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ORIGINAL COMMUNICATION

# Motor neuron disease of paraneoplastic origin: a rare but treatable condition

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## Abstract

Paraneoplastic motor neuron disorders (MND) are rare conditions; their exact clinical and electrophysiological phenotype have not been exhaustively described yet. The purpose of this study is to depict the main characteristics of paraneoplastic MND to highlight the features that may allow its diagnosis. Based on the description of eight original cases, and on the revision of 21 patients identified from a systematic review of the literature, the main features of paraneoplastic MND can be summarized as follows: (1) subacute; (2) lower motor neuron syndrome, associated or not with upper motor neuron involvement; (3) predominant asymmetric upper limb involvement; (4) presence of other non-motor neurological manifestations, including sensory neuronopathy; (5) signs of inflammation in the cerebrospinal fluid (CSF); (6) neurological improvement or stabilization after immunotherapy and tumor treatment. The diagnosis of paraneoplastic MND may be difficult because of its rarity, the absence of pathognomonic clinical features, and the frequent absence of prior tumor history. However, it is of capital importance to correctly identify patients with paraneoplastic MND, as this represents a potentially treatable condition. In the presence of subacute lower motor neuron impairment, especially when atypical clinical features for degenerative MND or other non-motor neurological manifestations are present, we recommend testing for onconeural antibodies. In the case, the search for onconeural antibodies is negative, but it exists a strong clinical suspicion for a paraneoplastic etiology; CSF analysis and total-body 18FDG-PET/CT imaging should be performed to circumstantiate diagnosis.

**Keywords** Motor neuron disease · Amyotrophic lateral sclerosis · Motor neuronopathy · Paraneoplastic neurological syndrome · Cancer

## Introduction

Motor neuron disorders (MND) are characterized by progressive impairment of lower (LMN) and/or upper (UMN) motor neurons, and include degenerative conditions such as

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amyotrophic lateral sclerosis (ALS), primary lateral sclerosis, and progressive muscular atrophy. These conditions are primarily diagnosed on clinical and neurophysiological grounds [1], after excluding non-degenerative conditions that can present with similar clinical phenotype, such as paraneoplastic neurological disorders [2–4].

Paraneoplastic neurological disorders are rare immune-mediated complications of cancer [2]. Although MND are not included among the "classical" phenotypes associated with paraneoplastic neurological syndromes, [3], a diagnosis of "definite" paraneoplastic MND is possible when well-characterized onconeural antibodies are present or when neurological improvement is observed after cancer treatment [3].

Cases of definite paraneoplastic MND have rarely been reported in the literature [5] and the description of the clinical and paraclinical phenotype associated with this condition remains incomplete. From the description of novel cases to a systematic review of the literature, the purpose of this study is to depict the main clinical and electrophysiological characteristics of paraneoplastic MND to highlight the elements that may help to distinguish these conditions from degenerative MND.

## Methods

### Case series

We performed a retrospective research in our institutional database for all patients diagnosed with "definite" paraneoplastic MND between January 2011 and January 2016. The clinical of MND was based on the evidence of UMN syndrome on clinical examination (spasticity, hyperreflexia, Babinski, or other pyramidal signs) and/or LMN impairment (muscle weakness, atrophy, cramps, and fasciculations) confirmed on electroneuromyography. The clinical and electrophysiological features of the patients with MND who matched the criteria for "definite" paraneoplastic neurological disorder [3] were collected and reviewed in detail.

### Literature review

We performed an electronic research in the MEDLINE and Embase data sets, for all papers published in English or French between 1980 and 2016, using the search terms detailed in the Appendix. We finally included, in the present study, only cases of "definite" paraneoplastic MND, [3] who had a minimal set of data available (age, sex, clinical features, and details on tumor screening). We crosschecked the reference lists of all included articles and any relevant review articles. A flow diagram of the studies that were screened, assessed for eligibility, and included in the present review was prepared according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines and is reported in Fig. 1 [6].

