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# Motor neuron disease with malignancy: Clinical and pathophysiological insights

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HIGHLIGHTS

- Motor neuron disease and malignancy (MND-M) forms continuum with motor neuron disease.
- Lower motor neuron phenotype predominates with MND-M.
- Cortical hyperexcitability is a pathogenic feature of MND-M.

ABSTRACT

*Objective:* While some regard an association between motor neuron disease (MND) and malignancy as co-incidental, others have argued that it could represent a distinct clinical entity. The present study undertook in depth phenotyping along with assessment of cortical function to further explore disease pathophysiology in MND with malignancy (MND-M) patients.
*Methods:* Clinical features along with assessment of peripheral and cortical function was undertaken in 13 MND-M and results were compared to sporadic and familial MND cohorts.
*Results:* From a cohort 13 patients (10 males; aged 65.2 ± 2.0 years), 38.5% were diagnosed with a haematological malignancy. The lower motor neuron phenotype predominated in the in the MND-M patients ($\chi^2 = 10.8$, $P < 0.01$), with the upper motor neuron (UMN) score being significantly reduced in MND-M patients compared to sporadic and familial MND cohorts ($\chi^2 = 6.84$, $P < 0.01$). The neurological deficits did not respond to treatment of the underlying malignancy in the majority of MND-M (92%) patients, and as such there were no significant differences in survival between the cohorts. Despite a paucity of UMN signs, cortical hyperexcitability was evident in MND-M patients, as indicated by reduction in short interval intracortical inhibition ($P < 0.01$) and increase in motor evoked potential amplitude ($P < 0.01$), that were similar to findings in sporadic and familial MND cohorts.
*Conclusions:* The present study suggests that MND-M falls within the spectrum of MND.
*Significance:* The concept of a co-incidental association between MND and malignancy is supported through the present study by the presence of cortical dysfunction, combined with clinical findings that can be explained within the spectrum of abnormality evident in classical MND phenotypes.


## 1. Introduction

An association between motor neuron disease (MND) and malignancy remains controversial. The co-occurrence of malignancy and MND (Gordon et al., 1997), along with reports that paraneoplastic antibodies may be evident in some MND patients exhibiting malignancy (Denny-Brown, 1948, Verma et al., 1996) and that improvement of neurological symptoms may occur after malignancy treatment (Gordon et al., 1997), has suggested a causal link between malignancy and MND. In contrast, epidemiological studies have suggested that any association between MND and malignancy is co-incidental (Chio et al., 1988, Fois et al., 2010,

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Freedman et al., 2005) and paraneoplastic antibodies were not identified in large series of sporadic MND patients (Stich et al., 2007). The notion of a co-incidental association between MND and cancer was further supported by a smaller case series (Forsyth et al., 1997), although it was suggested that malignancy should be excluded in patients with specific MND phenotypes.

Epidemiological processes derived from cancer biology have been used to model MND and have determined that the disease represents a multiple hits process (Al-Chalabi et al., 2014). In terms of linking malignancy to the processes that may trigger MND, no clear mechanism has yet been identified. An autoimmune response against antigens co-expressed on motor neurons and tumour cells has been proposed as a potential mechanisms for development of MND in patients with malignancy [MND-M] (Voltz, 2002). Consequently, MND-M could represent a distinct clinical entity that could respond to treatment of the underlying malignancy. If so, one may expect that process to interfere with normal motor cortical function.

Of relevance to such a proposition, assessment of cortical function appears to be a sensitive and specific biomarker of MND, distinguishing MND from potential mimicking disorders (Menon et al., 2015). In MND, cortical dysfunction may be heralded by reduction of short interval intracortical inhibition and cortical silent period duration along with increased motor evoked potential amplitudes or motor cortex inexcitability (Geevasinga et al., 2015, Menon et al., 2015, Vucic and Kiernan, 2006, Vucic et al., 2008). Moreover, cortical hyperexcitability was proposed as a potential pathogenic mechanism, contributing to progressive neurodegeneration in MND (Menon et al., 2017, Vucic and Kiernan, 2006, Vucic and Kiernan, 2010). Given the uncertainties of MND-M syndrome, the aim of the present study was to implement in-depth phenotyping along with the threshold tracking transcranial magnetic stimulation for cortical function assessment to further explore disease pathogenesis compared to sporadic and familial MND phenotypes.

