OBSERVATION

Geriatric Neurogenetics

Oxymoron or Reality?

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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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NEUROGENETIC DISEASES are typically considered to occur largely in children and young to middle-aged adults. Many of the classic disorders of neurogenetics are primarily pediatric, such as Tay-Sachs disease, leukodystrophies, Friedreich ataxia, and muscular dystrophies. Many of the adult-onset neurogenetic disorders, such as Huntington disease (HD) and the dominant cerebellar ataxias, typically have onset in the fourth and fifth decades of life and rarely in or after the seventh decade of life. When traditional diseases of elderly populations, such as Alzheimer disease (AD), are found to have a single-gene cause, the onset is frequently early, meaning in the fifth and sixth decades of life. We evaluated 8 elderly persons (median age, 83 years) who had mendelian single-gene neurogenetic diseases. The likely reasons for this phenomenon suggest that such patients will become much more commonly recognized in the future.

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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

Table. Elderly Patients With Neurogenetic Diseases

Patient No./ Sex/Age, y	Age at Onset, y	Age at Genetic Diagnosis, y	Disease	Gene	Mutation	Year Clinical Genetic Testing First Available
1/M/87	79	80	Huntington disease	*HD*	39 CAG repeats	1993
2/M/85	75	76	Huntington disease	*HD*	40 CAG repeats	1993
3/F/84	50	84	Limb-girdle muscular dystrophy type 2A	*CAPN3*	L189P R490W	2004
4/M/78	60 (13?)[a]	74	SCA14	*PRCKG*	H101Y	2004
5/M/86[b]	25	84	SCA5	*SPTBN2*	E523-M544del	2006
6/M/84	79	83	Familial AD	*PS1*	A79V	1998
7/M/87	70	Unknown	Hereditary neuropathy	Unknown	Unknown	
8/M/78	68	77	SCA6	*CACNA1A*	21 CAG repeats	1997

Abbreviations: AD, Alzheimer disease; SCA, spinocerebellar ataxia.
[a] This patient reported that he often stumbled in adolescence.
[b] Age at death.

at the age of 80 years, was described as being noticeably "fidgety." 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 8 (maximum score, 30). Interestingly, his sister died at the age of 83 years of both chorea and dementia, and brain autopsy results revealed neuropathologic signs of both HD and AD. It is likely that patient 2 also had both diseases.

PATIENT 3

Patient 3 was an 84-year-old woman who had onset of proximal weakness of both lower limbs at approximately 50 years of age (Table). Her weakness had been slowly progressive, but she could still ambulate slowly with a back brace and walker. She also had essential tremor and peripheral neuropathy of unknown cause. The results of several electromyograms and a muscle biopsy performed in the eighth decade of her life were consistent with a nonspecific myopathy. She had no family history of muscle disease, and her parents were not consanguineous. At the age of 84 years, the patient underwent several genetic tests associated with limb-girdle muscular dystrophy, which revealed that she was a compound heterozygote for 2 missense mutations in the *CAPN3* gene (HUGO/GDB 119751). Therefore, she had limb-girdle muscular dystrophy type 2A.

PATIENT 4

Patient 4 was a 78-year-old retired professional man with a graduate school degree who had onset of unsteady gait and dysarthria at approximately 60 years of age (Table). This condition was slowly progressive, forcing the patient to stop playing golf and start using a cane. In retrospect, he always considered himself to be clumsy and often stumbled in adolescence. However, these mild symptoms never interfered with his activities until much later in life. Magnetic resonance imaging of the brain revealed cerebellar atrophy, and he had a positive family history of ataxia. Spinocerebellar ataxia type 14 was diagnosed when the patient was 74 years old, with a mutation in the *PRKCG* gene (HUGO/GDB 128017).[1]

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 135682).[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.[4]

PATIENT 8

Patient 8 was a 78-year-old man with a 10-year history of slowly progressive ataxia (Table). He did not have alcoholism, and magnetic resonance imaging revealed prominent cerebellar atrophy. He had no family history of neurologic disease. His mother died at the age of 74 years and his father at the age of 58 years. Genetic test results reveled an abnormal CAG repeat expansion in the *CACNA1A* gene (HUGO/GDB 126432) diagnostic of spinocerebellar ataxia type 6.

COMMENT

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.[3] 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 neurogenetic 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.[5-7] 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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