## Results

Out of more than 2200 patients who were diagnosed with MND at our institution during the aforementioned time period, eight patients met the criteria for "definite" paraneoplastic neurological disorder. One patient (patient no. 1) was previously reported, [7], while the remaining seven patients represent original cases. Table 1 summarizes the clinical characteristics of the eight patients in our cohort. Six (75%) patients were male and 2 (25%) patients were female. Median age at the time of symptom onset was 61 years (range 59–76). The diagnosis of "definite" paraneoplastic MND resulted from the presence of well-characterized onconeural antibodies in the bloodstream of all patients (anti-Hu, $n=7$; anti-Yo, $n=1$). Main alternative infectious (Lyme disease, enterovirus, and HIV infection) and autoimmune etiologies (sarcoidosis and Sjögren's syndrome) were excluded by appropriate testing. None of the patients had familial history of neurological disorders, and none of them had been exposed to heavy metals or chemicals.

### Neurological presentation

Five (63%) patients had pure LMN syndrome, while the remaining 3 (37%) patients had both UMN and LMN involvement. Disease onset and evolution were subacute (i.e., less than 2 months) in 7 (88%) patients. Median modified Rankin Scale at the time of neurological symptoms onset was 3 (range 1–5), and motor deficit was, in most cases, restricted to the upper limbs (63%). One (12.5%) patient had bulbar symptoms and 2 (25%) patients had diaphragmatic involvement. Besides motor impairment, four (50%) patients showed one or more additional non-motor neurological symptoms, including proprioceptive impairment ($n=3$), memory deficits and behavioral disorders reflecting limbic encephalitis ($n=1$), and cerebellar ataxia ($n=1$).

### Neurophysiological findings

Electrophysiological data are summarized in Table 2 and in supplementary Table 1. In all cases, needle electrode examination of clinical affected muscles showed acute denervation (fibrillation potentials and positive sharp waves) and chronic neurogenic changes (neurogenic recruitment). Fasciculation potentials were only recorded in patient no. 4. On motor nerve conduction studies, compound muscle action potentials (CMAPs) were reduced or absent in the affected areas,

