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Geriatric Neurogenetics: Oxymoron or Reality?

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Abstract

Background—Primary genetic diseases are generally associated with pediatric and young adult populations. There is little information about the occurrence of single gene Mendelian diseases in the elderly.

Goal—To describe the occurrence of single gene neurogenetic disorders in a group of elderly patients.

Setting—Academic University and VA Medical Centers.

Results—Eight elderly patients are described with single gene neurogenetic diseases. They include two 87 and 85 year old men with Huntington's disease, an 84 year old woman with Limb Girdle Muscular Dystrophy Type 2A, a 78 year old man with SCA14, an 86 year old man with SCA5, an 85 man with a presenilin 1 familial Alzheimer's disease mutation, an 87 year old man with autosomal dominant hereditary neuropathy and a 78 year old man with SCA6. Three cases had no family history of neurological disease.

Conclusion—Single gene Mendelian neurogenetic diseases can be found in the oldest old. Such cases are presently under recognized 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 of onset of genetic diseases and 3: The availability of specific DNA-based genetic testing.

Introduction

Neurogenetic diseases are typically considered to occur largely in children and young to middle aged adults. Many of the classics of neurogenetics are primarily pediatric disorders such as Tay-Sachs, leukodystrophies, Freidreich's ataxia, and muscular dystrophies. Many of the adult onset neurogenetic disorders such as Huntington's disease and the dominant cerebellar ataxias typically have onset in the 30s and 40s and rarely after the age of 60. When traditional diseases of the elderly such as Alzheimer's disease are found to have a single gene cause the onset is frequently "early", meaning in the 40s and 50s. We have had the opportunity to evaluate eight elderly persons (median age 83 years) all of whom were discovered to have Mendelian single gene neurogenetic diseases. The likely reasons for this phenomenon suggest that such patients will become much more commonly recognized in the future.

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

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System. These studies were approved by the Institutional Human Subjects Review Committees (IRB). Past histories, physical examinations and genetic testing results were reviewed for each subject.

Case One

This 87 year old man had been a paratrooper during World War II and retired from his business at age 65. At age 79 he was noted to have mild and increasingly noticeable adventious movements. He had no family history of neurologic diseases. His father who died at age 80 years was described as being noticeably "fidgety." A DNA-based genetic test revealed 39 CAG repeats in the HD gene. This is considered a clearly abnormal result in the range of decreased penetrance. At age 87, he had obvious and moderate chorea of 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.

Case Two

This 85 year old man developed progressive memory loss at approximately age 75 and difficulty with his balance at approximately age 76. Because of a positive family history of Huntington's disease a DNA genetic test at age 76 was abnormal with 40 CAG repeats in the HD gene. Examination at age 85 showed mild chorea of his face, trunk, and all four limbs but he was able to walk without assistance. He had a global dementia with a mini mental status exam score of 8/30. Interestingly his sister died at age 83 with both chorea and dementia and brain autopsy revealed neuropathologic signs of both HD and Alzheimer's disease. It is likely that Case Two also has both diseases.

Case Three

This 84 year old woman had the onset of proximal weakness of both lower limbs at about age 50. Her weakness has been slowly progressive but she still ambulates slowly with a back brace and walker. She has also developed essential tremor and peripheral neuropathy of unknown cause. Several EMGs and a muscle biopsy in her 70s were consistent with a non-specific myopathy. She had no family history of muscle disease and her parents were not consanguineous. At age 84 a screen of several genetic tests associated with LGMD revealed that she was a compound heterozygote for 2 missense mutations in the calpain (CAPN3) gene. Therefore she has LGMD2A.

Case Four

This 78 year old retired professional with a graduate school degree had the onset of unsteady gait and dysarthria at approximately age 60. This was slowly progressive forcing him to stop playing golf and use 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. An MRI brain image showed cerebellar atrophy and he had a positive family history of ataxia. The diagnosis of SCA14 was made at age 74 with a mutation in the PRKCG gene (1).

Case Five

This man died at 86 after a long history of slowly progressive ataxia. He successfully completed service in the Army during World War II. He began to have clumsiness and unsteady gait at age 25 which caused him to become permanently unemployed at age 40. At age 80 he was very 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 SCA5 and a mutation in the SPTBN2 gene was discovered at age 84 (2).

Case Six

This retired salesman developed slowly progressive memory loss at age 79. At age 83 his Mini-Mental status examination score was 15/30. MRI showed mild to moderate diffuse cortical atrophy. He was noted to have a positive family history of earlier onset Alzheimer's disease in two siblings and several nephews. At age 83 this subject and other affected family members were discovered to have the A79V mutation in Presenilin-1 (3).

Case Seven

This 87 year old man was a World War II veteran and Pearl Harbor survivor. He had the onset of bilateral symmetrical motor and sensory neuropathy at age 70. He walks with bilateral ankle foot orthoses and a cane. Electrophysiological studies have shown a diffuse primarily axonal peripheral neuropathy. There have been multiple affected family members in many generations of his kindred compatible with autosomal dominant inheritance. No mutation has been discovered in 9 genes associated with CMT and the genetic defect in this family remains unknown (4).

