Geriatric Neurogenetics

Oxymoron or Reality?

Thomas D. Bird, MD; Hillary P. Lipe, ARNP; Ellen J. Steinbart, RN, MA

Background: Primary genetic diseases are generally associated with pediatric and young adult populations. Little information is available about the occurrence of single-gene mendelian diseases in elderly populations.

Objective: To describe the occurrence of single-gene neurogenetic disorders in a group of elderly patients.

Design: Retrospective review of neurogenetic cases in an academic medical center.

Setting: Academic university and Veterans Affairs medical centers.

Patients: Eight elderly patients with single-gene neurogenetic diseases were studied. These patients included an 87-year-old man and an 85-year-old man with Huntington disease, an 84-year-old woman with limb-girdle muscular dystrophy type 2A, a 78-year-old man with spinocerebellar ataxia type 14, an 86-year-old man with spinocerebellar ataxia type 5, an 85-year-old man with a presenilin 1 familial Alzheimer disease mutation, an 87-year-old man with autosomal dominant hereditary neuropathy, and a 78-year-old man with spinocerebellar ataxia type 6. Three patients had no family history of neurologic disease.

Main Outcome Measures: Medical histories, physical examination results, and genetic testing results.

Conclusions: Single-gene mendelian neurogenetic diseases can be found in the oldest old population (>85 years). Such cases are currently underrecognized and will become more commonly observed in the future. This phenomenon is a result of (1) the aging of the general population, (2) better recognition of the highly variable ages at onset of genetic diseases, and (3) the availability of specific DNA-based genetic testing.

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METHODS

Elderly persons with neurogenetic disease were selected from the neurogenetic clinic populations of the University of Washington Medical Center and VA Puget Sound Health Care System. These studies were approved by the institutional human subjects review committees. Medical histories, physical examination results, and genetic testing results were reviewed for each study participant.

PATIENT 1

Patient 1 was an 87-year-old man who had been a paratrooper during World War II and retired from his business at the age of 65 years. At the age of 79 years, he was noted to have mild and increasingly noticeable adventitious movements (Table). He had no family history of neurologic diseases. His father, who died...
at the age of 80 years, was described as being noticeably “quickly.” A DNA-based genetic test result revealed 39 CAG repeats in the HD gene (HUGO/GDB 119307). This is considered a clearly abnormal result in the range of decreased penetrance. At the age of 87 years, he had obvious and moderate chorea of the face, trunk, and arms. Behavior and cognitive function were normal. He could walk somewhat unsteadily without assistance and was still driving. He and his wife considered his most serious disability to be his marked deafness.

**PATIENT 2**

Patient 2 was an 85-year-old man who had progressive memory loss at approximately 75 years of age and difficulty with his balance at approximately 76 years of age (Table). Because of a positive family history of HD, a DNA genetic test was performed when the patient was 76 years old; the results of this test were abnormal, with 40 CAG repeats in the HD gene. Examination at the age of 85 years showed mild chorea of his face, trunk, and all 4 limbs, but he was able to walk without assistance. He had global dementia, with a Mini-Mental State Examination score of 15 of 30. Magnetic resonance imaging showed mild to moderate diffuse cortical atrophy. This retired salesman had slowly progressive memory loss at the age of 79 years (Table). At the age of 83 years, his Mini-Mental State Examination score was 15 of 30. Magnetic resonance imaging showed mild to moderate diffuse cortical atrophy. He was noted to have a positive family history of earlier-onset AD in 2 siblings and several nephews. At the age of 80 years, he was ataxic and mostly confined to a wheelchair, although he could walk a short distance with a walker. He had marked dysarthria and dysmetria. His mental status was normal. He was a member of the Lincoln family, with spinocerebellar ataxia type 5, and a mutation in the SPTBN2 gene (HUGO/GDB 9120550) was discovered at the age of 84 years.2

**PATIENT 5**

Patient 5 died at 86 years of age after a long history of slowly progressive ataxia (Table). He successfully completed service in the US Army during World War II. He began to have clumsiness and unsteady gait at the age of 25 years, which caused him to become permanently unemployed at the age of 40 years. At the age of 80 years, he was ataxic and mostly confined to a wheelchair, although he could walk a short distance with a walker. He had marked dysarthria and dysmetria. His mental status was normal. He was a member of the Lincoln family, with spinocerebellar ataxia type 5, and a mutation in the SPTBN2 gene (HUGO/GDB 9120550) was discovered at the age of 84 years.2

**PATIENT 6**

This retired salesman had slowly progressive memory loss at the age of 79 years (Table). At the age of 83 years, his Mini-Mental State Examination score was 15 of 30. Magnetic resonance imaging showed mild to moderate diffuse cortical atrophy. He was noted to have a positive family history of earlier-onset AD in 2 siblings and several nephews. At the age of 83 years, this patient and other affected family members were discovered to have the A79V mutation in the presenilin 1 gene (HUGO/GDB 133682).3