## 2. Methods

### 2.1. Patients

Thirteen patients with MND and malignancy (MND-M) were identified via systemic retrospective review of consecutive motor neuron disease presentations from the NHRMC Sydney Health Partners Multidisciplinary clinic (N = 400 patients). The diagnosis of MND was established in accordance with the Awaji criteria (de Carvalho et al., 2008), while the diagnosis of primary lateral sclerosis (PLS) was in keeping with Gordons' criteria, namely presence of pure upper motor neuron dysfunction for at least 4 years post-symptom onset (Gordon et al., 2006). MND mimicking disorders were excluded in all MND/PLS patients after extensive laboratory, neurophysiological and neuroimaging assessment as well as clinical follow-up for a least 12 months. Malignancy was present in all patients during the course of disease. All patients and controls provided written informed consent prior to assessment which were approved by the Western Sydney Local Health District Human Research Ethics Committee. Subject enrolment was performed in accordance with the principles of the Declaration of Helsinki.

## 3. Clinical examinations

Site of disease onset, disease duration (months), upper motor neuron score (Turner et al., 2004) and functional disability, as reflected by the ALS functional rating scale (ALSFRS-R) (Cedarbaum et al., 1999), were recorded in all patients. Muscle strength was assessed using the Medical Research Council (MRC) score (O'Brien, 2004), with the following muscle groups evaluated: shoulder abduction, elbow flexion and extension, wrist dorsiflexion, finger abduction and thumb abduction on both sides; hip flexion, knee extension and ankle dorsiflexion on both sides. In the upper limbs, the maximum MRC sum score was 60, while for the lower limbs it was 30 yielding a maximal MRC score of 90 when strength was normal. In addition, the frequency of riluzole therapy was recorded in each group. All MND-M patients underwent a thorough medical examination, incorporating laboratory, imaging and histopathological assessments by an oncology team. Results of anti-neuronal antibodies were checked for patients if available. Duration between MND onset and malignancy diagnosis as well as survival from MND onset was recorded in all patients.

## 4. Neurophysiological studies

The median nerve was electrically stimulated at the wrist, and the compound muscle action potential (CMAP) was recorded over the abductor pollicis brevis (APB) muscle using AgCl gel disc electrodes (10 mm diameter 3 M). The ground electrode placed over the dorsum of the same hand. Conventional nerve conduction studies and needle EMG were undertaken in all patients. The following muscles were assessed on needle EMG testing; trapezius, deltoid, biceps brachii, triceps brachii, the first dorsal interosseous, APB, vastus lateralis, tibialis anterior and medial gastrocnemius muscles. Needle EMG data was used to classify MND-M patients into an Awaji diagnostic category (de Carvalho et al., 2008). The peak-peak CMAP amplitude, distal motor latency and F-wave frequency were recorded. The neurophysiological index (NI) was calculated from the median nerve (de Carvalho and Swash, 2000).

Cortical excitability was assessed using the threshold tracking TMS technique according to a previously reported methodology (Vucic et al., 2006). Briefly, a 90 mm circular coil was used to stimulate the primary motor cortex. The coil position was adjusted to generate the optimal motor evoked potential (MEP). The following TMS parameters were recorded: (i) resting motor threshold; (ii) short-interval intracortical inhibition (SICI), interstimulus intervals (ISIs) of 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, and 7 ms; (iii) intracortical facilitation (ICF), ISIs 10, 15, 20, 25 and 30 ms; (iv) maximal MEP amplitude, expressed as a percentage of the CMAP response; (v) cortical silent period (CSP) duration, measured from MEP onset to resumption of EMG activity (Cantello et al., 1992). The TMS intensity was set to 150% of RMT for determination of both MEP amplitude and CSP duration, and three responses were recorded at this stimulus intensity (Vucic et al., 2006).

## 5. Statistical analyses

Clinical and neurophysiological findings in MND-M patients were compared to 20 age-matched sporadic MND [66, 51-79] and 14 familial MND patients with *C9orf72* gene mutation [58.9, 41-78], as well as 20 age-matched healthy controls [62.5, 52–83]. Prior to undertaking statistical analysis, data was tested for normality by using a Shapiro-Wilk test. Student's t-test were used to assess differences between means while an analysis of variance (ANOVA) or Kruskal-Wallis was used for multiple comparisons. Pearson's or Spearman's rho was used for correlations. All data is expressed as mean ± standard error mean (SEM) or median (interquartile range). A P value $<0.05$ was deemed significant.

