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Distal Spinal and Bulbar Muscular Atrophy Caused by Dynactin Mutation

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Abstract

Impaired axonal transport has been postulated to play a role in the pathophysiology of multiple neurodegenerative disorders. In this report, we describe the results of clinical and neuropathological studies in a family with an inherited form of motor neuron disease caused by mutation in the p150^{Glued} subunit of dynactin, a microtubule motor protein essential for retrograde axonal transport. Affected family members had a distinct clinical phenotype characterized by early bilateral vocal fold paralysis affecting the adductor and abductor laryngeal muscles. They later experienced weakness and atrophy in the face, hands, and distal legs. The extremity involvement was greater in the hands than in the legs, and it had a particular predilection for the thenar muscles. No clinical or electrophysiological sensory abnormality existed; however, skin biopsy results showed morphological abnormalities of epidermal nerve fibers. An autopsy study of one patient showed motor neuron degeneration and axonal loss in the ventral horn of the spinal cord and hypoglossal nucleus of the medulla. Immunohistochemistry showed abnormal inclusions of dynactin and dynein in motor neurons. This mutation of dynactin, a ubiquitously expressed protein, causes a unique pattern of motor neuron degeneration that is associated with the accumulation of dynein and dynactin in neuronal inclusions.

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Disruption of axonal transport has been implicated in the mechanism of frontotemporal dementia,¹ polyglutamine diseases,^{2,3} and amyotrophic lateral sclerosis.^{4,5} The importance of the dynein–dynactin microtubule motor proteins, which mediate retrograde axonal transport, has been further emphasized by recent studies showing that mutation or disruption of these motor proteins leads to late-onset motor neuron disease in mice.^{6,7} We recently reported on a family in which a G59S missense mutation in the p150^{Glued} subunit of dynactin is associated with an autosomal dominant form of motor neuron disease.⁸ In this study, we delineate the unique clinical, electrophysiological, and pathological effects of this mutation.

Subjects and Methods

This research protocol was approved by the National Institutes of Health Institutional Review Board. Twenty-seven family members gave written consent before participation in this study (Fig 1). All underwent detailed investigation of their histories and neurological and otolaryngological examinations. Investigations in four affected family members (Patients II-2, II-4, III-5, and III-7) were reported previously in abstract form.⁹

Otolaryngological examinations were performed using a Pentax PNL-10RP3 fiberoptic nasolaryngoscope (Pentax Precision Instruments, Orangeburg, NY) interfaced with the Kay Elemetrics Digital Stroboscope system (Kay Elemetrics Corporation, Lincoln Park, NJ) to evaluate the structure and function of the laryngeal mechanism.¹⁰

Nerve conduction studies, electromyography (EMG), and quantitative sensory testing were performed in eight family members. Nerve conduction studies of three or more motor nerves, three sensory nerves, and the phrenic nerve¹¹ were obtained using surface recording techniques. EMG included qualitative and quantitative motor unit assessment and quantitative interference pattern analysis. Laryngeal EMG was performed in one subject (III-12), sampling motor units during respiration and phonation in three locations of the thyroarytenoid muscle bilaterally.^{12–14}

Skin biopsies (3mm in diameter) were obtained from the foot and calf of two affected family members and two unaffected family members and were fixed in Zamboni's fixative. Sections (60µm) were stained with rabbit PGP 9.5 (Biogenesis, Kingston, NH) and mouse Col IV (Chemicon, Temecula, CA), as described previously.^{15,16} Microscopic images were collected with a CARV nonlaser confocal microscope imaging system (Atto Bioscience, Rockville, MD). A z series of optical sections 2µm apart at ×20 magnification was taken from four random fields per sample.^{15,16} Epidermal nerve fiber density (number of fibers per millimeter epidermis) was determined in two or three sections from each site and was compared with previously established normative data.¹⁶