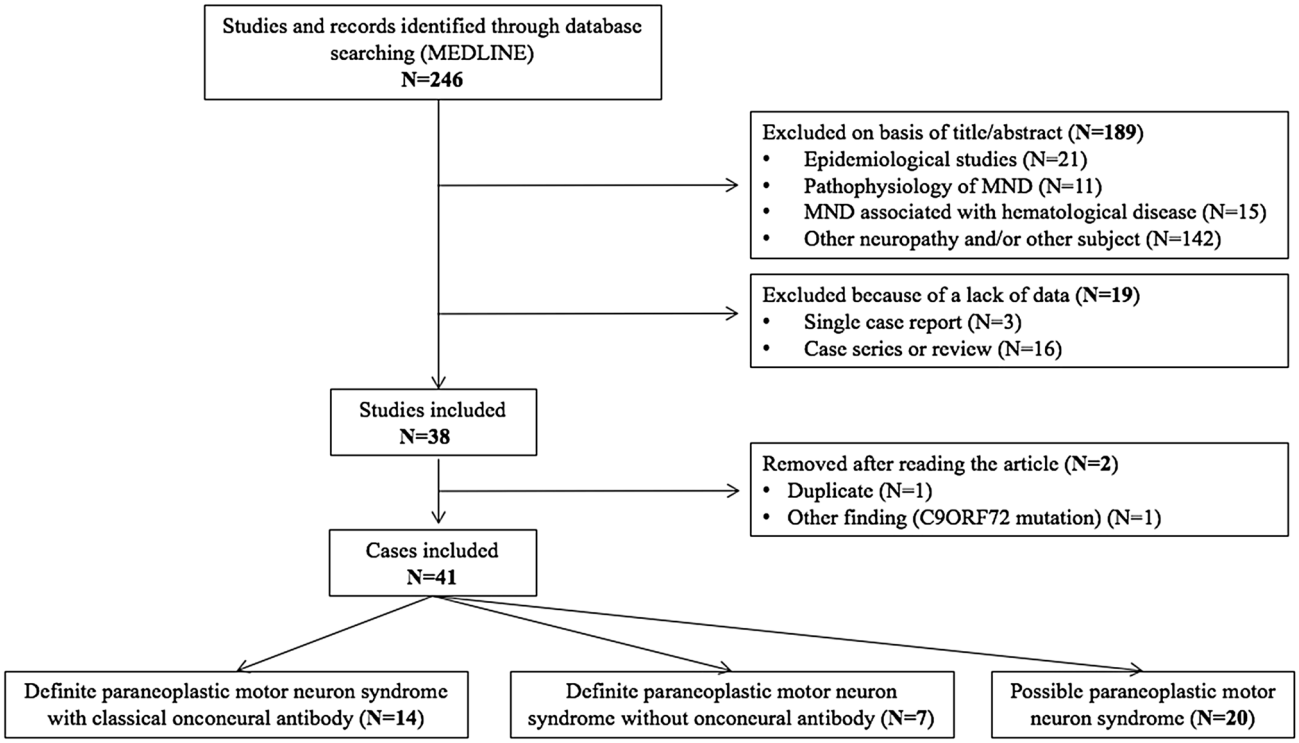


**Fig. 1** Flowchart

but conduction velocities were normal and there was no conduction block or abnormal temporal dispersion of CMAPs that would have suggested demyelination. Sensory nerve action potentials (SNAPs) were within the normal ranges except in patient nos. 2 and 6 who showed a non-length-dependent reduction in the amplitudes of SNAPs, suggesting a concomitant sensory neuronopathy. Length-dependent-reduced amplitudes of SNAPs in patient no. 8 were related to a long-standing history of diabetes.

## CSF analysis

CSF analysis showed inflammatory findings in 7 (88%) out of the 8 cases, including elevated protein levels in 7 patients (range 0.39–2.5 g/l) and CSF pleocytosis in 2 patients (10 and 62 cells/µl, respectively). CSF-restricted oligoclonal bands were observed in 3 (37%) patients. CSF cytology was negative for neoplastic cells in all cases.

## Cancer diagnosis

Seven (88%) out of the eight patients had cancer, corresponding to the following histology: small cell lung cancer ($n=3$), lung squamous cell carcinoma ($n=2$), breast cancer ($n=1$), and prostatic carcinoma ($n=1$). Only two out of the seven patients had a previous history of uncontrolled cancer, while the remaining five patients had their cancer diagnosed following neurological deterioration (median 5 months, range 2–18). One patient (patient no. 6) had no cancer detected during follow-up.

## Outcome and treatment

Cancer treatment was started within 2 months from diagnosis in all patients except for one patient (patient no. 4) who was treated a year later because of initial refusal. All patients received immunotherapy by long-term intravenous immunoglobulin (IVIg) (2 g/kg monthly), initiated in a median of 3 months (range 1–4) from the onset of neurological symptoms. Two patients also received oral corticosteroids (1 mg/kg) in association. Median follow-up duration in our cohort was 18 months (range 4–60). During follow-up, two patients switched to intravenous cyclophosphamide (1000 mg monthly) because of neurological worsening. This treatment allowed to reach clinical stabilization in 1 out of the 2 cases. At last follow-up, six patients were stabilized ($n=5$, 63%) or improved ($n=1$, 13%) compared to baseline. Two (25%) patients with uncontrolled cancer, deteriorated compared to baseline. One of the latter ultimately died because of cancer progression.

