Hereditary Spastic Paraplegia and Hereditary Ataxia

Part 2: A Family Demonstrating Various Phenotypic Manifestations With the SCA3 Genotype

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Background: Clinical descriptions of the dominantly inherited ataxic motor syndromes in a 7-generation family of German origin were first reported in 1951.

Objective: To provide follow-up clinical, pathological, and genetic data for 9 patients in this family.

Design: Clinical histories and neurologic findings, gross and microscopic pathological features, and DNA analysis.

Results: Clinical presentations in this closely followed up portion of the family include fairly uniform ataxic and upper motor neuron symptoms. Nystagmus was a conspicuous and early sign, but generational anticipation was not evident. Although often present, amyotrophy was not a major source of disability. Major pathological degeneration was noted in the pons, spinal cord, and upper brainstem, where ubiquitin-immunoreactive intranuclear inclusion bodies were demonstrated. The diagnosis of Machado-Joseph disease (SCA3 [spinocerebellar ataxia type 3] genotype) was established from autopsy tissue in 1 patient and from blood specimens in 6 others.

Conclusions: Clinical variation within this family and between this family and families with the SCA1 and SCA3 genotypes is so broad as to make the genetic diagnosis from clinical criteria alone practically impossible. The pathological definition of Machado-Joseph disease is more reliable, but some findings do overlap those of other genotypes. To our knowledge, the basis for the phenotypic variations in Machado-Joseph disease, genetic or otherwise, has not been established.

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The first report1 of this now 8-generation family reviewed the early reports of adult-onset hereditary motor system syndromes. At that time, the researchers concluded that this family, of German origin, most resembled the Schut family, which had been recently described by Schut and Haymaker.2,4 Two decades later, reports5-14 of dominantly inherited cerebellar ataxia in Portuguese families led to the reference eponym, Machado-Joseph disease. Similar families of non-Portuguese origin were also described,15 and Machado-Joseph disease is genetically identified as SCA3 (spinocerebellar ataxia type 3).16 Although clinically similar,7 the Schut family genotype turned out to be SCA1.17

One branch of this German family has been closely followed up for 50 years. We provide supplementary clinical and pathological data along with genetic identification.

RESULTS

CLINICAL AND PATHOLOGICAL OBSERVATIONS

Patient numbers refer to family tree locations in Figure 1 and in Figure 1 of a previous report.1

Patient V-51 was asymptomatic when she was first examined at the age of 22 years. She had sustained lateral gaze nystagmus in both directions and brisk tendon jerks. At about the age of 40 years, she became aware of stiffness and awkwardness of her lower extremities and she hurt her left shoulder in a fall at work. During the next several years, the lower extremity symptoms increased; she also developed clumsiness and stiffness of the upper extremities and slurred speech. At the age of 53 years, she had pseudobulbar blank expression, nasal slurred speech, and sustained nystagmus on lateral and upward gaze. Her gait was grossly stiff and ataxic; she was unstable standing...
PATIENTS AND METHODS

Clinical and pathological data are described for 9 patients from an 8-generation family with a dominantly inherited ataxic syndrome. For genetic analysis, each blood and tissue specimen was washed and prepared by standard methods. Amplification of the SCA3 gene locus was achieved using the polymerase chain reaction. The polymerase chain reaction products were separated on 6% polyacrylamide denaturing gels, dried, and exposed to x-ray film overnight. Each amplified DNA sample was sized by comparison with a sulfur 35–labeled M13 DNA sequence ladder.

in the Romberg position with her eyes open. There was moderate ataxia while performing the finger-nose and heel-knee tests. Tendon jerks were hyperactive except for trace ankle jerks. Plantar reflexes were extensor. There was no muscle atrophy or fasciculation. Vibration sense was slightly decreased in her feet and hands. Position sense was slightly decreased in her toes. The results of nerve conduction studies and electromyographic studies were normal. Lower extremity muscle cramps were partly relieved by baclofen. At her last examination at the age of 63 years, she could not stand alone and had a mild degree of mental confusion. At the age of 70 years, she died of urosepsis with secondary bronchopneumonia.

PATHOLOGICAL FINDINGS

Gross Description

The unfixed brain of patient V-51 weighed 1200 g and demonstrated only slight, if any, cerebral cortical atrophy (Figure 2), accompanied by mild ventricular dilation with blunting of the lateral angles (Figure 3). The basal ganglia were remarkable only for some tissue loss and discoloration of the globus pallidus (Figure 3, arrow). The external aspects of the brainstem were shrunken, particularly the basis pontis (Figure 2), findings confirmed on transverse pontine sectioning (Figure 4). The substantia nigra showed marked pallor. The cerebellum was not atrophic (Figure 2 and Figure 5). The external and cut surfaces of the spinal cord were diffusely atrophic and discolored.