## 6. Results

### 6.1. Clinical features

Malignancy was diagnosed after the onset of MND in 11 patients, with the median time between MND and malignancy

diagnosis being 10 months (5–25). In two patients, malignancy preceded the onset of MND by 36 and 48 months respectively. The diagnosis of malignancy was heralded by specific symptoms (*see* table 1 legend), rather than being detected on screening tests performed during the MND diagnostic assessment. All patients were investigated with neuroimaging (MRI brain, cervical, thoracic and lumbosacral spinal cord) along with the following a laboratory tests; electrolytes, urea, creatinine, full blood count, vasculitic screen (ANA, ENA, ANCA, ACE, IEPG), metabolic and infective screens, coeliac disease serology and antiganglioside antibodies, including voltage-gated $K^+$ channels. Once the diagnosis of MND was established, patients were offered standard care incorporating riluzole therapy and management in a multidisciplinary MND clinic.

Haematological malignancies were most frequently diagnosed (lymphoma N = 4; multiple myeloma, N = 1), followed by lung cancer (N = 2, one small cell and one adenocarcinoma), breast cancer (N = 1), sarcoma (N = 1), colorectal adenocarcinoma (N = 1), prostate cancer (N = 1), thyroid cancer (N = 1) and undifferentiated skull osteosarcoma (N = 1). Paraneoplastic antibodies were tested in four patients and were evident in two (anti-PCA and anti-Ma2). Interestingly, c9orf72 hexanucleotide expansion was detected in the patient exhibiting anti-Ma2 antibodies. Four patients underwent chemotherapy treatment, 1 was treated with surgery, 2 had a combination of surgery and chemotherapy, while three patients were treated with radiotherapy and chemotherapy, 1 received a hormonal therapy and 2 were managed conservatively. Motor symptoms stabilised in one MND-M patient after chemotherapy treatment of his lymphoma. Specifically, over a 12 month follow-up period, the ALSFRS-R score changed from 42 to 44, while the MRC total sum score increased from 79 to 86. In this patient, whole body PET study along with MRI of the whole spine, conducted for lymphoma staging, did not reveal intraneural lymphoma. The remaining 12 patients progressed and exhibited a typically MND course, eventually dying from consequences of MND. Post-mortem pathological investigations in one patient demonstrated pTDP-43 pathology. The median survival from disease onset in the MND-M patients was 36 months (24–51 months), which was comparable to sporadic (31, 25–46 months) and familial MND (46, 36–53.3 months, P = 0.52) cohorts.

**Table 1**
Clinical details for the motor neuron disease (MND) patients.

| Parameter | MND-M | Sporadic MND | Familial MND |
|---|---|---|---|
| **Male:Female** | 10:3 | 13:7 | 1:1 |
| **Mean age (years)** | 65.2 | 66 | 59 |
| **(SEM)** | 2.0 | 1.7 | 3.2 |
| **Phenotype (N)** | 6 | 2 | 2 |
| **PMA** | 6 | 18 | 12 |
| **ALS** | 1 | 0 | 0 |
| **PLS** | | | |
| **Site of onset** | 77 | 70 | 64 |
| **-Limb (%)** | 23 | 30 | 36 |
| **-Bulbar (%)** | | | |
| **Disease duration** | 12 | 7.5 | 7.5 |
| **months** | (9.5–27) | (6–13.5) | (4–20.5) |
| **(IQR)** | | | |
| **ALSFRS-R** | 42 | 43 | 42 |
| **(IQR)** | (37–43) | (40.8–46.3) | (36.8–44) |
| **UMN** | 3 | 12 | 14 |
| **Score** | (0–11) | (11–12) | (12–14) |
| **(IQR)** | | | |
| **MRC** | 80 | 82.5 | 83 |
| **sum score** | (77–86) | (79.3–89.5) | (81–88) |
| **(IQR)** | | | |
| **MRC** | 54 | 55 | 57 |
| **UL score** | (52–58) | (51.5–60) | (51–60) |
| **(IQR)** | | | |
| **MRC** | 28 | 29 | 29 |
| **LL score** | (25–30) | (26.5–30) | (28–30) |
| **(IQR)** | | | |
| **Survival** | 36 | 27.5 | 47 |
| **(months)** | (23.5–50.5) | (24–36.3) | (44.5–53.3) |
| **(IQR)** | | | |