Case Eight

This 78 year old man had a 10 year history of slowly progressive ataxia. He was non-alcoholic and an MRI showed prominent cerebellar atrophy. There was no family history of neurologic disease. His mother died at age 74 years and his father at age 58 years. Genetic testing reveled an abnormal CAG repeat expansion in the CACNA1A gene diagnostic of SCA6.

Discussion

The eight elderly subjects described here have a variety of histories and diseases, but share one 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 cases had onset of symptoms at much younger ages, but survived many decades and did not have specific genetic diagnoses made until relevant genetic tests became available in their senior years. The other five cases had late onset of symptoms. Case 1 was discovered to have HD during a general screen for causes of unexplained senile chorea. Cases 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 causing the CMT phenotype in Case 5 remains to be discovered. It could be argued that Case 4 simply has late onset AD. However, he has a mutation in PS1 that has been associated AD in multiple other family members and reported twice in the literature as associated with later onset cases of familial AD (3). It seems likely that this mutation plays a role in his dementia.

This phenomenon of the recognition of single gene genetic diseases in the elderly has at least three 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 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's ataxia and muscular dystrophy, although most common in the pediatric population, are now recognized to occur in adults (5–7). This is nicely demonstrated by Cases 1 and 6 in the present study who could be considered among the oldest old but have Huntington's disease and Limb-Girdle Muscular Dystrophy. Family history may be negative because the disease is autosomal recessive (Case 7), because other family members died prior to the onset of symptoms (probably Case 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. Subjects in this study would have been considered to have senile chorea, senile dementia, and unexplained myopathy prior to the advent of such testing.

The phenomenon of geriatric neurogenetics described here is not a theoretical possibility but a reality. Such cases are likely to be under recognized 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. Hopefully they will someday also have implications for management and treatment. For the reasons discussed above the diagnosis of neurogenetic diseases in the elderly will assuredly become more common. Training programs in Neurology and Geriatric Medicine should incorporate this issue into their curricula.

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References

1. Chen DH, Cimino PJ, Ranum LP, Zoghbi HY, Yabe I, Schut L, Margolis RL, Lipe HP, Feleke A, Matsushita M, Wolff J, Morgan C, Lau D, Fernandez M, Sasaki H, Raskind WH, Bird TD. The clinical and genetic spectrum of spinocerebellar ataxia 14. Neurology 2005;64:1258–60. [PubMed: 15824357]
2. Ikeda Y, Dick KA, Weathersppon MR, Gincel D, Armbrust KR, Dalton JC, Stevanin G, Durr A, Zuhlke C, Burk K, Clark HB, Brice A, Rothstein JD, Schut LJ, Day JW, Ranum LPW. Spectrin mutations cause spinocerebellar ataxia type 5. Nature Genetics 38(2):184–90. [PubMed: 16429157]
3. Brickell KL, Leverenz JB, Steinbart EJ, Rumbaugh M, Schellenberg GD, Nochlin D, Lampe TH, Holm IE, Van Deerlin V, Yuan W, Bird TD. Clinicopathological Concordance and Discordance in Three Monozygotic Twin Pairs with Familial Alzheimer's Disease. J Neurol Neurosurg Psych 78(10):1050–5.
4. Bennett CL, Lawson VH, Brickell KL, Isaacs K, Seltzer W, Lipe HP, Weiss MD, Carter GT, Flanigan KM, Chance PF, Bird TD. Late Onset Hereditary Axonal Neuropathies. Neurology. in press
5. Frey LC, Ringel SP, FIlley CM. The Natural History of Cognitive Dysfunction in Late-Onset GM_2 Gangliosidosis. Arch Neurol 2005;62:989–994. [PubMed: 15956171]
6. Rauschka H, Colsch B, Baumann N, Wevers R, Schidbauer M, Krammer M, Turpin J-C, Lefevre M, Olivier C, Tardieu S, Krivit W, Moser H, Moser A, Gieselmann V, Zalc B, Cox T, Reuner U, Tylki-Szymanska A, Aboul-Enein F, LeGuern E, Bernheimer H, Berger J. Late-onset metachromatic Leukodystrophy: Genotype strongly influences phenotype. Neurology 2006;67:859–863. [PubMed: 16966551]
7. Bhidayasiri R, Perlman SL, Pulst S-M, Geschwind DH. Late-onset Friedreich Ataxia:Phenotypic Analysis, Magnetic Resonance Imaging Findings, and Review of the Literature. Arch Neurol 2005;62:1865–1869. [PubMed: 16344344]

Table 1

Elderly Patients with Neurogenetic Diseases.

Case	Age	Sex	Onset Age	Genetic Diagnosis Age	Disease	Gene	Mutation	Date Clinical Genetic Testing First Available
1	87	M	79	80	Huntington's Disease	HD	39 CAG	1993
2	85	M	75	76	Huntington's Disease	HD	40 CAG	1993
3	78	M	60(13?)	74	SCA14	PRCKG	H101Y	2004
4	d.86	M	25	84	SCA5	SPTBN2	E523- M544d el	2006
5	84	M	79	83	Familial Alzheimer's	PS1	A79V	1998
6	87	M	70	Unk	Hereditary Neuropathy	Unk	Unk	----
7	84	F	50	84	LGMD2 A	Calpain (CAPN3)	L189P R490W	2004
8	78	M	68	77	SCA6	CACNA 1A	21 CAG	1997