Microscopic Description

The cerebral cortex of patient V-51 showed preservation of the complement of cortical neurons without evidence of significant numbers of senile plaques, neurofibrillary tangles, cortical Lewy bodies, Pick bodies, or swollen neurons. Although only mild neuron loss accompanied by astrocytosis was found in the caudate, putamen, and external aspects of the globus pallidus, the internal aspect of the globus pallidus demonstrated increased numbers of fibrillary astrocytes and neuron loss. Oligodendroglial or neuronal inclusions, as might be expected in multiple system atrophy, were not identified.

The dorsal mesencephalon, red nucleus, and especially the substantia nigra had lost neurons (Figure 6); however, the complement of neurons in the oculomotor nucleus and periaqueductal gray was well maintained. The pons, markedly shrunken on gross inspection, demonstrated substantial loss of neurons and astrocytosis (Figure 7, top) involving the pontine nuclei and loss of transverse pontine axons in the presence of preserved corticospinal tracts. The medullary inferior olivary nuclei showed preservation of the neuronal population; similarly, there was no compelling evidence for the loss of facial motor and hypoglossal neurons.

Ubiquitin-immunoreactive intranuclear inclusions, a recently discovered histopathologic finding in various diseases that have in common expanded (CAG)n trinucleotide repeats, were identified in affected brain regions, including pontine neurons (Figure 7, bottom) and, to a lesser extent, the basal ganglia, dentate nuclei, and substantia nigra.20,21

Thorough sampling of the cerebellar vermis and hemispheres showed relatively mild overall Purkinje cell loss, although scattered axonal spheroids arose from proximal Purkinje cell axons in the granular cell layer (Figure 8, top). The dentate nuclei showed substantial neuron loss and astrocytosis (Figure 8, bottom), and were surrounded by gliotic white matter.

Motor neurons were decreased in the spinal cord, thoracic more than lumbosacral, a finding that was supported by decreased numbers of axons in the ventral roots and neurogenic atrophy in the quadriceps femoris muscle (Figure 9, top). Significant numbers of neurons were lost from lumbosacral dorsal root ganglia, as confirmed by the demonstration of numerous nodules of Nageotte (Figure 9, bottom, arrows), ie, satellite cell clusters representing foci of neuron loss and loss of myelin and axons in the dorsal columns. The dorsal and ventral spinocerebellar tract axons and the Clarke column neurons were markedly depopulated. Lateral corticospinal tracts and preganglionic sympathetic neurons of the thoracic intermediolateral nuclei were preserved.

Brain tissue analysis showed that one of the SCA3 alleles was expanded to 72 repeats. The repeat numbers of SCA2 alleles were 21 and 22, which are within normal limits. Expansion of the SCA3 allele precluded detection of SCA1 alleles.

Patient IV-33 was the paternal uncle of patient V-51 and the father of patient V-74. Initial symptoms of stiff gait began when he was 37 years old. When he was examined at the age of 56 years, he displayed generalized hyperreflexia; clasp-knife reaction to passive stretch; extensor plantar reflexes; prominent nystagmus; and ataxia, most prominent in the upper extremities. There was diffuse muscle atrophy in both hands but no fasciculations. He died 3 years later.

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Neither tissue nor microscopic slides were available. The specific observations by Haymaker included loss of por-
tions of the dorsal columns and gracile nuclei, dorsal and ventral spino-cerebellar tracts, marked loss of anterior horn motor neurons, and degeneration of the hypoglossal nuclei, nuclei ambigu, and brachia conjunctiva. Although Haymaker surmised that this case fits the “Schut-Haymaker” category\(^3\) (now known to be SCA3\(^{17}\)) in the monograph by Greenfield,\(^22\) the findings are quite similar to those in our patient (V-51).

Patient V-93 belonged to a different major branch of the family (great grandmother, II-2) from that of the other patients in this report (offspring of her sister, II-1). He first noted stiffness in his lower extremities at the age of 23 years. After 4 or 5 years, there was change in speech and dysphagia. A physical examination at the age of 30 years revealed slurred nasal speech and a spastic diple-gic gait. His pupils were unequal, the left somewhat larger, but they reacted well to light and to near accommodation. Marked nystagmus was noted in the primary position and on lateral and upward gaze. There was subtle left facial weakness, and the palate was elevated to the right. Fine fibrillations were seen in the tongue. Spasticity was generalized, much more prominent in the lower extremities. There was some unsteadiness in the performance of finger-nose and heel-knee tests. Tendon jerks, including the jaw jerk, were hyperactive with bilateral Hoffman and extensor plantar reflexes. Abdominal and cremasteric reflexes were present. Eight years later, he had become bedridden. There was mental deterioration with moderate weight loss, severe generalized spasticity, and moderate ataxia. His speech was severely dysar-
thric, and there was slight dysphagia. He died of aspiration pneumonia at the age of 39 years.