The amyotrophic lateral sclerosis functional rating scale-revised (ALSFRS-R) was comparable across the groups. The upper motor neuron (UMN) score was reduced in MND patients with malignancy (MND-M). The lower motor neuron phenotype (progressive muscular atrophy, PMA) was more frequent in MND-M patients when compared to the frequency of PMA phenotype in sporadic and familial ALS patients. Muscle strength assessed by the Medical Research Council (MRC) score was comparable across the groups in both the upper (UL) and lower limbs (LL). All data are expressed as mean (standard error of mean, SEM) or median (interquartile range, IQR). The upper motor neuron score consists of pathologically brisk triceps, biceps brachii, brachioradialis, finger, knee and ankle reflexes along with the presence of extensor plantar responses bilaterally and brisk jaw and facial jerks. The score ranges from 0 (no UMN signs) to 16 (significant UMN signs). The specific symptoms heralding malignancy were varied and included: (i) Haematological malignancies presented with fever, night sweats, severe weight loss, lymphadenopathy, anaemia or pancytopenia and elevated M protein/lytic bone lesions (multiple myeloma); (ii) Lung cancer presented with haemoptysis, breathlessness and axillary/supraclavicular lymphadenopathy; (iii) Breast cancer presented with a breast mass; (iv) Thyroid cancer-enlarged nodular thyroid gland; (v) Sarcoma-thigh pain and mass; (vi) Colorectal adenocarcinoma- altered bowel habits and rectal bleeding; (vii) Prostate cancer- urinary frequency and difficulty voiding; (viii) Undifferentiated skull osteosarcoma-headaches.

From an MND perspective, the mean age of onset in MND-M patients was 63.3 ± 2.0 years (Table 1) and was comparable to sporadic and familial MND patients (P = 0.08). Five MND-M patients (38%) were classified in the Awaji probable/definite diagnostic category, while 8 patients (62%) were categorized as Awaji possible MND. In the MND-M patients, the LMN clinical phenotype was significantly more common, while the mixed upper and lower motor phenotype (ALS) was less frequent compared to sporadic and familial MND patients ($\chi^2 = 10.8$, $P < 0.01$). Consequently, the UMN score was significantly reduced in MND-M when compared to familial MND ($\chi^2 = 6.84$, $P < 0.01$) patients. The UMN score was also lower in MND-M patients than in sporadic MND patients, although it was not significant (P = 0.06). In addition, the ALSFRS-R score in MND-M patients (42, IQR 37–43) was comparable when compared to sporadic MND patients (43, IQR 40.8–46.3, P = 0.07) and familial MND patients (42, IQR 36.8–44, P = 0.70).

The male: female ratio was higher in the MND-M patients, although this difference was not significant (P = 0.27). Furthermore, limb onset disease was evident in 77 % while bulbar onset disease was reported by 23 % of MND-M patients and was comparable to sporadic and familial MND cohorts (P = 0.53). The degree of muscle weakness was also comparable across the three MND groups as reflected by the MRC sum score (P = 0.34), the upper limb MRC score (P = 0.40) and lower limb MRC score (P = 0.98). Importantly, the cancer incidence rates in the MND-M cohort was calculated as being 325/100, 000 and was lower than the reported cancer incidence rates in the general Australian population (470/100, 000).

## 7. Cortical function

Prior to undertaking an assessment of cortical function, the degree of lower motor neuron dysfunction was assessed in MND-M patients. There was a significant reduction in CMAP amplitude in MND-M patients (5.5 ± 2.7 mV) when compared to controls (9.3 ± 2.8 mV, F = 16.8, P < 0.01). The degree of CMAP reduction was similar compared to sporadic (6.5 ± 3.8 mV, P = 1.0) and familial (6.6 ± 2.0 mV, P = 1.0) MND patients. In addition, the NI was significantly reduced in MND-M patients (1.2 ± 1.0) compared to controls (2.3 ± 0.7, F = 14.2, P < 0.01), but was comparable to sporadic MND (1.3 ± 1.0, P = 1.0) and familial MND (2.0 ± 1.1, P = 0.23) patients.