Neuropathology and Immunohistochemistry

An affected family member who died of pneumonia after long-term tracheostomy at aged 76 years (Case I-1) underwent an autopsy (with family permission) with standard gross and histological inspection. Paraffin-embedded sections of the medulla at the level of the hypoglossal nucleus from the affected case and from a control subject without neurological disease (autopsy material obtained from the Pathology Laboratory of the National Cancer Institute) were stained with hematoxylin and eosin. For immunohistochemical studies, slides were soaked in xylene, dipped in ethanol at increasing dilutions, rehydrated in water, and treated with heated tris(hydroxymethyl)aminomethane buffer. Three antibodies were used on separate slides: SMI 32, a monoclonal antibody that reacts with nonphosphorylated epitopes in neurofilament H (Sternberger Monoclonals, Baltimore, MD)¹⁷; a mouse monoclonal antibody specific for the p50 (dynamitin) subunit of dynactin¹⁸ (BD Biosciences, San Jose, CA); and an affinity-purified rabbit polyclonal antibody to the intermediate chain of

cytoplasmic dynein (DIC), UP1467, generated in the Department of Physiology at the University of Pennsylvania.¹⁹ Staining was visualized using the avidin-biotin complex Elite kit (Vector Laboratories, Burlingame, CA) protocol and the diaminobenzidine tetrahydrochloride reaction (Sigma, St. Louis, MO). Slides were counterstained with hematoxylin (Vector).

Results

Case Report: Patient III.12

The proband is a 54-year-old woman who first recognized symptoms at aged 23 years (Table 1). She experienced occasional choking while drinking, with one event necessitating admission to the hospital. Six years later, she experienced stridor when walking upstairs. At aged 38 years, she underwent laryngeal surgery for severe respiratory distress; this left vocal fold “tie-back” procedure relieved the respiratory symptoms, but left her with a breathy, aphonic voice. At aged 40 years, she gradually experienced weakness and atrophy in the hands that caused difficulty with writing, opening jars, and fine finger control. Difficulty with walking began in her early 50s. At the time of evaluation, she reported that she had to walk slowly and rest frequently because of leg weakness.

Neurological examination indicated that the patient had a severely breathy, whispered voice with dyspnea while talking. There was mild-to-moderate weakness of the facial muscles, but the jaw and neck muscles were strong. There was weakness but no fasciculation in her tongue. In her hands, there was atrophy and weakness of the first dorsal interosseus and thenar muscles, but her hypothenar muscle bulk and strength was relatively preserved. In her legs, the ankle dorsiflexors and toe extensors were moderately weak. She had normal bulk of the toe flexors, and there was no pes cavus deformity. Sensation was intact to all modalities. Tendon reflexes were normal, except the ankle reflexes, which were absent. She was ambulatory with bilateral foot drop. Otolaryngological examination demonstrated that the left vocal fold was fixed in the paramedian position due to surgery, and the right vocal fold was in the midline. Attempts at phonation resulted in ventricular fold approximation and produced a rough, breathy voice.

Clinical Findings in Affected Family Members

The age of disease onset averaged 34 years and ranged from 23 to 39 years (see Table 1). In six of nine affected family members, stridor and shortness of breath during exercise were the first and most predominant symptoms. Life expectancy had been shortened in previous generations because of respiratory complications. Three of the seven affected members had undergone either a vocal fold tie back or an arytenoidectomy on the left side to provide an adequate airway (Table 2). Hand weakness occurred after the symptoms of vocal fold paresis in most patients (see Table 1). The weakness invariably involved the thenar more than the hypothenar muscles. Affected family members also experienced development of other bulbar problems, including facial weakness, dysphagia, and dysarthria. Bulbar and hand weakness was usually followed several years later by mild-to-moderate weakness in the distal lower extremities. Older patients had steppage gait, but none became wheelchair bound. The affected individuals did not experience development of sensory loss or upper motor neuron involvement. The severity of the disease manifestations in patients of the same age was similar.

