

FINGER EXTENSION WEAKNESS AND DOWNBEAT NYSTAGMUS MOTOR NEURON DISEASE SYNDROME: A NOVEL MOTOR NEURON DISORDER?

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Received 3 December 2016; Revised 26 March 2017; Accepted 17 April 2017

ABSTRACT: *Introduction:* Disturbances of eye movements are infrequently encountered in motor neuron diseases (MNDs) or motor neuropathies, and there is no known syndrome that combines progressive muscle weakness with downbeat nystagmus. *Methods:* To describe the core clinical features of a syndrome of MND associated with downbeat nystagmus, clinical features were collected from 6 patients. *Results:* All patients had slowly progressive muscle weakness and wasting in combination with downbeat nystagmus, which was clinically most obvious in downward and lateral gaze. Onset was in the second to fourth decade with finger extension weakness, progressing to other distal and sometimes more proximal muscles. Visual complaints

were not always present. Electrodiagnostic testing showed signs of regional motor axonal loss in all patients. *Discussion:* The etiology of this syndrome remains elusive. Because finger extension weakness and downbeat nystagmus are the discriminating clinical features of this MND, we propose the name *FEWDON-MND syndrome*.

Muscle Nerve 56: 1164–1168, 2017

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Abbreviations: ALS, amyotrophic lateral sclerosis; ANA, antinuclear antigen; CSF, cerebrospinal fluid; dHMN, distal hereditary motor neuropathy; FEWDON-MND syndrome, finger extensor weakness and downbeat nystagmus motor neuron disease syndrome; GAD, glutamic acid decarboxylase; MMN, multifocal motor neuropathy; MND, motor neuron disorder; SMA, spinomuscular atrophy; VOR, vestibulo-ocular reflex

Key words: downbeat nystagmus; FEWDON-MND; muscle wasting; motor neuron disease; finger extension

Funding: This work was supported by the Interuniversity Attraction Poles of the Belgian Federal Science Policy Office (program P7/16), the Flemish Fund for Scientific Research (FWO-Vlaanderen) under the frame of E-RARE-2, the ERA-Net for Research on Rare Diseases (PYRAMID), and by an EU Joint Programme - Neurodegenerative Disease Research (JPND) project (STRENGTH). P. Van Damme is a senior clinical investigator of the FWO-Vlaanderen and is supported by the Belgian ALS Liga. K. Poesen is supported by a start-up grant from the Group of Biomedical Sciences KU Leuven and by the clinical research fund of University Hospitals Leuven. R. Saunders-Pullman received support from the National Institute of Neurological Disorders and Stroke (grant No. K02 NS073836), the National Institutes of Health (grant No. 1U01NS094148-01), the Bigglesworth Foundation, and the Michael J. Fox Foundation for Parkinson's Research. I. A. Meijer is supported by a grant from the American Academy of Neurology Clinical Research Scholarship.

Conflicts of Interest: The authors report no financial conflicts of interest.

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Published online 25 April 2017 in Wiley Online Library (wileyonlinelibrary.com).
DOI 10.1002/mus.25669

Disturbances of eye movements are rarely encountered in motor neuron diseases (MNDs) or motor neuropathies.^{1–3} Limited upgaze, saccadic intrusions, and slow saccades have been reported, most commonly seen in MND patients with bulbar onset or frontal impairment.^{4–9} Nystagmus is extremely rare in MNDs.^{4,10} In 2006, we first reported 3 cases with the exceptional combination of a motor neuron syndrome and downbeat nystagmus.¹¹ Here we describe 3 additional cases with the same condition and provide follow-up information on the previously reported cases, confirming that this is a novel clinical disease entity, an MND with distal upper extremity extensor muscle weakness and downbeat nystagmus.

METHODS

A retrospective chart review was performed on the identified cases. Clinical parameters and the results of investigations were collected and analyzed. The study was approved by institutional ethics committees, and the patients provided written informed consent.

RESULTS

Detailed descriptions of the clinical presentations and the results of investigations of 3 novel patients and follow-up information on 2 of the 3 earlier reported patients¹¹ are given in the Supporting Information online. The combination of a slowly

progressive motor syndrome with prominent early finger extensor weakness and the eventual development of downbeat nystagmus characterize this syndrome. The core clinical characteristics and investigation results of the 6 patients are presented in Table 1.

The age at onset was during adolescence or early adulthood in all patients. All patients presented with unilateral finger extension paresis, slowly spreading to other muscle groups in the arms but also with progression to the legs. Over time, all patients developed gait difficulties, with reduced stability during walking. Over more than 30 years of follow-up, none of the patients experienced functionally important bulbar or respiratory involvement, pseudobulbar affect, or cognitive impairment.