**PATIENT 7**

Patient 7 was an 87-year-old man who was a World War II veteran and Pearl Harbor survivor. He had onset of bilateral symmetrical motor and sensory neuropathy at the age of 70 years (Table). He walked with bilateral ankle-foot orthoses and a cane. Electrophysiologic study results revealed a diffuse, primarily axonal peripheral neuropathy. He had multiple affected family members in many generations of his kindred compatible with autosomal dominant inheritance. No mutation was discovered in 9 genes associated with Charcot-Marie-Tooth disease, and the genetic defect in this family remains unknown.5

### Table. Elderly Patients With Neurogenetic Diseases

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Age at Onset, y</th>
<th>Age at Genetic Diagnosis, y</th>
<th>Disease</th>
<th>Gene</th>
<th>Mutation</th>
<th>Year Clinical Genetic Testing First Available</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/87</td>
<td>79</td>
<td>80</td>
<td>Huntington disease</td>
<td>HD</td>
<td>39 CAG repeats</td>
<td>1993</td>
</tr>
<tr>
<td>2/M/85</td>
<td>75</td>
<td>76</td>
<td>Huntington disease</td>
<td>HD</td>
<td>40 CAG repeats</td>
<td>1993</td>
</tr>
<tr>
<td>3/F/84</td>
<td>50</td>
<td>84</td>
<td>Limb-girdle muscular dystrophy type 2A</td>
<td>CAPN3</td>
<td>L189P R490W</td>
<td>2004</td>
</tr>
<tr>
<td>4/M/78</td>
<td>60 (13?)³</td>
<td>74</td>
<td>SCA14</td>
<td>PRKG</td>
<td>H101Y</td>
<td>2004</td>
</tr>
<tr>
<td>5/M/96b</td>
<td>25</td>
<td>84</td>
<td>SCA5</td>
<td>SPTBN2</td>
<td>E523-M544del</td>
<td>2006</td>
</tr>
<tr>
<td>6/M/84</td>
<td>79</td>
<td>83</td>
<td>Familial AD</td>
<td>PS1</td>
<td>A79V</td>
<td>1998</td>
</tr>
<tr>
<td>7/M/87</td>
<td>70</td>
<td>Unknown</td>
<td>Hereditary neuropathy</td>
<td>Unknown</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>8/M/78</td>
<td>68</td>
<td>77</td>
<td>SC6</td>
<td>CACNA1A</td>
<td>21 CAG repeats</td>
<td>1997</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; SCA, spinocerebellar ataxia.

This patient reported that he often stumbled in adolescence.

³Age at death.

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The 8 elderly patients described herein have a variety of histories and diseases but share 1 common finding: each has a single-gene neurogenetic disorder. Their median age of 83 years is remarkable because genetic diseases are generally assumed to be relegated to much younger populations.

Three of these patients had onset of symptoms at much younger ages but survived many decades and did not receive specific genetic diagnoses until relevant genetic tests became available in their senior years. The other 5 patients had late onset of symptoms. Patient 1 was discovered to have HD during a general screen for causes of unexplained senile chorea. Patients 4 and 5 were considered to have unexceptional senile dementia or peripheral neuropathy until their family histories became known several years after the onset of their symptoms. The genetic abnormality that caused the CMT phenotype in patient 5 remains to be discovered. It could be argued that patient 4 simply had late-onset AD. However, he had a mutation in presenilin 1 that was associated with AD in multiple other family members and that has been reported twice in the literature as associated with later-onset cases of familial AD. It is likely that this mutation played a role in his dementia.

This phenomenon of the recognition of single-gene genetic diseases in elderly patients has at least 3 explanations. First is the increasing lifespan of the general population, often referred to as “the graying of America.” Persons with chronic diseases are living longer. Thus, it should not be surprising to find such cases among populations of the oldest old (>85 years). This obviously includes genetic diseases. Second, we are becoming much more aware of the wide range of symptom onset in genetic disorders, including those originally thought to occur primarily in children. Tay-Sachs disease, leukodystrophies, Friedreich ataxia, and muscular dystrophy, although most common in the pediatric population, are now recognized to occur in adults. This is demonstrated by patients 1 and 6 in the present study, who could be considered among the oldest old population but have HD and limb-girdle muscular dystrophy. Family history may be negative because the disease is autosomal recessive (patient 7), because other family members died before the onset of symptoms (probably patient 8), or because of a de novo mutation. Third is the recent advent of DNA-based genetic testing. The specific diagnosis of genetic diseases is readily available to a degree completely unknown a few years ago. Patients in this study would have been considered to have senile chorea, senile dementia, and unexplained myopathy before the advent of such testing.

The phenomenon of geriatric neurogenetics described herein is not a theoretical possibility but a reality. Such cases are likely to be underrecognized because of a low index of suspicion on the part of today’s physicians. The diagnoses are not just academic or trivial because they have important implications for genetic counseling of children and grandchildren. It is hoped that these diagnoses will someday also have implications for management and treatment. For the reasons discussed herein, the diagnosis of neurogenetic diseases in elderly populations will assuredly become more common. Training programs in neurology and geriatric medicine should incorporate this issue into their curricula.

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REFERENCES