Fiberoptic video-nasolaryngoscopy in those family members who had not had laryngeal surgery showed either a symmetric reduction in vocal fold abduction or a vocal fold abduction deficit greater on the left than the right side (Fig 2; see Table 2). The three patients who had undergone laryngeal surgery had a constant glottic gap on laryngoscopic examination and a severely breathy voice. A fourth subject (III-6) had a less than 2mm gap on examination and

subsequently underwent an arytenoidectomy. All unaffected family members had normal vocal fold movements.

On electrophysiological study, all family members had normal sensory nerve responses and normal motor nerve conduction velocities. The amplitude of the motor response from the thenar muscles was markedly reduced or absent in all five affected members, but response amplitudes from the hypothenar muscles were normal or minimally reduced (Table 3). Four patients had reduced amplitudes of peroneal innervated foot muscles, but these responses were always greater than the responses from the thenar muscles. Phrenic nerve responses were normal in all patients (see Table 3). Electrophysiological studies were normal in the three unaffected family members who were evaluated. Quantitative sensory testing showed normal thresholds for vibration and cold detection in two unaffected and two affected family members.

In all affected family members, needle EMG was consistent with chronic denervation. In the limbs, there were scattered fibrillations in distal muscles; high-amplitude, long-duration motor unit potentials in proximal and distal muscles; and reduced recruitment by qualitative and quantitative measures. No fibrillations were observed in the facial muscles, but motor unit durations were mildly increased, with reduced recruitment. Complex repetitive discharges were present in a number of muscles, but fasciculations were rare. Laryngeal EMG in the proband (III-12) during quiet respiration showed positive sharp waves and complex repetitive discharges in the thyroarytenoid muscles bilaterally. On attempts at phonation, only sparse, large motor unit firings were seen.

Epidermal nerve fiber density was in the reference range in skin biopsies from two affected (III-5 and III-12, aged 56 and 57 years, respectively, at biopsy) and two unaffected family members (III-14 and IV-7, aged 54 and 29 years, respectively, at biopsy). The mean number of axonal swellings per millimeter²⁰ was increased in affected family members, 6.2 and 6.1 at the foot and 3.3 and 5.4 at the calf, compared with unaffected family members, 1.7 and 1.8 at the foot and 0.8 and 0.7 at the calf. Affected patients also showed an increased number of basement membrane fibers that coursed horizontally along the dermal-epidermal surface instead of vertically (crawlers). The mean number of crawlers was 3.8 and 4.6 at the foot and 4.9 and 4.7 in the calf in affected patients compared with 0.8 and 0.6 at the foot and 2.6 and 1.0 at the calf in unaffected patients.

Additional testing included brain MRI on Patient III-5, which was normal, and on Patient II-2, which showed age-related changes. Brainstem auditory-evoked potentials were normal in two patients (III-5 and III-7), and median nerve somatosensory-evoked potentials were normal in three patients (III-5, III-7, and II-2). Results of muscle biopsies in three patients showed evidence of fiber-type grouping of types I and II.

Neuropathology

Gross examination results of the neocortex, brainstem, cerebellum, and spinal cord were normal. Microscopic examination showed a normal number and appearance of neurons in the occipital cortex, temporal lobe, hippocampus, entorhinal cortex, basal forebrain, putamen, thalamus, internal capsule, and cerebellum. Hematoxylin and eosin–stained sections from the medulla and cervical spinal cord showed loss of motor neurons in the hypoglossal nuclei (Fig 3A) and ventral horn. Although approximately half of the remaining motor neurons appeared normal, neighboring motor neurons were abnormally reduced in size or had a swollen, ballooned appearance (see Fig 3A). Some neurons had eccentric placement of the nucleus with loss of Nissl substance. Silver stains of patient sections demonstrated a loss of neuronal processes in the hypoglossal nucleus. Other neuronal populations within the medulla appeared normal.