**Table 1** Characteristics of eight patients with paraneoplastic motor neuron disease

| Pa. no. | Sex/age (y) | Initial symptoms/mRS | Other neurological manifestation | Clinical and paraclinical syndrome | Type of tumor, time of diagnosis, and treatment | Anti-neuronal antibody | CSF (cells/prot) | Immunotherapy | Evolution/duration of follow-up/mRS |
|---|---|---|---|---|---|---|---|---|---|
| 1 | M/60 | Symmetric weakness of the four limbs and tetrapyramidal signs/1 | Proprioceptive deficit and cerebellar ataxia | UMN and LMN syndrome, sensory neuronopathy, and cerebellar syndrome | Prostatic adenocarcinoma<br>(+) 18mo<br>Surgery, Ht, Rt | Anti-Yo | Abnormal (0/µl, 0.45 g/l)<br>OB− | IVIG | Stable, unlimited walking perimeter/2y |
| 2 | F/64 | Symmetric weakness of the upper limbs/3 | Proprioceptive deficit | LMN syndrome and sensory neuronopathy | Metastatic breast carcinoma<br>(−) 12mo<br>Ct, Rt | Anti-Hu | Abnormal (1/µl, 0.39 g/l)<br>OB + | IVIG<br>Cyclo (IV) | Worsening of weakness/2y |
| 3 | M/64 | Asymmetric weakness of the upper limbs, diaphragmatic paralysis and tetrapyramidal signs/4 | None | UMN and LMN syndrome | Squamous cell lung carcinoma<br>Concomitant to relapse<br>Surgery, Ct | Anti-Hu | Abnormal (2/µl, 0.51 g/l)<br>OB− | IVIG | Oncological worsening leading to death/4mo |
| 4 | M/60 | Asymmetric weakness of the lower limbs/3 | None | LMN syndrome | Small cell lung cancer<br>(+) 3mo<br>Ct | Anti-Hu | Abnormal (10/µl, 2.5 g/l)<br>OB− | IVIG | Stable/2y |
| 5 | M/59 | Asymmetric weakness of the upper limbs/3 | None | LMN syndrome | Small cell lung cancer<br>(+) 2mo<br>Ct, Rt | Anti-Hu | Abnormal (1/µl, 0.70 g/l)<br>OB− | IVIG<br>Corticosteroids (oral) | Significant improvement/5y |
| 6 | M/59 | Asymmetric weakness of the four limbs (predominant in the upper limbs) /3 | Proprioceptive deficit | LMN syndrome and sensory neuronopathy | None | Anti-Hu | Normal<br>OB− | IVIG | Stable/1y |
| 7 | M/59 | Symmetric weakness of the upper limbs and tetrapyramidal signs/3 | Amnesia and behavioral disorder | UMN and LMN syndrome, and limbic encephalitis | Small cell lung cancer<br>(+) 6 mo<br>Ct, Rt | Anti-Hu | Abnormal (2/µl, 1.18 g/l)<br>OB + | IVIG<br>Cyclo (IV) | Stable/1y |
| 8 | F/61 | Symmetric weakness of the upper limbs, diaphragmatic paralysis, and bulbar dysfunction/5 | None | LMN syndrome | Squamous cell lung carcinoma<br>(−) 4 mo<br>Surgery | Anti-Hu | Abnormal (62/µl, 0.66 g/l)<br>OB + | IVIG<br>Corticosteroids (oral) | Stable/1y |

*IV* intravenous, *IVIG* intravenous immunoglobulin, *F* female, *Ht* hormonotherapy, *LMN* lower motor neuron, *M* male, *Mo* month, *mRS* modified Rankin Scale, *No* number, *OB* oligoclonal IgG bands (− absent, + present), *Pa*. patient, *Rt* radiotherapy, *UMN* upper motor neuron, *Y* year, *Ct* chemotherapy, *Cyclo* cyclophosphamide

