Is there a paraneoplastic ALS?

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Abstract

Our objective was to examine the strength of evidence in support of the paraneoplastic syndrome (PNS) as one cause of ALS and, if the association appears more likely than chance, determine which features of ALS imply concurrent malignancy. We reviewed the literature on concurrent ALS and neoplasia assessing the strength of evidence for the association. Most accounts of ALS and neoplasm are case reports or small uncontrolled series. In order of strength of evidence, three clinical situations that support a paraneoplastic aetiology for ALS are: 1) laboratory evidence of well-characterized onconeuronal antibodies, most often anti-Hu, anti-Yo or anti-Ri; 2) co-occurrence of ALS and a neoplasm known to cause PNS, usually lymphoma or cancer of the breast; and 3) combined ALS and a neoplasm not classically associated with PNS, without detectable onconeuronal antibodies. Clinical features that warrant evaluation of neoplasm include upper motor neuron disease in elderly females, rapid progression, non-motor signs, and young onset. In conclusion, most examples of ALS and neoplasm do not constitute a classically established PNS. Rare instances of elevated onconeuronal antibody titres or typical neoplasm, implies that, albeit rare, the PNS is one of a multitude of causes of ALS.

Key words: Motor neuron diseases, paraneoplastic, review

Introduction

Currently, the diagnosis of amyotrophic lateral sclerosis (ALS) is made clinically and only after exclusion of other diseases that could produce similar symptoms. One disorder that is commonly investigated is neoplasm or ALS as a paraneoplastic syndrome.

Paraneoplastic neurological syndromes are the result of an abnormal autoimmune reaction launched against certain antigens found in both the tumour and the nervous system. Considerable progress has been made in screening methods for paraneoplastic neurological syndromes through advances in immunological research, resulting in the identification of a growing panel of what are referred to as onconeuronal antibodies. In most cases, these antibodies are pathognomonic for the paraneoplastic nature of the neurological disorder.

ALS and motor neuron diseases do not constitute one of the classically established paraneoplastic syndromes. Most published examples are of single cases or small series, casting doubt on the existence of an association.

In this article, we review the current understanding of concurrent ALS and neoplasia with the aim of determining whether, in 2014, it is still possible to suggest that ALS could sometimes be induced by an underlying neoplasm and, if so, to identify the circumstances most likely to give rise to paraneoplastic ALS.

Motor neuron diseases

Motor neuron diseases (MND) are a group of neurological disorders that lead to the degeneration of upper (UMN) or lower motor neurons (LMN). Three major categories include primary lateral sclerosis (PLS) with features restricted to the UMN: progressive muscle atrophy (PMA) in which only LMNs are involved and amyotrophic lateral sclerosis (ALS), which is characterized by degeneration of UMN as well as bulbar and spinal LMNs (1). Patients with ALS die from respiratory failure in a...
median of 36 months after symptom onset (1). In the absence of diagnostic markers, other conditions mimicking ALS are excluded before the diagnosis is made with certainty. A paraneoplastic syndrome is one possible explanation when a patient develops motor neuron degeneration.

While a number of studies have explored the incidence, phenotype and prognosis of paraneoplastic ALS, a growing body of literature is also exploring non-paraneoplastic relationships between neoplasm and motor neuron disease. Among possible explanations for this broader convergence is the effect of physiological mechanisms disturbing cell machinery during ALS and carcinogenesis (irreversibility in opposition to resistance to cell death, respectively); epidemiological studies that focus on the cooccurrence of seemingly disparate diseases could point the way toward better understanding of both disorders conditions (2–4).

Studies that examine the overlap of MND and cancer have used heterogeneous methodological approaches, but some consistent findings have surfaced. While large studies have not shown a higher risk of mortality due to ALS among all patients with all types of neoplasia, an increased risk of ALS has been found with specific types of cancer, including melanoma and, to a lesser degree, brain tumours and cancer of the tongue. These associations (mostly consistent across studies) could be real, or due to bias related to retrospective study design with multiple statistical comparisons.

## Paraneoplastic neurological syndromes

Paraneoplastic neurological syndrome (PNS) is a term used to describe many conditions affecting the nervous system in patients with cancer but which are not caused by the cancer itself. PNS are therefore not related to tumour invasion, metastatic spread or an infectious, iatrogenic or metabolic disorder. Symptoms arise as a result of an immune cross-reaction between antigen epitopes in the tumour and epitopes present in the nervous system. PNS occur in less than 1% of cancer patients (5).

A major difficulty in making the diagnosis of a PNS lies in establishing a clear causal link between the tumour and the neurological condition, since arbitrary combinations of disorders can occur. Cancer is a common disease and the diagnosis of a tumour in a patient with a neurological disorder does not necessarily mean that the neurological symptoms are caused by immune cross-reactivity as described above or are even related to the tumour.