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Haymaker’s analysis showed no cerebral cortical atrophy or myelin loss. The inferior part of the internal capsule was described as degenerated with concomitant astrocitosis that extended into the adjacent globus pallidus. In the brainstem, he observed loss of portions of the mesencephalic tegmentum and the gracile nucleus, with sparing of the inferior olivary nuclei. Cerebellar sections showed minimal loss of Purkinje cells in the presence of marked neuronal loss in the dentate nucleus. Spinal cord involvement consisted of patchy degeneration of the spino-cerebellar and pyramidal tracts and dorsal columns.

**ADDITIONAL CLINICAL OBSERVATIONS**

**Patient V-55**

This patient is the brother of patient V-51. At the age of 14 years, he had only prominent lateral gaze-sustained
nystagmus. Seen next at the age of 46 years, he was a successful masonry contractor. He reported that his balance had been “off” progressively for about 6 years and for a year he had had nocturnal cramps especially after heavy work. An ocular examination revealed 2 to 3 beats of nystagmus on lateral gaze and occasionally on upward gaze. Gait and somatosensory examination results were normal. However, there was mild ataxia for fine movements in the upper and lower extremities. Except for equivocal ankle jerks, all of the tendon jerks were hyperactive, including the jaw jerk. Plantar reflexes were extensor. Fasciculations were observed in the calf muscles. The results of an electromyogram revealed intensive fasciculations in the gastrocnemius soleus and tibialis anterior muscles, exaggerated after voluntary contraction; there were no fibrillations. There was slowed motor conduction in the peroneal and posterior tibial nerves and sensory nerve slowing in the H reflex. The results of a computed tomographic scan of the head were normal.

The motor disability progressed so that he had to cease working at the age of 54 years. By that time, ataxia interfered with dressing and turning pages. Vibration sense was absent below the midcalves. Baclofen relieved the muscle cramps. During the next several years, he complained of morning episodes of severe vertigo, sometimes with nausea and vomiting. At the age of 62 years, there was still only slight nystagmus on lateral gaze. Fasciculations were observed in both upper extremities, thighs, and calves. Muscle pain was helped by nonsteroidal anti-inflammatory drugs. By the age of 64 years, there was atrophy of the calves. DNA analysis showed 70 to 75 repeats of one of the SCA3 alleles. SCA1 and SCA2 CAG repeat sizes were normal.

**Patient V-57**

This patient is the sister of patient V-51. A full-time bookkeeper-secretary, she became aware of stumbling at the age of 42 years. She had a slightly wide-based ataxic gait, mild upper limb ataxia, and generalized hyperreflexia, including the jaw jerk, with flexor plantar responses. She experienced slow sustained lateral gaze nystagmus and fine rapid nystagmus on upward gaze. She required treatment for vascular hypertension and nocturnal leg cramps. At the age of 54 years, she began using a cane. In recent years, she has used a walker but continues effective work as a financial manager. Her mental function was well preserved at the age of 60 years. DNA analysis showed 70 to 75 repeats of one of the SCA3 alleles. SCA1 and SCA2 CAG repeat sizes were normal.

**Patient V-74**

This patient is the first cousin of patient V-51. She first noted unsteadiness of gait and balance in her late 40s and used a walker before she had to retire from her position as a legal secretary when she was 55 years old. By then, she noticed slight difficulty with swallowing and impairment of dexterity of the upper extremities. Her vision and
somatic sensation were good. The results of a magnetic resonance imaging scan showed moderate cerebellar and cervical spinal cord atrophy and slight atrophy of the basis pontis. At the age of 56 years, ataxia and dysmetria were increased, but she was mentally intact and still able to drive an automobile. There was slight diminution of vibration sense in her toes. Tendon jerks were brisk, including the jaw jerk, but there were no ankle jerks. The plantar reflexes were extensor. There was slight limitation of upward gaze with eyelid retraction but otherwise full and conjugate eye movements. There was sustained gaze-evoked nystagmus on lateral gaze but not on vertical gaze. Frequent square wave jerks, often continuous, resembled flutter. DNA analysis showed an amplified CAG repeat of 73 of the SCA3 gene on one chromosome and a normal repeat of 21 on the other. The repeat size (29 and 30) of SCA1 on both chromosomes was normal (Molecular Genetics Laboratory, Mayo Clinic, Rochester, Minn, unpublished data, 1997).