(+) diagnosis of tumor after onset of symptoms

(−) diagnosis of tumor before onset of symptoms

**Table 2** Electrophysiological presentation of right patients with paraneoplastic motor neuron disease

| Pa. no. | ENMG conclusion | Most important site of denervation | Amplitudes of compound muscle action potentials | Amplitudes of sensory nerve action potentials | Needle electromyography at rest/during maximum contraction | Evolution of electrophysiological parameters |
|---|---|---|---|---|---|---|
| 1 | LMN syndrome, sensory neuronopathy | Myotome S1 of both LL | Reduced in the LL | Slightly reduced in the LL | Fib, PSW/neurogenic recruitment | Stabilization of all parameters (2y) |
| 2 | LMN syndrome and sensory neuronopathy | Widespread denervation of both UL | Reduced in the UL | Reduced in the UL | Fib, PSW/neurogenic recruitment | Worsening of all parameters (2y) |
| 3 | LMN syndrome | Widespread denervation of both UL | Reduced in the UL | Normal | Fib, PSW/neurogenic recruitment | Worsening of all parameters (2mo) |
| 4 | LMN syndrome | Denervation in the left LL (L5) and the right LL (S1) | Reduced in the LL | Normal | Fib, PSW/neurogenic recruitment | Stabilization of all parameters (18mo) |
| 5 | LMN syndrome | Widespread denervation in the left UL | Reduced in the UL | Normal | Fib, PSW/neurogenic recruitment | Improvement of all parameters (5y) |
| 6 | LMN syndrome and sensory neuronopathy | Predominant denervation in the left UL | Reduced in the UL and LL | Reduced in the four limbs | Fib, PSW/neurogenic recruitment | Stabilization of all parameters (1y) |
| 7 | LMN syndrome | Predominant denervation in the right UL | Reduced in the UL | Normal | Fib, PSW/neurogenic recruitment | Stabilization of all parameters (1y) |
| 8 | LMN syndrome | Widespread denervation of both UL | Reduced in the UL | Normal | Fib, PSW/neurogenic recruitment | No data |

*LMN* lower motor neuron, *M* male, *Mo* month, *Pa.* patient, *UL* upper limb, *Fib* fibrillation potentials, *PSW* positive sharp waves, *FPs* fasciculation potentials, *Y* year, *F* female, *LL* lower limb

### Systematic review of the literature

Among 246 studies identified through database searching, 38 studies describing 41 unique cases matched the criteria for paraneoplastic MND (Fig. 1). Among the latter, 21 patients matched the definition of "definite" paraneoplastic MND [8–20]. The diagnosis of "definite" paraneoplastic MND resulted from the presence of well-characterized onconeural antibodies in 14 cases, and from the remission of neurological symptoms after tumor removal in the remaining 7 cases. Table 3 summarizes the main clinical characteristics in these 21 patients. Median age at the time of neurological symptom onset was 63 years (range 32–81). Fifteen (71%) patients were women and 6 (29%) patients were men. Twelve (57%) patients had an exclusive involvement of the lower motor neuron, six (29%) patients had combined upper and lower motor neuron impairment, and 3 (14%) patients an isolated upper motor neuron syndrome. In two-thirds of cases, disease onset and evolution were subacute (i.e., less than 2 months). Motor deficit at the time of symptom onset was restricted to the upper limbs in 7 (33%) cases and was asymmetric in 5 (24%). Diaphragmatic involvement was observed in 2 (9%) cases. No patient showed bulbar involvement. Besides the motor neuronopathy, five (24%) patients had additional neurological manifestations evoking a paraneoplastic disorder, including limbic encephalitis (9%), sensory neuronopathy (9%), autonomic dysfunction (5%), and opsoclonus-myoclonus (5%). Cerebrospinal fluid analysis showed inflammatory findings in 5 out of 15 (33%) cases. The most represented onconeural antibody type was anti-Hu ($n=6$, 43%), followed by anti-Ri ($n=2$, 14%), anti-Yo ($n=2$, 14%), anti-Ma2/Ta ($n=3$, 21%), and anti-CV2 antibodies ($n=1$, 7%). Seventeen (88%) patients had an associated cancer, including breast ($n=6$), renal cell ($n=4$), lung ($n=3$), ovarian ($n=1$), testicular ($n=1$), gall bladder-duodenal cancer ($n=1$), and thymoma ($n=1$). In 9 (53%) cases, cancer was diagnosed after the onset of neurological symptoms. Thirteen (65%) patients improved or stabilized soon after the start of immunotherapy and cancer treatment. At last follow-up (median 17.5 months; range 2–48), five (24%) out the 21 patients had died because of uncontrolled cancer and/or neurological worsening.

