



## EMG Case No. 77, December 2005

### Presenting Symptom(s):

**Progressive weakness affecting the upper and lower extremities**

## **This case is no longer available for CME credit.**

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**Disclosures:** D.Cohen, None; J. Russell, None.

**Appropriate Audience:** Residents and practicing physicians.

**Learning Objectives:** After completing this educational activity, participants will be able to: (1) Name the cardinal features of Kennedy's disease; (2) Be able to differentiate Kennedy's disease from ALS; (3) Describe the electrodiagnostic findings seen in Kennedy's disease.

**Level of Difficulty:** Intermediate.

### History

The patient is a 47-year-old male with a chief complaint of weakness affecting his upper and lower extremities. Seven years previously, he notices that his lower limbs would occasionally give out when walking. He begins to have slowly progressive weakness affecting initially his lower limbs. One and a half years prior to his presentation, he begins to notice some weakness in his upper limbs. Within seven months of his presentation he notices that he is unable to walk a significant distance without getting short of breath, has difficulty-lifting things such as a gallon of iced tea, and occasionally has some numbness in his left foot. Overall, he notices a diffuse loss of muscle bulk.

- Prior to continuing, please develop a differential diagnosis and list each possible diagnosis in order of likelihood.
  - Motor neuron disease (spinal muscular atrophy)
  - Inclusion body myositis
  - Dystrophic myopathies e.g. facioscapulohumeral muscular dystrophy, limb girdle muscular dystrophy etc.
  - Myasthenia Gravis or other neuromuscular junction disorders
  - Mitochondrial myopathy
  - Polyradiculopathy
- Is there any additional information regarding the clinical history that might be helpful in clarifying your differential list or changing its order of priority?
  - Are there any bulbar symptoms?
  - Were there any ocular symptoms?
  - Was there any family history?
  - Had he ever noticed muscle cramping or difficulty releasing his grip?

## Commentary I

The above history is suggestive of a diffuse, slowly progressive disorder affecting the motor system. From the above history it is difficult to differentiate whether he has a myopathic or neuropathic disorder, as both can cause diffuse weakness. If bulbar symptoms are present, a disorder such as motor neuron disease is more likely (Although bulbar can be seen in some myopathies such as oculopharyngeal muscular dystrophy or inclusion body myositis). The presence of ocular symptoms such as diplopia can be seen in disorders such as myasthenia gravis. Myasthenia gravis is not very likely from the above history, as the patient did not describe prominent ocular symptoms or fatigable weakness. Furthermore, a patient with myasthenia gravis would not be expected to have such a protracted course of progressive weakness.

The significance of the mild sensory changes he has noticed is unclear. He could have a structural polyradiculopathy causing weakness and sensory changes, but it would be unusual without back pain or prominent sensory complaints in the extremities. A metabolic polyradiculopathy from diabetes or vitamin B12 deficiency is possible but the minimal sensory changes would argue against these disorders.

## History, continued

On questioning, he admits to occasional swallowing difficulties and a change in his speech. He also notices that his tongue has changed. He is aware of quivering movements and a loss of muscle bulk. He denies diplopia, ptosis, fatigable weakness, or myotonia. He has never had myoglobinuria.

He has no significant prior medical history and has been on no medications. There is no family history of neuromuscular disease. He has a sister who is living and three healthy sons.

- If necessary, revise your differential diagnosis based on the additional clinical history.
- On which details of the physical examination should you focus at this point?

## Commentary II

The above information indicates that in addition to the diffuse limb weakness, he has also has bulbar symptoms, such as dysphagia and dysarthria. He has not had any ocular symptoms or family history of neuromuscular disease. This would make autosomal dominant disorders unlikely (such as facioscapulohumeral muscular dystrophy or oculopharyngeal muscular dystrophy).

## Physical Examination

General examination (with the patient in a gown) was unremarkable. On exam, he has a flaccid dysarthria. His mental status is intact to a detailed history. He has no ptosis and has full eye movements. Facial strength is normal. He has a small atrophic tongue with prominent fasciculations. **See Figure 1.**

He has obvious atrophy of his hand intrinsic muscles, deltoids, and biceps in a symmetrical fashion. Strength is rated (right/left) as deltoid 4+/4+, biceps 4-/4, triceps 4-/4-, wrist extension 5-/5-, hip flexion 4+/4+, knee flexion 5-/5-, knee extension 5-5-, dorsiflexion

4+/4+, and plantar flexion 4+/4+. Reflexes were graded 1+ at the biceps and brachioradialis, trace at the patellae, and absent at ankles bilaterally. There was no ankle clonus. The toes were downgoing to plantar stimulation.