Symptoms were always purely motor; none of the patients reported sensory symptoms or pain. Disease progression was slow in all patients. All patients with current follow-up information (5/6) were still alive after a disease duration ranging from 3 to 43 years. Family history was negative for MNDs in all patients.

Ocular manifestations of the syndrome were asymptomatic or absent in early disease stages in 3/6 patients. The other 3 patients noticed oscillopsia or mild diplopia, which coincided with the onset of muscle weakness. After a disease duration ranging from less than 1 year to 7 years, 5/6 patients reported visual symptoms, and only 1 patient remained asymptomatic. The most distinctive feature of the disease was downbeat nystagmus in all patients (see Supporting Information video). Most accompanying oculomotor findings were also attributable to cerebellar dysfunction and included skew deviation, comitant esophoria, saccadic dysmetria, abnormal smooth pursuit, impaired suppression of the vestibulo-ocular reflex (VOR), and gaze-evoked nystagmus. Less localizing was the presence of excessive saccadic intrusions in 2 patients.

Muscle weakness was most pronounced in distal arm and leg muscles, with extensor muscles generally more affected than flexor muscles. In 4 patients, the disease progressed to involve proximal musculature as well. The weakest muscles were usually atrophic with visible fasciculations, suggesting lower motor neuron involvement. Many patients had brisk reflexes at least in some body regions, sometimes with a slight increase in muscle tone, but manifest upper motor neuron involvement with spasticity or extensor plantar responses was not encountered. No signs of upper or lower motor neuron involvement were seen in the bulbar region except for patient 3 with tongue fasciculations. Results of the sensory exam were normal for all patients. There was no truncal or appendicular ataxia.

Electrodiagnostic testing confirmed lower motor neuron involvement, with signs of denervation (pos-

itive sharp waves and fibrillation potentials) and fasciculation potentials, in combination with signs of reinnervation (large amplitude-long duration motor unit potentials with reduced recruitment) in multiple regions.

Eye movement recordings were performed in 3 patients. Downbeat nystagmus was confirmed in all patients. Other clinical findings are detailed in Table 1.

Laboratory investigations did not reveal consistent abnormalities. Aside from variably increased antinuclear antigen (ANA) titers in 3 patients, low level of antiglutamic acid decarboxylase (GAD) and antigliadin antibodies in 1 patient, and antithyroglobulin/thyroperoxidase antibodies in another patient, autoimmune screening results were normal. Genetic testing for spinal muscular atrophy (SMA; assessing *SMN1*), amyotrophic lateral sclerosis (ALS; assessing *C9ORF72*, *superoxide dismutase 1*, *TAR DNA-binding protein 43*, *fused in sarcoma*, *senataxin*), Kennedy disease, and episodic ataxia type 2 (each performed in some of the patients) did not reveal pathogenic mutations.

Cerebrospinal fluid (CSF) was normal in each of 4 patients in whom it was tested, without evidence of pleocytosis, elevated protein, or intrathecal antibody synthesis. In 1 patient, CSF neurofilaments (phospho-neurofilament heavy and neurofilament light chain) were measured and were below the cutoff for ALS.¹²

Results of MRI of the brain were normal in 3 patients (Table 1). Fluorodeoxyglucose-positron emission tomography was performed in 1 patient, revealing mild hypometabolism in the motor cortex, as can be seen in ALS.^{13–15} A trial with plasma exchange (patient 1) and intravenous immunoglobulins (patient 2) did not alter the disease course.

DISCUSSION

We describe a novel motor syndrome, characterized by progressive muscle weakness with onset in finger extensor muscles and a downbeat nystagmus. In published reports of series of patients with downbeat nystagmus, a concomitant motor syndrome is not mentioned.^{16,17} As an acronym that captures the core clinical features for finger extensor weakness and downbeat nystagmus motor neuron disease, we suggest *FEWDON-MND syndrome*. With only 6 reported patients to date, the incidence is anticipated to be low. However, increased awareness of this clinical disease entity may lead to identification of additional patients and research into its pathophysiology.