Advances in immunology and the identification of onconeural antibodies – currently one of the key elements in the diagnosis – have had a major impact on the understanding of PNS. PNS arise while the tumour is still clinically occult in two-thirds of cases or develop once treatment for cancer has commenced (6). Several presentations have been described, the most common being a cerebellar syndrome or sensory neuronopathy, which are thought to represent about half of all PNS. Paraneoplastic motor neuron disorders appear to be much rarer with estimated frequency of 2% (6). The cancers most frequently associated with PNS are small-cell lung cancer (SCLC) and gynaecological cancers (breast and ovarian), which together account for nearly two-thirds of PNS. Lymphoma is diagnosed in 6% of cases (6).

The diagnosis of PNS is now confirmed by the presence of onconeural antibodies that nonetheless go undetected in 18.3% of cases (6). The most commonly identified syndromes related to specific antibodies include neuronopathy with anti-Hu (anti-neuronal nuclear antibody type 1 (ANNA-1)) antibodies, typically in association with SCLC; subacute cerebellar degeneration and anti-Yo (type 1 Purkinje cell cytoplasmic autoantibodies (PCA-1)) antibodies, due most often to gynaecological cancers; and opsoclonus-myoclonus and anti-Ri (anti-neuronal nuclear antibody type 2 (ANNA-2)) antibodies, usually in association with breast or SCLC (7). Antibodies are detected with immunohistochemical stains of blood specimens. The international classification currently contains two levels of evidence for PNS: definite and possible (Table I).

### Table I. Diagnostic criteria for paraneoplastic neurological syndromes (PNS) (according to Graus et al., 2004) (7).

<table>
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<th>Definite:</th>
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<tr>
<td>1. Classical neurological syndrome (encephalomyelitis, limbic encephalitis, cerebellar degeneration, opsoclonus-myoclonus, sensory neuronopathy, gastrointestinal pseudo-obstruction, Lambert-Eaton syndrome, dermatomyositis) combined with cancer developing within five years after onset of the neurological syndrome.</td>
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<tr>
<td>2. Non-classical neurological syndrome that regresses or is significantly improved after specific treatment for cancer without immunomodulator therapy supporting the absence of a spontaneous remission of the neurological symptoms.</td>
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<td>3. Non-classical neurological syndrome associated with a high titre of a well-characterized onconeural antibody (‘well-characterized’ refers to Hu, Yo, Ri, CV2/CRMP5, or amphiphysin antibodies) and a cancer that develops within five years after onset of the neurological syndrome.</td>
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<tr>
<td>4. Classical neurological syndrome with or without a high level of well-characterized onconeural antibodies without cancer.</td>
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<th>Possible PNS:</th>
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<td>1. Classical neurological syndrome without onconeural antibodies or cancer but with a high risk of cancer.</td>
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<tr>
<td>2. Classical neurological syndrome with or without partially characterized onconeural antibodies and no cancer.</td>
</tr>
<tr>
<td>3. Non-classical neurological syndrome without onconeural antibodies but with cancer discovered within two years after onset of the neurological syndrome.</td>
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Although motor impairment is one of the neurological symptoms of paraneoplastic encephalomyeloneuropathies, this paper deals with paraneoplastic motor neuron diseases only.

**Motor neuron diseases with onconeural antibodies**

Few case series have reported well-characterized onconeural antibodies in patients with MND. The antibodies most often described were Hu and, rarely, Ri, Yo or CV2/CRMP5 antibodies.

Elevated Hu antibody titres have been reported in five patients with MND, consisting of four cases of typical ALS and one of ‘flail arm syndrome’. With the exception of the case reported by Lee et al. (8), whose initial symptoms developed around the age of 30 years, all were males aged approximately 60 years (9,10). Motor impairment was accompanied by dysautonomic symptoms, cognitive deterioration, sensory signs or cranial nerve impairment in three cases and was purely motor in the remainder (9,10).

In four cases, three with SCLC associated with Hu antibodies and one with prostate cancer, the tumour was diagnosed within the year following onset of neurological signs. In the remaining case, no tumour was found despite an exhaustive work-up (8). Chemotherapy led to a modest improvement in two of the five cases, with death occurring after 5–30 months. One patient died as a direct result of the motor impairment. In the case reported by Forsyth et al., an inflammatory infiltrate in the grey matter of the anterior horn was found at autopsy (10).

A 49-year-old female suffered from combined high titres of Ri antibodies and MND, manifest as progressive weakness related to LMN degeneration. The neurological impairment extended beyond the motor neuron system to involve abnormalities in proprioception and vigilance (11). Although treatment of her lymphoma did not produce neurological improvement until immunomodulator therapy was instituted, the link between reduced antibody levels, neurological improvement and immunolabelling of the tumour with anti-Ri antibodies supports a paraneoplastic aetiology.