## Discussion

The differential diagnosis between degenerative and non-degenerative MND is of capital importance, as the latter may be associated with potentially treatable conditions. Cases of paraneoplastic MND are rarely observed and, as a result, no exhaustive data are available on the exact clinical and neurophysiological phenotype associated with this

**Table 3** Review of the 21 cases of definite paraneoplastic motor neuron disease identified in the literature

| Sex/age (y) | Initial symptoms | Presence of UMN | Other neurological manifestation | Mode of installation | Clinical and electrophysiological syndrome | Anti-neuronal antibody | Type of tumor, time of diagnosis, and treatment | CSF (cells/prot) | Immunotherapy | Evolution | Ref. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| F/81 | Symmetric weakness of the four limbs | No | None | Subacute | Symmetric motor neuronopathy affecting the four limbs | Anti-CV2 | Thymoma (+) 2mo Surgery, Rd | Normal | IVIG Corticosteroids Azathioprine | Significant improvement (2y) | VA |
| F/66 | Asymmetric weakness of the upper limbs | No | None | Subacute | Asymmetric motor neuronopathy affecting the four limbs | Anti-Hu | None | Normal OB | IVIG Corticosteroids Cyclo | Decease (5mo) | VA |
| F/48 | Symmetric weakness of the lower limbs | No | None | Subacute | Symmetric LMN syndrome | None | Breast cancer (+) 2mo Surgery, Rt, Ct, Ht | Normal OB | IVIG Corticosteroids Azathioprine Rituximab | Significant improvement after tumor removal (4y) | VA |
| F/80 | Asymmetric weakness of the upper limbs | No | None | Subacute | Symmetric motor neuronopathy affecting the four limbs | Anti-Ri | Breast cancer (−) 4y Surgery, Rd, Ht | Abnormal (0/µl, 0.57 g/l) | IVIG Corticosteroids | Significant improvement (3y) | DC |
| F/60 | Symmetric spastic tetraparesis predominant in the lower limbs | No | None | Subacute | Symmetric UMN syndrome | None | Breast cancer (+) 6mo Surgery, Rt, Ct | Normal | None | Improvement within 2mo after tumor removal (3y) | SR |
| F/49 | Unilateral weakness of the left lower limb | No | Opsoclonus-myoclonus syndrome | Subacute | Asymmetric motor neuronopathy affecting the LL | Anti-Ri | Breast cancer (+) 3mo Surgery, Rd, Ct | Normal | IVIG PE | Sustained improvement (6mo) | YD |
| F/32 | Symmetric weakness of the upper limbs | No | Autonomic dysfunction | Chronic | Symmetric motor neuronopathy affecting the UL | Anti-Hu | None | Normal OB | IVIG PE Corticosteroids Cyclo | Decease (11mo) | LJ |
| F/50 | Symmetric spastic paraparesis | No | None | Chronic | Symmetric LMN syndrome affecting the LL | Anti-Ma2 | None | Normal OB | Corticosteroids | Severe spastic paraparesis (4y) | PG |
| F/54 | Symmetric weakness of the lower limbs | No | None | Subacute | Motor neuronopathy | Anti-Yo | Breast cancer (−) No data | No data | None | No data | DB |

