

A report on paraneoplastic motor neuron disease

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To the Editor: Motor neuron disease (MND) is marked by upper (UMN) or lower (LMN) motor neuron signs and symptoms,^[1] which in various combinations form the basis for MND classification. In this regard, amyotrophic lateral sclerosis (ALS) is the most common subtype.^[2] Although otherwise deemed an untreatable degenerative disease, there is now increasing evidence of more heterogeneous pathogenesis, signaling a link between MND and paraneoplastic syndromes.^[3]

Paraneoplastic neurologic syndromes (PNSs) are remote expressions of malignancy due primarily to autoimmune reactions.^[4] However, MND is viewed as a non-classical PNS.^[5] According to criteria developed by Graus *et al*^[5] at least one of three conditions must be met for justifiable categorization as a non-classical PNS: (1) post-therapeutic abatement of culprit neurologic manifestations, in the absence of immune modulation; (2) well-characterized onconeural antibodies; or (3) partially characterized onconeural antibodies and malignancy presenting within 5 years after onset of neurologic abnormalities.^[5]

The MND as a variant of PNS is rarely encountered. Related publications largely consist of case reports, singly or in limited series. In reporting nine new cases, we endeavored to detail the clinical circumstances and therapeutic responses of this unusual illness. Inpatients diagnosed with MND at our facility between February 1982 and April 2018 were reviewed in retrospect, finding only nine who clearly met PNS criteria. Each diagnosis of MND was established by a qualified specialist. LMN and UMN defects were documented by physical examinations, using electrophysiologic tests to pinpoint LMN deficits and applying Awaji criteria in instances of ALS.^[6] Adhering to Chinese diagnostic guidelines for ALS, we performed needle electromyography (EMG) in four bodily regions (bulbar, cervical, thoracic, and lumbosacral) as warranted. Motor and sensory nerve conduction studies, as well as F-wave examinations, focused on at least two nerves of upper (UL) and lower (LL) limbs, respectively.^[7]

Additional testing, including various laboratory diagnostics (eg, anti-GM1, anti-GD1b, anti-GQ1b antibodies, and serum protein electrophoresis) and radiologic studies (cranial and spinal magnetic resonance imaging [MRI]), was also undertaken to exclude other similar disorders, such as multifocal motor neuropathy, acute motor axonal neuropathy, and chronic inflammatory demyelinating polyneuropathy. PNS was diagnosed in accord with Graus criteria.^[5] All patients with potential paraneoplastic MND underwent appropriate antibody profiling, thorough screening for malignancy, and diligent follow-up monitoring, in addition to comprehensive laboratory workups ruling out possible infection, nutritional deficits, intoxication, or endocrine abnormalities.

Among 1129 inpatients diagnosed with MND at our hospital during the aforementioned period, only nine unequivocally met the stipulated PNS requirements. Subtypes of MND manifested and corresponding clinical characteristics are listed in Table 1. The average age at symptom onset was 55.1 years (range, 32–70 years). Initially, upper limbs were involved in three patients, lower limbs in four patients, and four limbs in two patients. Five patients developed both LMN and UMN symptoms, whereas three patients displayed LMN deficits primarily. Weakness was confined to distal ULs in Patient 7 and LLs in Patient 8. The others showed diminished muscle strength in all four limbs, and symptoms tended to be asymmetric. At least three patients demonstrated bulbar paralysis. Aside from prominent ataxia in Patient 5, neurologic symptoms other than motor neuron dysfunction (ie, sensory abnormalities, cognitive impairment, or autonomic dysfunction) were not evident in these patients.

Electrophysiologic examinations in eight patients showed denervation in differing muscle territories, which was widespread (ie, at least three bodily regions involved) in six patients. Action potential amplitudes, as well as conduction velocities of the motor and sensory fibers, were normal for all patients. Cranial and spinal MRI studies were performed in all patients and showed a decreased thoracic

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Table 1: Clinical characteristics of patients with paraneoplastic MND (N=9).

Patient no.	Age (years)/ sex	Onset to diagnosis interval (months)	Neurologic symptoms	Electro physiologic presentation	Anti-neuronal antibody	CSF	Other systemic abnormalities	Tumor	Type of MND	Treatment	Follow-up
1	59/F	5	Asymmetric weakness of four limbs, UMN symptoms +	Widespread denervation	Anti-Yo	Pro 0.43 g/L, OB+	Breast nodule (BI-RADS grade 3-4, hypermetabolic by PET-CT)	None	Clinically definite ALS	Refused	Worsening weakness, death from respiratory failure/ 14 months
2	55/M	48	Asymmetric weakness of four limbs, dysphagia, UMN symptoms +	Widespread denervation	Anti-Yo	Normal		None	Clinically definite ALS	Refused	Exacerbation of weakness and dysphagia, death from aspiration and airway obstruction/ 20 months
3	70/M	6	Symmetric weakness of four limbs, UMN symptoms±	Denervation all four limbs	Anti-Yo	OB+, MBP 8.44 nmol/L	Fever, weight loss, elevated ESR and hsCRP	None	Clinically probable ALS/PMA	Refused	Weakness stable Fever and weight loss improved without treatment/ 46 months
4	53/F	35	Stiffness of four limbs, slight weakness of both LLs, UMN symptoms +	Widespread denervation	Anti-Hu	Normal	Probable malignant vertebral lesions on MRI, patient refused further examination	None	Clinically definite ALS	Refused	Lost to follow-up
5	64/M	4	Asymmetric weakness of four limbs, dysarthria, ataxia, UMN symptoms +	Widespread denervation	Anti-Hu	Normal		None	Clinically definite ALS	Refused	Exacerbation of weakness requiring respirator/ 18 months Death from pulmonary infection/ 87 months