Patient VI-47

This patient is the son of patient V-51. At the age of 32 years, he first noted vertiginous “dizziness” when he was doing sit-ups. During the next several years, this symptom increased along with difficulty running and walking, particularly in the dark. He was treated for benign paroxysmal postural vertigo once. At the age of 46 years, at Walter Reed Hospital, Washington, DC, a physical examination showed prominent nystagmus on gaze in all directions, hyperactive stretch reflexes, flexor plantar responses, and spastic ataxic gait. The following year, he had extensor plantar reflexes, loss of vibration sense below the knees, and slight decrease of pinprick sensation in the same areas; no muscle atrophy or fasciculation was found. At the age of 50 years, he reported the persistence of vertigo if he lay flat on his back. Ataxia on finger-nose and heel-shin tests was mild, even as the spastic wide-based gait became worse. DNA analysis showed 70 to 75 repeats of one of the SCA3 alleles. SCA1 and SCA2 CAG repeat sizes were normal.

Patient VI-88

This patient is the son of patient V-51. At the age of 31 years, he was working successfully in a large printing plant, using a computer and handwriting. He had no symptoms, but requested a checkup. His eye movements were normal. There was slight decrease of vibration sense at the ankles. His coordination, strength, and reflexes were normal. By the age of 37 years, he became aware of gait instability, particularly on rough ground. By the age of 47 years, he required a cane and developed bowel urgency and urinary dribbling. Sexual function was still satisfactory. He became aware of vertigo when he lay flat, sufficiently severe so that he learned to sleep with his head elevated. He had a spastic gait, hyperreflexia, extensor plantar reflexes, only mild upper extremity ataxia, and sustained nystagmus on lateral gaze. The following year, he retired from his position. DNA analysis showed 70 to 75 repeats of one of the SCA3 alleles. SCA1 and SCA2 CAG repeat sizes were normal.

Patient VI-89

This patient is the daughter of patient V-51. She began to have trouble with balance while walking when she was about 35 years old, but she continued to cope successfully with homemaking tasks. At the age of 46 years, a physical examination showed questionable optic disc temporal pallor. There was marked lateral gaze nystagmus and decreased voluntary upward gaze. Her facial expression was stolid with slight dysarthria. Vibration sense was slightly decreased in her toes. Her gait was wide based, diplegic. The results of finger-nose and heel-knee tests showed mild ataxia. Tendon jerks were hyperactive with unsustained ankle clonus and extensor plantar reflexes. The Romberg sign performance was unsteady. There was no muscle atrophy or fasciculation. Paraspinal muscle pain was relieved by analgesic medication. The results of a thoracic spine computed tomographic scan were normal. A wheeled walker facilitated her independence. DNA analysis showed 70 to 75 repeats of one of the SCA3 alleles. SCA1 and SCA2 CAG repeat sizes were normal.

COMMENT

The clinical course among the most closely related 8 patients in this report is relatively benign and uniform, with survival into the sixth and seventh decades of life. There is no systematic anticipation of symptoms with earlier morbidity in younger generations of any branch of the family. We have no data regarding the number of CAG repeats in those patients who died in early adult life. None of our patients had many of the symptoms described in family groups with Machado-Joseph disease: ophthalmoplegia, facial and lingual fasciculations, dystonia, or retinal degeneration. Matilla et al16 observed that “other than SCA3 dominant ataxias exhibit a bewildering array of clinical phenomenology.” We are similarly impressed by the lack of uniformity of clinical symptom emphasis and morbidity in our large family with the SCA3 genotype.

Transient vertigo was an unusual symptom in 3 of our patients, V-55, VI-47, and VI-88. Two brothers were specifically afflicted if they lay supine unless they tilted their heads upward. This suggests a specific impairment of part of the labyrinthine system or its brainstem projection.

Our pathological findings, supported by the clinical presentation, pattern of inheritance, and molecular studies, establish the diagnosis of Machado-Joseph disease (SCA3 genotype).15,16,20,21,23,24 The (CAG)n repeat in SCA3 involves the gene for an isoform of ataxin-3 and results in a polyglutamine repeat in its protein product, which is demonstrable in the ubiquinated intranuclear inclusions in neurons of affected brain regions. Although the absence of gross cerebellar atrophy is an important criterion of SCA3 pathologic change, one of our living patients, V-74, had prominent cerebellar degeneration on a magnetic resonance imaging examination. The appropriate reference term for this family’s condition is Machado-Joseph disease (SCA3 genotype).25
REFERENCES