Immunohistochemistry for neurofilament with SMI 32 showed abundant diffuse staining of neurofilaments in neuronal cell bodies and axons in the control sections (see Fig 3D). In patient sections, SMI 32 staining highlighted the substantial axonal and neuronal loss in the hypoglossal nucleus (see Fig 3C), but no alteration in the distribution of neurofilament staining was seen in remaining motor neurons. Staining with antibodies to the p50 subunit of dynactin, dynamitin, and the intermediate chain subunit of dynein, DIC, showed diffuse, fine granular staining of neuronal cell body cytoplasm, dendrites, and axons in neurons throughout the medulla (see Figs 3F, H). In patient sections, there was a redistribution of dynactin and dynein staining in approximately half of the hypoglossal neurons. In some of these neurons, dynactin and dynein staining showed more intense staining and coarser and more irregularly shaped granules. In other neurons, larger, inclusion-like particles were evident (see Figs 3E, G). Accumulations of dynactin and dynein were seen in the neuronal cell body, proximal axon, and more distal neurites. Neighboring neuronal populations, including neurons of the dorsal motor nucleus of the vagus, showed no abnormality in the distribution of dynactin and dynein.

Discussion

Mutation of the motor protein dynactin is associated with a motor neuron disease that has unique clinical and electrophysiological characteristics. The symptoms begin in the second and third decades of life and progress slowly. Most patients' initial symptom is stridor resulting from vocal fold paresis, then later hand weakness, and finally distal leg weakness. Electrophysiological studies confirm preferential involvement of distinct motor neuron populations. The motor neurons that innervate the vocal folds are severely affected, whereas those that innervate the diaphragm are spared. Similarly, the motor neurons that innervate the thenar muscles are more affected than those innervating the hypothenar and peroneal muscles. This is a distinctive clinical and electrophysiological pattern not seen in other disorders.

Vocal fold paresis may be overlooked during a typical neurological evaluation. Some disorders with laryngeal paralysis involve primarily abductor (opening) muscles leading to potentially life-threatening airway obstruction,^{21,22} whereas others affect mainly adductor (closing) muscles, leading to a breathy voice and risk for aspiration.^{23,24} When vocal fold paralysis occurs with a length-dependent axonal neuropathy, the left vocal fold usually is affected initially,^{25,26} because of the greater length of the left recurrent laryngeal nerve.²⁷ In this family, stridor was the presenting symptom, indicating bilateral abductor paralysis.^{28–30} This opening defect restricted air intake during exercise, and as the paresis progressed, the vocal folds were sucked into the glottis on inspiration, causing obstruction. Denervation of the thyroarytenoid muscles, however, indicates that there is also adductor muscle involvement in this disorder. The proband's first symptom of aspiration on swallowing was likely caused by difficulties with rapid and complete laryngeal closure.

Vocal fold paresis is a prominent feature in some forms of distal spinal muscular atrophy and hereditary motor and sensory neuropathy; however, these are clinically distinct from the disorder we describe in this report. In distal spinal muscular atrophy with vocal fold paralysis, linked to chromosome 2q14,^{31,32} hand weakness begins in the first or second decade of life. This is coincident with or followed by unilateral more often than bilateral vocal fold paresis and no other bulbar involvement. In Charcot–Marie–Tooth disease (CMT) type 2C, linked to chromosome 12q23–24,³³ involvement of the recurrent laryngeal nerves is accompanied by involvement of the phrenic nerve causing life-threatening respiratory insufficiency in the first or second decade of life.²⁶ In CMT type 4A, which is caused by mutation in the gene encoding the ganglioside-induced, differentiation-associated protein 1,^{34–36} weakness begins in the feet and hands in the first decade of life with only some patients experiencing vocal fold paralysis in the second decade of life. Patients with CMT types 2C and 4A also have clinical evidence of sensory nerve involvement. Our patients had no clinical or electrophysiological

evidence of sensory nerve involvement; however, skin biopsy results showed mild morphological abnormalities of epidermal nerve axons, indicating that sensory nerves may not be completely spared in this disorder.

