at least 1 neuroimaging study available; 19 underwent CT, 9 underwent magnetic resonance imaging, and 4 underwent both procedures. In these 32 individuals, cerebellar atrophy was noted in 21 (66%) and cortical atrophy in 7 (22%). Among the 19 cognitively impaired patients who had available studies, cerebellar atrophy was found in 12 (63%), whereas cortical atrophy was noted in 5 (26%). Among 13 cognitively unimpaired patients who had available studies, cerebellar atrophy was found in 9 (69%), whereas cortical atrophy was noted in 2 (15%). The reports were not usually specific with regard to which cerebellar regions, if any, were involved.

Patients with LGG may display florid neurobehavioral manifestations as a component of their disease. In addition, their psychiatric and cognitive impairments frequently reach a stage in which they may require care similar to that provided for patients with Alzheimer disease.
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 GM2 gangliosidoses may be considered under the heading of subcortical dementia.37 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.38 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.1 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.39,40

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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Author Contributions: Study concept and design: Frey, Ringel, and Filley. Acquisition of data: Frey, Ringel, and Filley. Analysis and interpretation of data: Frey and Ringel. Drafting of the manuscript: Frey and Filley. Critical revision of the manuscript for important intellectual content: Ringel and Filley. Administrative, technical, and material support: Filley. Study supervision: Filley.