Vibration was intact throughout. Pinprick was decreased in the fifth finger bilaterally and decreased in a patchy distribution in the arms.

- At this point, review your differential diagnosis and revise as appropriate.
- Are there additional observations on physical examination that might be helpful in narrowing your differential list?

*Figure 1*



### **Commentary III**

The examination would be consistent with a diffuse myopathic process or a pure lower motor neuron process. There are no upper motor neuron findings on examination, which would make amyotrophic lateral sclerosis unlikely. The pattern of weakness does not fit one particular pattern of a muscular dystrophy. He has prominent weakness and atrophy both proximally and distally. This would make inclusion body myositis unlikely. The bulbar symptoms with tongue atrophy and fasciculations are suggestive of a neuropathic process. The apparent sensory loss would also be consistent with a neuropathic process.

### **Physical Examination, continued**

Upon further inspection, the patient has gynecomastia bilaterally. **See Figure 2.**

- If necessary, revise your differential diagnosis based on the additional physical findings.
- Design your approach to the electrophysiologic examination based on the existing data.

Figure 2



**Electrophysiologic Data**

NR = no response

SENSORY NERVE CONDUCTION STUDIES						
NERVE	SIDE	STIM SITE	RECORD	AMPL	LAT	CV
Sural	L	Calf	NR			
Ulnar	L	Wrist	NR			
Ulnar	R	Wrist	NR			
Radial	L	Forearm		6.9	2.7	50
Radial	R	Forearm		7.7	2.5	52.6
Median	L	Wrist		4.1	3.8	46.7
Median	R	Wrist		6.1	3.9	58.8

MOTOR NERVE CONDUCTION STUDIES						
NERVE	SIDE	STIM SITE	RECORD	AMPL	LAT	CV
Peroneal	R	Ankle		1.1	6.2	
Peroneal	R	Below Knee		0.8	12.6	42.2



Tibial	R	Ankle		8.4	5.7	
Median	L	Wrist		5.0	4.6	
	L	Elbow		4.2	9.8	46.2
Ulnar	L	Wrist		5.2	4.3	
	L	Below Elbow		4.3	8.6	47.7
	L	Above Elbow		4.0	10.4	55.6

**NEEDLE ELECTROMYOGRAPHY**

INSERtional activity: normal, sustained (sust), unsustained (unsust)

FIBrillation: 0, 1+, 2+, 3+, 4+

OTHer: 0 or fasciculation (fascic), complex repetitive discharge (CRD), myotonia, myokymia

EFFort: normal, decreased

RECruitment: normal (N), increased (↑) or decreased (↓) 1+, 2+, 3+, 4+

AMPliitude: normal (N), increased (↑) or decreased (↓) 1+, 2+, 3+, 4+

DURation: normal (N), increased (↑) or decreased (↓) 1+, 2+, 3+, 4+

POLyphasia: normal (N), increased (↑) or decreased (↓) 1+, 2+, 3+, 4+

R/L	MUSCLE	INSER	FIB	OTH	EFF	REC	AMP	DUR	POL
L	Tibialis Anterior	N	0	0	N	↓2-	↑1+	↑2+	↑1+
L	Vastus lateralis	unsust	0	0	N	↓3-	↑4+	↑4+	↑2+
L	Medial gastrocnemius	sust	1+	fascic	N	↓2-	↑3+	↑1+	N
L	Abductor Hallicus	unsust	0	0	N	↓3-	↑3+	↑3+	↑3+
L	Biceps	sust	2+	CRD	N	↓2-	↑2+	↑2+	↑1+
L	First dorsal interosseus of the hand	sust	2+	0	N	↓2-	↑4+	↑3+	↑2+
L	Low lumbar paraspinals	N	0	0					
L	Midthoracic paraspinals	unsust	0	0					
	Tongue	N	0	0	N	N	↑2+	N	N

- On the basis of both the clinical and electrophysiologic evaluations, formulate your diagnostic impression. List the most likely diagnosis first and follow in order with the other possibilities that are not excluded by the data. Eliminate those diagnoses not supported by the data.
  - Motor and sensory axonal neuropathy
  - Motor neuron disease
  - Left carpal tunnel syndrome



- Make the final revisions of your diagnostic impression(s).