The unusual motor neuron disease described here is associated with a point mutation in the CAP-Gly motif of p150^{Glued}, the largest subunit of dynactin.⁸ The dynein–dynactin microtubule motor complex has multiple functions in cells, including endoplasmic reticulum to Golgi vesicular transport, neurofilament transport, messenger RNA localization, and mitotic spindle assembly.³⁷ In neurons, the dynein–dynactin complex is the major motor that mediates the retrograde axonal transport of vesicles and organelles along microtubules. The mutation in this family impairs dynactin's ability to bind to microtubules⁸ and is predicted to lead to slower or less effective retrograde transport. Motor neuron survival is dependent on neurotrophic factors that are transported retrogradely from muscle to the neuroal cell body.³⁸ Motor neuron degeneration in this family could result from a shortage of trophic factors. Alternatively, slow transport could lead to accumulation of cargo and “axonal strangulation” with congested transport along axons in both directions.

Recently, three other mutations in the dynactin p150^{Glued} gene have been described in patients who carry a diagnosis of amyotrophic lateral sclerosis.³⁹ It is not yet clear whether these mutations are disease causing; however, an increasing number of neurological disorders have now been associated with mutations in the microtubule motor proteins, including the kinesins, resulting in neuropathy and hereditary spastic paraparesis.³⁷ This strongly suggests that impairment of axonal transport alone might be sufficient to cause neuronal dysfunction and death. However, we found striking accumulations of the dynactin–dynein complex in the hypoglossal motor neuron cell bodies and neurites. Accumulations in the cell bodies could be because of inefficient export (anterograde transport) of the complex from the perikaryon or enhanced, mis-regulated retrograde transport. The accumulated dynein and dynactin is reminiscent of the inclusions of misfolded proteins seen in other neurodegenerative disorders.⁴⁰ Neurofilament was not present in the inclusions; it remains to be determined whether other proteins are sequestered. Neuronal inclusions may contain aggregates of misfolded protein that are inefficiently cleared by the ubiquitin–proteasome system. It has been debated whether inclusions are directly toxic to neurons or form as a protective response of the cell to manage accumulating, misfolded protein. Further investigations are needed to determine whether motor neuron degeneration caused by dynactin mutation occurs primarily because of a loss of function of the normal protein or a toxic gain of function, or both.

In conclusion, the distal spinal and bulbar muscular atrophy with vocal fold paralysis described in this report is a late-onset, slowly progressive syndrome that is quite distinct from other motor neuron disorders and sensorimotor neuropathies that have vocal fold involvement. Neuropathologically, there are inclusions of the dynactin–dynein complex proteins within motor neurons, suggesting that this disorder is a proteinopathy that might have a common mechanism with other neurodegenerative diseases.

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Fig 1.
Solid symbols represent the clinically affected family members. Members of the fourth generation (IV) may be too young to manifest symptoms.

Fig 2.

Laryngeal video images of an unaffected family member (unaffected) and three affected family members (who had not undergone laryngeal surgery) during deep inspiration (top row) and during phonation (bottom row). All images were recorded with flexible fiberoptic nasoendoscopy. All affected family members had reduced vocal fold abduction bilaterally during inspiration.

Fig 3.

Photomicrographs of medulla sections in the region of the hypoglossal nucleus from an affected family member (A, C, E, and G) and from a control subject without neurological disease (B, D, F, and H). Hematoxylin and eosin stains show a severe reduction of hypoglossal motor neurons in the patient (A) compared with the control subject (B). Approximately half of the remaining motor neurons in the patient appear healthy; however, other neurons are fragmented or show an abnormal ballooned appearance. SMI 32 immunostaining for neurofilament also shows loss of motor neuron cell body density, as well as severe loss of axons, in the patient (C) compared with the control subject (D). Dynactin p50 subunit immunostaining shows diffuse staining of neuronal cell bodies and processes in the control subject (F), but

accumulation of dynactin into inclusions in the cytoplasm of an enlarged motor neuron in the patient (E). Dynein immunostaining also shows inclusions in the cell bodies of some motor neurons in the patient (G). Calibration bars = 200 μ m (A–D) and 100 μ m (E–H).