**Table 3** (continued)

| Sex/age (y) | Initial symptoms | Presence of UMN | Other neurological manifestation | Mode of installation | Clinical and electrophysiological syndrome | Anti-neuronal antibody | Type of tumor, time of diagnosis, and treatment | CSF (cells/prot) | Immunotherapy | Evolution | Ref. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| M/59 | Symmetric weakness of the upper limbs, then affecting the lower limbs | No | None | Chronic | Symmetric LMN syndrome | None | Recurrent renal cell carcinoma (+) 5mo Surgery, Ct | No data | None | Disease-free for 4y after first tumor removal Improvement within 3mo after second surgery | TH |
| F/63 | Unilateral spastic weakness of the right upper limb | No | None | Subacute | Asymmetric UMN syndrome affecting the right UL | Anti-Hu | Lung cancer (−) 20mo Cryotherapy, Rt, Ct | Normal OB | None | Stable (11y) | TG |
| M/70 | Symmetric weakness of the four limbs with pyramidal signs | Yes | None | Chronic | Symmetric UMN and LMN syndrome affecting the four limbs | Anti-Ta | None | Abnormal (0/µl, 0.52 g/l) | None | Stable (no data) | HL |
| M/36 | Symmetric weakness of the upper limbs with pyramidal signs | Yes | Limbic encephalitis | Subacute | Symmetric UMN and LMN syndrome affecting the UL | Anti-Ma2 | Testicular cancer (−) 6mo Surgery | Abnormal (5/µl, 0.83 g/l) | IVIG Corticosteroids | Significant improvement (2mo) | WM |
| F/68 | Symmetric weakness of the four limbs | No | Limbic encephalitis and sensory neuronopathy | Subacute | Symmetric motor neuronopathy affecting the four limbs | Anti-Hu | Lung cancer (+) 2mo No data | Abnormal (6/µl, 1.19 g/l) | IVIG PE | Decease (4mo) | GB |
| F/80 | Symmetric weakness of the four limbs with pyramidal signs | Yes | Sensory neuronopathy | Subacute | Symmetric UMN and LMN syndrome affecting the four limbs | Anti-Hu | Gall bladder and duodenal cancer (+) 5mo No data | Abnormal (19/µl, 0.73 g/l) | None | Decease (8mo) | OM |
| M/52 | Bilateral diaphragmatic paralysis | No | None | Subacute | LMN syndrome affecting the phrenic nerves | None | Renal cell carcinoma Concomitant Surgery | No data | None | Slow but progressive recovery (30mo) | RB |

**Table 3** (continued)

| Sex/age (y) | Initial symptoms | Presence of UMN | Other neurological manifestation | Mode of installation | Clinical and electrophysiological syndrome | Anti-neuronal antibody | Type of tumor, time of diagnosis, and treatment | CSF (cells/prot) | Immunotherapy | Evolution | Ref. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| F/72 | Monoparesis preceding a quadriparesis | No | None | Subacute | Asymmetric LMN syndrome | None | Breast cancer (+) 4mo Surgery | No data | IVIG PE Corticosteroids Azathioprine | Significant improvement after tumor removal (no data) | FF |
| F/70 | Symmetric weakness of the four limbs and diaphragmatic paralysis | No | None | Subacute | Symmetric LMN syndrome affecting the phrenic nerve | None | Renal cell carcinoma Concomitant Surgery | Normal | None | Rapid and significant improvement after tumor removal (1y) | FD |
| F/67 | Symmetric weakness of the four limbs with pyramidal signs | Yes | None | Subacute | Symmetric UMN and LMN syndrome affecting the four limbs | Anti-Yo | Metastatic ovarian carcinoma (+) 4mo Surgery | Normal | None | Neurological worsening (no data) | KS |
| M/51 | Symmetric weakness of the upper limbs with pyramidal signs | Yes | None | Chronic | Symmetric UMN and LMN syndrome affecting the four limbs | Anti-Hu | Lung cancer Concomitant No data | No data | IVIG PE Corticosteroids Cyclo | Decease (23mo) | VA |
| M/74 | Symmetric weakness of the four limbs and pyramidal signs | Yes | None | Subacute | Symmetric UMN and LMN syndrome | None | Renal cell carcinoma Concomitant Surgery | No data | None | Improvement within 4mo after tumor removal | EB |

*Cyclo* cyclophosphamide, *Ht* hormonotherapy, *IVIG* intravenous immunoglobulin, *F* female, *LL* lower limb, *LMN* lower motor neuron, *M* male, *Mo* month, *OB* oligoclonal IgG bands, *PE* plasma exchange, *Rd* radiotherapy, *Ref.* reference, *UL* upper limb, *UMN* upper motor neuron, *Y* year, *Ct* chemotherapy

(+) diagnosis of tumor after onset of symptoms

(−) diagnosis of tumor before onset of symptoms

condition. Here, we present an institutional series of patients with definite paraneoplastic MND, together with a systematic review of the literature. Our 8 cases were collected in less than 5 years and represented 0.4% of patients referred to our reference center for MND during the same time period, confirming that, if paraneoplastic MND exists, it is overall a rare entity.