(continued)

Table 1
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Patient no.	Age (years)/ sex	Onset to diagnosis interval (months)	Neurologic symptoms	Electro physiologic presentation	Anti-neuronal antibody	CSF	Other systemic abnormalities	Tumor	Type of MND	Treatment	Follow-up
6	59/F	30	Asymmetric weakness of four limbs, dysarthria, UMN symptoms +	Denervation all four limbs	Anti-Ri	MBP 4.83 nmol/L	Multiple enlarged mediastinal lymph nodes on CT, with elevation of CA24-2, Cyfra211, and TPA	None	Clinically definite ALS	Refused	Lost to follow-up
7	56/F	4	Symmetric weakness of distal ULs, UMN symptoms ±	Widespread denervation	Anti-Ma2	Normal	Rheumatoid arthritis receiving MTX	None	Clinically definite ALS/PMA	Refused	Improvement of weakness/ 63 months
8	60/M	9	Asymmetric weakness of LLS, UMN symptoms + (left UL and bilateral LLS)	Normal	Anti-Yo	Normal		None	Clinically possible ALS	Refused	Exacerbation of weakness in four limbs/ 71 months
9	32/M	3	Symmetric weakness of four limbs, UMN symptoms -	Widespread denervation, diminished F-wave persistence	None	Pro 0.93 g/L, OB+		Papillary carcinoma of thyroid	PMA	Surgery, I ¹³¹	Improvement of weakness/ 72 months

+: Diagnosis of tumor after onset of symptoms; -: Diagnosis of tumor before onset of symptom; ALS: Amyotrophic lateral sclerosis; BI-RADS: Breast imaging reporting and data system; BI-RADS; Breast Imaging Reporting and Data System; CSF: Cerebrospinal fluid; ESR: Erythrocyte sedimentation rate; hs-CRP: High-sensitivity C-reactive protein; LL: Lower limb; LMN: Lower motor neuron; MBP: Myelin basic protein; MND: Motor neuron disease; MTX: Methotrexate; OB: Oligoclonal bands (- absent, + present); PET-CT: Positron emission tomography-computed tomography; PMA: Primary muscular atrophy; Pro: Protein; TPA: Tissue polypeptide antigen; UL: Upper limb; UMN: Upper motor neuron.

spinal cord diameter in Patient 8. Abnormalities in other patients were minor and could not account for their neurologic symptoms. Cerebrospinal fluid (CSF) analysis revealed oligoclonal bands in three patients, as well as slight elevations of protein content in Patients 1 and 9. Patients 3 and 6 had abnormally high myelin basic protein (MBP) levels, but lacked any clinical or electrophysiologic evidence of prominent demyelination.

Rationales for obtaining anti-neuronal antibody panels in patients with MND were as follows: (1) imaging suggestive of potential malignancy (Patients 1, 4, 6, 7, and 9, albeit subsequent sacral biopsy in Patient 7 proved benign); (2) unexplained significant wasting (Patients 2 and 3); and (3) rapidly progressive motor neuron symptoms and widespread neural system involvement. Anti-neuronal antibodies were present in eight patients (anti-Yo, $n=4$; anti-Hu, $n=2$; anti-Ri, $n=1$; and anti-Ma2, $n=1$). All patients underwent thorough imaging and serologic examinations, and most completed positron emission tomography-computed tomography scans to screen for probable malignancy. Ultimately, malignancy was confirmed in Patient 9 only (papillary carcinoma of thyroid), although several other patients showed abnormalities suspicious of malignancy. These patients refused further diagnostic pursuits for financial reasons.

Unfortunately, immunosuppressant therapy was declined by all patients due to economic factors. Two of the nine patients were lost to follow-up, three acknowledged stable or improved weakness, and the other four proceeded to deteriorate. Final follow-up visits took place 14 to 87 months after discharge. Although Patient 9 showed significant improvement in muscle strength after tumor resection, an EMG study done 5 months after surgery showed persistent widespread denervation.

Symptoms of non-paraneoplastic MND usually start insidiously, and the course is not fulminant. The interval between symptom onset and involvement of a secondary region proved to be 17.7 months on average in an ALS cohort reported by Roche *et al*^[8]. Nevertheless, some instances of paraneoplastic MND may progress rapidly (Patients 1, 3, 5, and 9 in our series). Another distinguishing feature is the autoimmune aspect of CSF examination. These clinical features, if present, may necessitate a search for onconeural antibodies and procedures to screen for underlying malignancy. Timely and accurate diagnosis of a paraneoplastic etiology and subsequent treatment of the primary tumor may be beneficial in terms of neurologic symptomatology.

To our knowledge, this series of patients is the first in which paraneoplastic MND was associated with thyroid carcinoma. Unfortunately, immunotherapy and cancer treatment were refused by most of our patients, for whom costs were prohibitive. This preempted any observation of outcomes after therapeutic intervention. Still, we were able to witness the natural course of paraneoplastic MND. In Patients 3 and 7, weakness seemed to improve or remain stable without treatment. Spontaneous remission of PNS has been reported previously in the context of paraneoplastic mesodiencephalic and brainstem encephalitis.^[9] On

such occasions, the predisposing malignancies are perhaps eradicated through immune mechanisms.^[10]

There are certain limitations of the present study, one being inadequate knowledge of the occult malignancies harbored by these patients. Through imaging and serum examinations launched at the time of diagnosis revealed cancer in one patient only; and thereafter, such screening attempts generally lapsed. Graus *et al*^[5] have shown that in some patients with PNS and onconeural antibody positivity, no tumors were found after 3 years of follow-up. However, the latter encompassed no more than 10%.^[5] Further studies are needed to determine the means by which malignancies actually incite motor neuron symptoms.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Conflicts of interest

None.

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