## Diagnostic Impression

There is electrodiagnostic evidence of a motor and sensory axonal neuropathy. In addition, there is a lower motor neuron process affecting proximal and distal muscles of the extremities as well as the thoracic paraspinal muscles and tongue. Because there is diffuse involvement of all limb muscles, thoracic paraspinals, tongue and bulbar involvement, a motor neuron process is likely. A polyradiculoneuropathy would not account for these signs. Although the needle examination showed ongoing denervation, there is also evidence of chronic denervation. The patient has hyporeflexia and a clinical course that are not consistent with amyotrophic lateral sclerosis that would normally present with a more acute history, hyperreflexia and normal sensory nerve conduction studies. Given the presence of gynecomastia in addition to the other clinical and electrodiagnostic findings, a diagnosis of Kennedy's disease should be considered. This disease is associated with clinical evidence of both spinal muscular atrophy and peripheral neuropathy.

- What other diagnostic procedures (laboratory tests, etc.), if any, are needed?
  - Kennedy's disease DNA Test
  - If the DNA test were negative then an extensive diagnostic evaluation for other causes of a spinal muscular atrophy and peripheral neuropathy would need to be obtained.
  - Glucose regulation should be assessed with an oral glucose tolerance test.
- What treatment would you recommend?
  - Supportive care (physical therapy, occupational therapy, speech pathology)

## Commentary IV

Lab results in this patient were consistent with a diagnosis of Kennedy's disease. DNA testing revealed greater than 40 CAG repeats (an SMBA full mutation). No other causes for a sensorimotor polyneuropathy were identified.

Kennedy's disease is a X-linked recessive disorder (Xq12), also known as spinobulbar muscular atrophy. It is a trinucleotide repeat disorder affecting a gene that codes for the androgen receptor gene that leads to lengthening of the polyglutamine tract in the androgen receptor protein. Loss of normal androgen receptor activity is most likely related to a decrease in receptor expression and function. However, in Kennedy's disease it is a 'toxic gain of property' rather than a loss of function that results in the neuronal degeneration. Although the pathogenesis of Kennedy's disease is uncertain, animal models show that androgens exacerbate Kennedy's disease by translocation of mutant androgen receptor from the cytoplasmic compartment in cells to the nucleus an event that is associated with disease pathogenesis in other polyQ expansion diseases, for example Huntington's disease.

It is a slowly progressive pure lower motor neuron disease. The disease characteristically affects only male patients, the onset is usually age 30–50 years, and is associated with gynecomastia, testicular atrophy, reduced fertility, and a mild sensory axonal neuropathy. Unlike amyotrophic lateral sclerosis, there are no upper motor neuron signs seen in Kennedy's disease. Kennedy's disease has a slower rate of progression as compared to



amyotrophic lateral sclerosis, with slow progression over decades (whereas amyotrophic lateral sclerosis patients progress to death within several years after diagnosis). Patients with Kennedy's disease are also more likely to have diabetes or impaired glucose tolerance and this should be assessed.

Kennedy's disease is associated with sensory abnormalities on electromyography testing. Unlike amyotrophic lateral sclerosis, which has pure motor abnormalities, patients with Kennedy's disease have a mild associated polyneuropathy. In a 19 patient series by Ferante and Wilbourn, 95% of patients studied had sensory nerve action potential abnormalities. Characteristically, the sensory nerve action potentials had low amplitude or were absent. Compound muscle action potential abnormalities were identified in 37% of patients, again with low amplitudes. On needle examination, all 19 patients had changes suggestive of both acute and chronic denervation. Fibrillation potentials, fasciculation potentials, and chronic neurogenic changes were widespread. The chronic neurogenic changes were more widespread than the fibrillations. The clinical onset can be heterogenous bulbar, upper limb, lower limb, or combination presentation. The electrodiagnostic findings can be predominantly sensory, motor, or sensorimotor. Focal onset is common (79%). The electrodiagnostic findings are consistent with chronic degeneration of the anterior horn cells and dorsal root ganglia.

Kennedy's disease is an important electrodiagnostic consideration, as it has very important implications for the patient. As mentioned above, it is an X-linked recessive disorder so female offspring and sisters of the affected individual would be carriers. Kennedy's disease is a motor neuron disease, though has a much more protracted course (which would be important for the patient's care and prognosis). Heterozygous female carriers have been reported to display subclinical manifestations of the disease but may be protected either by X-chromosome inactivation (lionization) or because of lower circulating androgen levels in women.

There are no therapeutic options available for Kennedy's disease, although animal models of both Kennedy's and Huntington's disease have shown that inhibition of expression of the mutant protein can reverse the neurodegeneration. Development of therapies that inhibit translocation of the mutant protein to the nucleus and subsequent expression may achieve this effect. Androgen supplements may worsen the neurodegeneration. Diabetes, or impaired glucose tolerance, should be treated. All patients diagnosed with Kennedy's disease should have regular follow up with a speech pathologist to assess swallowing function.

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