The differential diagnosis of FEWDON-MND syndrome is broad. The initial diagnoses included ALS, SMA, multifocal motor neuropathy (MMN), and distal hereditary motor neuropathy (dHMN). MNDs or motor neuropathies often have onset in the distal upper extremities. However, onset with

Table 1. Demographic and clinical characteristics of patients with FEWDON-MND syndrome

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Sex	W	M	W	W	W	M
Age at onset (years)	23	37	30	16	38	40
Duration of disease at last follow-up (years)	3	29	16	43	21	8
Finger extension weakness	+	+	+	+	+	+
Other areas of weakness (always less obvious than the finger extension weakness)	Elbow and wrist flexors, wrist extensors, hip flexors	Neck flexors and extensors, wrist and hand flexors and extensors, finger flexors	Arm abductors and extensors, wrist extensors, finger flexors and abductors, hip flexors and extensors, foot extensors	Wrist extensor, leg muscles	Wrist and elbow extensors	Wrist extensors, shoulder girdle muscles
Deep tendon reflexes	Brisk in UL and LL	Absent in UL, brisk in LL	Brisk in LL	Normal in UL, reduced in LL	Brisk in UL and LL	Absent in UL and reduced in LL
Unsteady gait	+	-	+	-	+	-
Muscle cramps	-	+	+	+	+	-
Downbeat nystagmus	+	+	+	+	+	+
CSF examination	Normal	NP	Normal	Normal	Normal	NP
ANA (titer)	Negative	Negative	Negative	Positive (1:40)	Positive (1:640)	Positive (1:40)
Anti GAD antibodies	Negative	Negative	Negative	Positive	Negative	NP
MRI brain	Normal	Normal	Normal	Nonspecific white matter lesions	Mild cerebral and cerebellar atrophy	Nonspecific white matter lesions
EMG: positive sharp waves or fibrillation potentials	1 region (cervical)	1 region (cervical)	2 regions (cervical, thoracic)	2 regions (cervical, lumbosacral)	2 regions (cervical, thoracic)	1 region (cervical)
Quantitative analysis of eye movements	Downbeat nystagmus, impaired smooth pursuit, VOR suppression, OKN with saccadic intrusions	NP	NP	Downbeat nystagmus, alternating skew deviation	Downbeat nystagmus, bursts of horizontal saccadic oscillations, impaired smooth pursuit	NP
Initial diagnosis	ALS	MMN, ALS	ALS	SMA	dHMN	MND

+, present; -, absent; ALS amyotrophic lateral sclerosis; ANA, antinuclear antigen; GAD, glutamic acid decarboxylase; CSF, cerebrospinal fluid; dHMN, distal hereditary motor neuropathy; EMG, electromyography; FEWDON-MND syndrome, finger extensor weakness and downbeat nystagmus syndrome; LL, lower limb; M, man; MMN, multifocal motor neuropathy; MND, motor neuron disease; NP, not performed; OKN, optokinetic nystagmus; SMA, spinotomuscular atrophy; UL, upper limb; VOR, vestibulo-ocular reflex; W, woman

finger and wrist extensor muscle weakness is not frequent. MMN can start with finger extension weakness¹⁸; however, none of the patients had signs of demyelination on electrodiagnostic testing or positive monosialotetrahexosylganglioside (GM1) antibodies. Low-titer GAD antibodies were found in 1 patient. GAD antibodies can present with ataxia or eye movement disorders, including downbeat nystagmus. However, in 5 of our patients, those antibodies were negative. In addition, muscle paresis is not described in patients with GAD antibodies.¹⁹

Downbeat nystagmus has not been reported in the setting of MND.^{20,21} Although downbeat nystagmus is at times clinically obvious, its presence may be more subtle. By definition, it should be present in central fixation; however, as was seen in all of our patients, it is enhanced and most clinically obvious in downward and lateral gaze (so-called “side-pocket” nystagmus).³ Provocative maneuvers such as horizontal and vertical head shaking, hyperventilation, and supine and supine head-hanging positions^{22–25} can increase the sensitivity of detection of downbeat nystagmus.

Several mechanisms related to impairment of the cerebellum or its inputs have been shown to result in downbeat nystagmus. These include asymmetry of vertical VOR, dysfunction of otolith-ocular reflex regulation, altered vestibulocerebellar or neural integrator function, and impaired smooth pursuit.³ They are not mutually exclusive and several may be involved, even in an individual patient. The gravitational dependence of the downbeat nystagmus in our patient 3 suggests a component of impairment of otolith-ocular reflexes in this patient,²² although it is clear that additional characterization of the downbeat nystagmus in this condition is required.

The etiology of FEWDON-MND syndrome remains unknown. We believe that infectious or postinfectious mechanisms, nutritional deficiency, intoxication, neoplastic or paraneoplastic mechanisms, and central nervous manifestation of internal organ dysfunction are unlikely. An immune-mediated or genetic origin seems most likely at this stage. Over the past decade, several neuroimmunological diseases linked to autoantibodies against neuronal proteins have been identified.²⁶ Whether FEWDON-MND syndrome is a neuroimmunological condition remains unknown. Arguments favoring this hypothesis are the presence of elevated ANA titers, GAD antibodies, antigliadin, and antithyroglobulin/thyropoxidase antibodies in some patients. Ataxia associated with GAD antibodies can present with downbeat nystagmus.¹⁹ However, these antibodies were present in only 1

patient in low titer, and none of the patients with FEWDON-MND syndrome had ataxia.