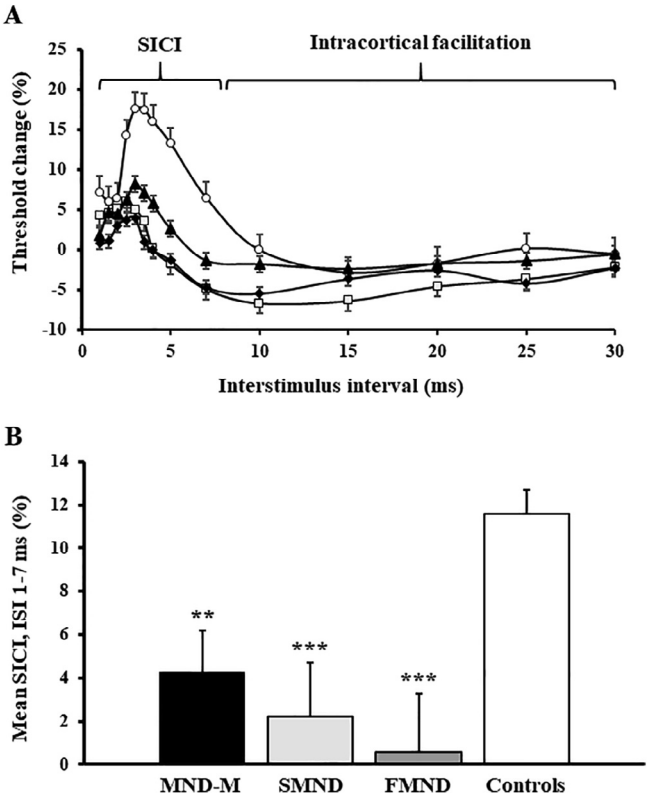


**Fig. 1. (A)** Short interval intracortical inhibition (SICI) was significantly reduced in motor neuron disease with malignancy (MND-M, black triangles), sporadic MND (SMND, white squares) and familial MND (FMND, black diamonds) patients when compared to controls (white circles). **(B)** The mean SICI, between interstimulus intervals (ISI) of 1–7 ms, was significantly reduced. **P < 0.01; ***P < 0.001, when compared to controls.

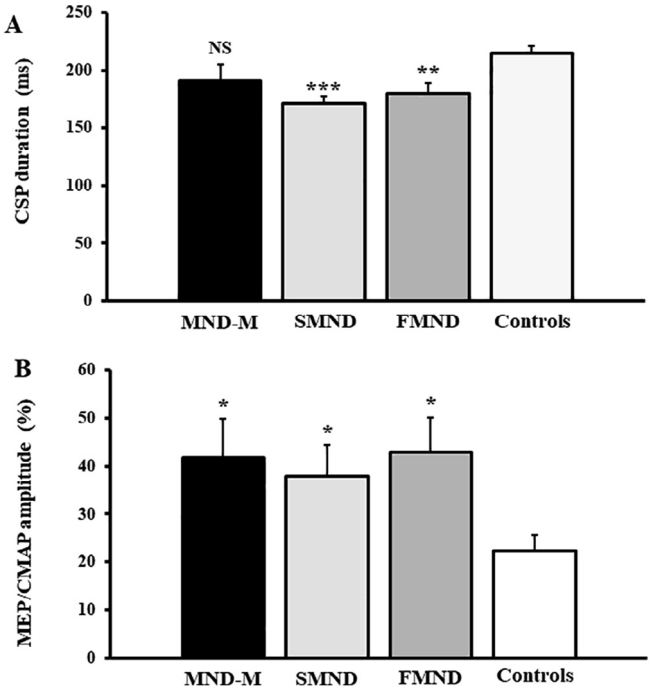


**Fig. 2. (A)** The cortical silent period duration (CSP) was significantly reduced in sporadic motor neuron disease (SMND) and familial MND (FMND) patients but not in the motor neuron disease with malignancy (MND-M) patients. **(B)** The motor evoked potential (MEP) amplitude, expressed as a percentage of the compound muscle action potential (CMAP), was significantly increased. *P < 0.05; **P < 0.01; ***P < 0.001; NS = not significant when compared to controls.

The motor cortex was inexcitable in two MND-M patients. Short interval intracortical inhibition was significantly reduced in the MND-M patients when compared to controls (P < 0.01, Fig. 1A). Sub group analysis disclosed a comparable reduction of mean SICI across the MND cohorts (Fig. 1B). In contrast, there was no significant increase of intracortical facilitation (Fig. 1A).