Table 1

Neurological Symptoms and Signs in Affected Family Members

Patient No.	Age (yr)	Sex	Age at Onset (yr)	First Symptom	Facial Weakness	Arm Weakness		Leg Weakness		Reflexes (arm/leg) ^a	Sensory Signs
						Proximal	Distal	Proximal	Distal		
II.2	64	F	44	Hand Weakness	Mild	Mild	Severe	Mild	Severe	0/0	None
II.4	49	M	35	Stridor	Mild	Mild	Moderate	Mild	Moderate	2/2	None
III.1	60	F	38	Hand Weakness	Moderate	None	Severe	None	Severe	2/2	None
III.5	53	F	32	Stridor	Moderate	Mild	Severe	None	Severe	0/0-1	None
III.6	43	F	33	Stridor	Mild	None	Moderate	None	Moderate	2/2	None
III.7	54	F	37	Stridor	Moderate	Mild	Moderate	None	Mild	2/2	None
III.9	46	M	39	Stridor	Moderate	None	Moderate	None	Mild	2/2	None
III.12	54	F	23	Dysphagia	Mild	Mild	Severe	None	Moderate	2/0-2	None
IV.1	39	F	28	Stridor	Mild	None	Moderate	None	Mild	2/2	None

^a 2 is normal, 1 is decreased, 0 is absent.

Table 2
Laryngeal Symptoms and Movement Abnormalities in Affected Family Members

Patient No.	Dyspnea	Aspiration	Dysphonia	Vocal Fold Adduction		Vocal Fold Abduction		Comments
				Left	Right	Left	Right	
III.1	^a +	+	^b +	2	2	2	1	Left arytenoidectomy
III.5	^a +	+	^b +	2	2	2	2	Left arytenoidectomy
III.6	+	-	+	1.5	1.5	2	2	Stridor at rest, high-pitched voice
III.7	+	-	+	2	1	2	1	Stridor, husky voice, left vocal fold atrophy
III.9	+	+	+	1.5	1.5	1.5	1.5	False fold adduction, left vocal cord atrophy
III.12	+	+	^b +	2	2	2	2	Left vocal fold tie back procedure
IV.1	+	-	+	2	1	2	1	False fold adduction, left vocal fold atrophy

Vocal fold movement: 0 = normal, 1 = impaired mobility, 2 = immobile.

^a Improved after surgery.

^b Postoperative sequella.

Table 3

Nerve Conduction Study Findings

Patient No.	Median		Ulnar		Phenic	
	SNAP Amplitude (uV)	APB CMAP Amplitude (mV)	SNAP Amplitude (uV)	ADM CMAP Amplitude (mV)	Sural, SNAP Amplitude (uV)	Peroneal, EDB CMAP Amplitude (mV)
III.1	45	nd	32	8.3	6	2.4
III.5	12 ^a	NR	22	3.1	14	0.2
III.6	28	2.4	33	8.9	21	3.7
III.7	16 ^a	0.9	25	8.3	9	1.4
III.12	33	NR	38	5.5	11	1.7
Laboratory norms	>14	>4.4	>14	>4.5	>5	>2.4
						>0.2
						0.9
						0.2
						0.5
						0.6
						0.7
						0.4
						0.4
						0.5
						>0.2

^aReduced velocity across the carpal tunnel, with normal proximal conduction velocity.

NR = no response; SNAP = sensory nerve action potential; CMAP = compounds motor action potential; APB = abductor pollicis longus; ADM = abductor digiti minimi; EDB = extensor digitorum brevis; ND = Not done, marked thenar atrophy.