No support for an autoimmune hypothesis was found by examination of CSF. In addition, therapeutic trials with immune-modulating therapies, such as intravenous immunoglobulins or plasma exchange, did not affect the disease course.

A genetic origin of FEWDON-MND syndrome is also possible. Family history was negative for disease for all patients, but this would still be compatible with an autosomal recessive inheritance pattern with a rare carrier frequency or with sporadic or *de novo* mutations. Next-generation sequencing efforts on DNA samples from the patients and their parents are underway to explore a putative genetic cause.

The authors thank Professor R. John Leigh for his valuable contributions to the description of the ocular manifestations of this syndrome and the patients for their cooperation in this study.

Ethical Publication Statement: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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QUANTITATIVE ELECTROMYOGRAPHY IN AMBULATORY BOYS WITH DUCHENNE MUSCULAR DYSTROPHY

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Accepted 24 April 2017

ABSTRACT: *Introduction:* This study's objective was to evaluate quantitative electromyography (QEMG) using multiple-motor-unit (multi-MUP) analysis in Duchenne muscular dystrophy (DMD). *Methods:* Ambulatory DMD boys, aged 5–15 years, were evaluated with QEMG at 6-month intervals over 14 months. EMG was performed in the right biceps brachii (BB) and tibialis anterior (TA) muscles. Normative QEMG data were obtained from age-matched healthy boys. Wilcoxon signed-rank tests were performed. *Results:* Eighteen DMD subjects were enrolled, with a median age of 7 (interquartile range 7–10) years. Six-month evaluations were performed on 14 subjects. QEMG showed significantly abnormal mean MUP duration in BB and TA muscles, with no significant change over 6 months. *Discussion:* QEMG is a sensitive electrophysiological marker of myopathy in DMD. Preliminary data do not reflect a significant change in MUP parameters over a 6-month interval; long-term follow-up QEMG studies are needed to understand its role as a biomarker for disease progression.

Muscle Nerve 56: 1168–1171, 2017

Motor strength in boys with Duchenne muscular dystrophy (DMD) has been monitored using the 6-minute walk test (6MWT), North Star Ambulatory Assessment (NSAA), Brooke upper extremity scale, and Vignos lower extremity scale.^{1,2} These functional

test results can be influenced by the subject's age, weight, height, motivation, cardiopulmonary status, and the examiner's encouragement/coaching.^{3–5} Objective measures of muscle strength independent of these factors would be useful to assess and monitor myopathy in young DMD boys. Quantitative electromyography [QEMG; i.e., multiple-motor-unit (multi-MUP) analysis] is one such objective measure of muscle fiber function and has been used to study inflammatory myopathies and muscular dystrophies.^{6–9} The objective of this study was to utilize the QEMG technique in ambulatory DMD boys to determine the extent and progression of myopathy.

METHODS

This study was conducted at the pediatric neuromuscular clinics of a tertiary care children's hospital from January 2015 to March 2016. Ambulatory boys, 5–15 years of age, with a genetic confirmation of DMD and receiving standard-of-care treatment, were included as study participants. The exclusion criterion was contraindication for needle EMG. Subjects were evaluated 6 months apart with QEMG and functional scores (6MWT, NSAA, and Brooke and Vignos scales). Age-matched boys seen in the pediatric EMG laboratory for suspected neuromuscular weakness with normal motor and NCS/EMG examination acted as controls. Written consent and assent were obtained from all research subjects. The study was approved by the local institutional review board (IRB #00078677).

EMG was performed using a Nicolet EDx system and Synergy software program (Natus

Additional supporting information may be found in the online version of this article.

Abbreviations: 6MWT, 6-minute walk test; BB, biceps brachii; CK, creatine kinase; DMD, Duchenne muscular dystrophy; EMG, electromyography; IQR, interquartile range; MUP, motor unit potential; NSAA, North Star Ambulatory Assessment; QEMG, quantitative electromyography; TA, tibialis anterior

Key words: 6-minute walk test; Duchenne muscular dystrophy; multi-MUP analysis; myopathy; North Star Ambulatory Assessment; quantitative EMG

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© 2017 Wiley Periodicals, Inc.
Published online 29 April 2017 in Wiley Online Library (wileyonlinelibrary.com).
DOI 10.1002/mus.25678