Based on the description of our eight patients, and of the 21 reported in the literature, the main features of paraneoplastic MND can be summarized as follows: (1) subacute (less than 2 months); (2) LMN syndrome, associated or not with UMN involvement; (3) predominant asymmetric upper limb involvement; (4) concomitant presence of other non-motor neurological manifestations, including subacute sensory neuronopathy; (5) signs of inflammation in the CSF; (6) neurological stabilization or improvement after immunotherapy and tumor treatment.

Several of these clinical and paraclinical features are non-specific for a paraneoplastic etiology, and they can also be detected in degenerative MND. Amyotrophic lateral sclerosis can also present with asymmetric upper limb involvement and be associated with an aggressive clinical course, especially when related to some genetic alterations [21, 22]. However, subacute course in paraneoplastic MND seems to be a clue for this condition. Non-motor symptoms, such as autonomic dysfunction and cerebellar ataxia, have also been reported in patients with ALS [23, 24], which is increasingly recognized as multisystem disorder rather than a pure motor neuron disease. However, elevated protein levels and/or CSF-restricted oligoclonal bands are observed in only 5.8% of patients with ALS [25] when it reach 93% of patients with paraneoplastic neurological syndromes [26].

The absence of bulbar dysfunction may be a peculiar feature pointing to a paraneoplastic etiology, although it is still compatible with the initial ALS. Early diaphragmatic involvement may be observed in both degenerative and paraneoplastic MND, highlighting that the two etiologies do not differ with regard to potential clinical severity.

Electroneuromyography brings the demonstration of a progressive LMN syndrome for which, in contrast with ALS, fasciculation potentials are overall absent. In the context of a largely predominant motor neuropathy, it conveys arguments for a paraneoplastic origin when a concomitant infraclinical sensory neuronopathy is detected.

Overall, the diagnosis of paraneoplastic MND may be difficult because of its rarity, the absence of pathognomonic clinical features, and the frequent absence of previous tumor history. However, it is of capital importance to correctly identify patients with paraneoplastic MND, as most of them can improve or at least stabilize following immunotherapy and tumor treatment.

In the presence of subacute LMN disease, and especially if one or more atypical features for degenerative MND and/or non-motor neurological manifestations evoking a paraneoplastic etiology are present, we recommend testing for onconeural antibodies. When onconeural antibodies test is negative, but it exists a strong suspicion for a paraneoplastic etiology, clinicians should perform CSF analysis eventually followed by total-body 18FDG-PET/CT imaging to circumstantiate diagnosis, [27] as it is known that paraneoplastic syndrome test is negative for onconeural antibodies in about 50% of cases [28].

## Conclusion

Paraneoplastic MND often present as subacute LMN syndromes, which are frequently associated with additional non-motor neurological symptoms and with inflammatory CSF findings. Recognition of paraneoplastic MND is essential, because an early management with immunotherapy and cancer treatment can lead to neurological improvement or stabilization.

### Compliance with ethical standards

**Conflicts of interest** The authors declare that they have no competing interests.

**Ethical standard** The study was approved by the local ethics committee.

## Appendix: Search terms

("motor neuron" OR "motor neurons" OR "motor neuropathy" OR "motor neuron disease" OR "motor neuron diseases" OR "amyotrophic lateral sclerosis" OR "neuromuscular disease" OR "neuromuscular diseases" OR "muscular atrophy") AND ("paraneoplastic" OR "paraneoplastic neuropathy" OR "paraneoplastic polyneuropathy" OR "paraneoplastic syndrome" OR "paraneoplastic syndromes" OR "paraneoplastic neurological syndrome" OR "paraneoplastic neurological syndromes") AND ("english"[Language] OR "french" [Language]) AND ("1980/01/01″[Date—Publication] : "2017/11/15" [Date—Publication]).

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