Of further relevance, there was a significant reduction of CSP duration in the MND groups when compared to controls ($\chi^2$ = 16.0, P < 0.001). Subgroup analysis disclosed that the reduction in CSP duration was significant for sporadic (170.9 ± 6.1 ms, P < 0.001) and familial (179.4 ± 8.8 ms, P < 0.01) MND patients. In the MND-M patients there was a trend for CSP to be reduced, although this reduction was not significant (190.6 ± 14.0 ms, P = 0.08, Fig. 2A). In addition, the MEP amplitude was significantly increased in the three MND groups when compared to controls ($\chi^2$ = 6.78, P < 0.01). Subgroup analysis revealed a significant increase of MEP amplitude in the MND-M, sporadic and familial MND patients when compared to controls (Fig. 2B).

The resting motor threshold was significantly reduced in familial MND patients (51.4 ± 2.1%) when compared to controls (61.4 ± 1.7%, F = 12.5, P < 0.01). Interestingly, the RMT was not significantly reduced in the MND-M (56.8 ± 4.5%, P = 0.18) and sporadic MND (59.1 ± 2.1%, P = 0.20) patients.

## 8. Discussion

In the present study, we further delineated an MND phenotype associated with malignancy as being characterised by a clinically lower motor neuron syndrome, with reduced upper motor neuron scores, when compared to sporadic and familial MND patients. Despite subtle phenotypic differences, there was inexorable disease progression in MND-M patients, and the overall survival was similar to sporadic and familial MND cohorts. Cortical dysfunction was evident in MND-M patients and was similar to findings in sporadic and familial MND cohorts. Taken together, the present findings suggest that MND-M represents a phenotypic variant of MND characterised by a predominant lower motor neuron syndrome and that any association between malignancy and MND is co-incidental.

## 9. Motor neuron disease and cancer

Previous epidemiological studies have failed to establish a link between cancer and MND (Chio et al., 1988; Fois et al., 2010; Freedman et al., 2005). Data derived from nine US population-based cancer registries did not report an increased risk of ALS mortality in patients suffering with cancer. Specifically, the previously suggested association between MND and lymphoproliferative diseases was not established (Freedman et al., 2005, Gordon et al., 1997). The lack of association between MND and malignancy was subsequently confirmed by a UK epidemiological study (Fois et al., 2010). The conclusions from these epidemiological studies were that any association between MND and malignancy was co-incidental. Although MND-M patients in the current cohort exhibited subtle phenotypic differences to other MND cohorts, the inexorable disease progression, comparable survival, and presence of cortical dysfunction, suggest that MND-M is a phenotypic variant of MND. This notion is further supported by pathological findings of TDP-43 inclusions on post-mortem studies.

The notion of a co-incidental association between MND and malignancy was also supported by a smaller observational study (Forsyth et al., 1997), although it was suggested that in patients

presenting with a rapidly progressive MND phenotype or PLS-like presentation, a careful search for malignancy may be warranted. The present study extends these findings by suggesting that in predominantly LMN MND phenotypes, malignancy surveillance may be warranted.

Cortical hyperexcitability appears to be an important pathophysiological mechanism in sporadic and familial MND phenotypes (Geevasinga et al., 2015, Vucic and Kiernan, 2007, Vucic and Kiernan, 2006, Vucic et al., 2008, Vucic et al., 2013). Supporting this notion are findings that cortical hyperexcitability is an early and specific feature of MND, at times preceding the development of LMN dysfunction, and correlating with biomarkers of peripheral neurodegeneration (Menon et al., 2015, Vucic et al., 2006). In addition, specific clinical features of sporadic MND, such as the split-hand signs (Menon et al., 2014), as well as the patterns of disease spread (Menon et al., 2017), appear to be associated with cortical hyperexcitability. In the present study, MND-M patients exhibited cortical dysfunction that was within the spectrum inherent for classical sporadic and familial MND cohorts, thereby implying a similarity of pathophysiological processes across the MND cohorts.

In conclusion, the present study suggests a co-incidental association between MND and malignancy. This is underscored by cortical dysfunction and clinical findings which seems within the spectrum of abnormality evident in classical MND phenotypes.

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## Declaration of Competing Interest

Dr. Higashihara, Dr. Menon, Dr. Geevasinga, Dr. Van den Bos report no disclosures. Dr. Kiernan reports other from Editor-in-Chief of Journal of neurology, neurosurgery and psychiatry, non-financial support from Motor Neurone Disease Handbook. Dr. Vucic reports honoraria from Merck Serono Australia, Sanofi Genzyme, and CSL Behring.

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