Combined Yo antibodies and ALS were reported in a 67-year-old female with ovarian cancer whose neurological condition did not improve once the tumour was removed (12). CV2/CRMP5 antibodies were detected in a 29-year-old male who after three years of close monitoring, had no identifiable malignancy (13). Ferracci et al. reported a patient with pure LMN degeneration, which preceded the discovery of breast cancer by four months (14). A novel onconeural antibody that reacted with epitopes located in the nodes of Ranvier was identified. Further investigation showed that the epitope was β-spectrin which, to date, has only rarely been identified as a target of autoantibodies (14,15). The clinical features supporting a paraneoplastic aetiology included young age and the acute or subacute onset of motor impairment.

The rare instances of subacute MND, identifiable onconeural antibodies, and improvement with immunomodulatory therapy support a paraneoplastic aetiology. Most reports, however, suggest rhomboencephalitis more than pure ALS or MND underlying the neurological findings. These reports also highlight the need to exercise caution in assuming a causal relationship when a neurological disorder and onconeural antibodies occur in the same patient. Therefore, routine testing for PNS seems to not be justified in most patients. In one sample of 145 patients with MND and no other neurological signs, no patient had highly elevated titres of onconeural antibodies (16).

**Motor neuron disease and lymphomas**

Hodgkin’s and non-Hodgkin’s lymphoma is one of the most common cancers reported in association with MND (17). Different forms of MND observed with lymphoma include isolated LMN disease, PLS and ALS (11,17–19). For many years it was thought that the most common neurological syndrome consisted of progressive, subacute, asymmetric and moderately disabling leg weakness due to LMN degeneration, sometimes with spontaneous recovery, but this view has now been called into question (10,20).

In one early paper, 88% of patients had signs of ALS, with motor impairment generally preceding discovery of the lymphoma (17). The temporal occurrence provides an index of the relationship between disorders. When lymphoma preceded ALS in one series, the delay between diagnoses ranged from four to 25 years; a PNS becomes an increasingly unlikely explanation for the association as time-span between the disorders increases (17). In the same series, clues to the presence of a lymphoma in a person diagnosed as having ALS included age of onset younger than 40 years, monoclonal gammopathy, or CSF protein level higher than 0.75 g/l (17).

**Motor neuron disease and Hodgkin’s disease**

Gordon et al. compiled 56 patients with MND and a lymphoproliferative disease (LPD), 26 evaluated by the investigators and 30 taken from the literature (17). While the tumour and the MND occurred concurrently in most patients, the link between the two was uncertain. The notion of a PNS is particularly dubious when the neurological symptoms can be attributed to delayed iatrogenic complications of the lymphoma itself rather than a paraneoplastic syndrome. In nine patients the lymphoma preceded onset of MND by an average of 10.8 years. In 16 patients the diagnosis of LPD was made during the work-up for ALS (17). A long interval between
diagnosis of LPD and MND makes a paraneoplastic cause unlikely, although the spectrum of PNS is still incompletely defined. Other associations between the disorders are possible, including a medical trigger of motor neuron degeneration in a predisposed individual. Strength of the study is the large sample relative to other reports. Weaknesses include referral and selection bias at this centre with a particular interest in the association, and absence of a control group.

Motor neuron disease and non-Hodgkin’s lymphoma

Briani et al. recently extracted the files of 62 patients with PNS and lymphoma from the PNS Euronet-work database (18). This has been the only study to include screening for onconeural antibodies in patients with lymphoma.

In the database, MND was recorded with non-Hodgkin’s lymphoma, but not Hodgkin’s lymphoma. Of four patients, three had ALS and one had PLS. None of these patients had onconeural antibodies or cerebrospinal fluid anomalies. No improvements in the neurological condition were reported after the lymphoma was treated (18).

Motor neuron diseases and other malignant blood disorders

Malignant blood disorders other than lymphoma are occasionally found underlying a PNS. Gordon et al. reported multiple myeloma and Waldenström’s macroglobulinaemia in 23% of their cohort (17). One patient showed clinical stabilization of clinical PMA for 34 months following treatment of myeloma with prednisone, melphalan and radiation therapy. Other disorders in the series included chronic lymphocytic leukaemia and follicular cell carcinoma. More research is needed to establish a causal link between LPD and MND with certainty.

Motor neuron disease and solid cancers

Breast cancer

SCLC represents almost 40% of the tumours associated with PNS (6), but MND appears to be more common in patients with cancer of the breast than of the lung.

ALS can occur, but the most frequently reported form of MND in the setting of breast cancer is PLS (10,21,22). It should also be noted that co-occurrence of the disorders does not establish causality owing to the high incidence of breast cancer in females at the ages most susceptible to MND.

The link between breast cancer and MND is discussed in numerous articles, but few cases meet criteria for a PNS. A short interval between the two events or changes in the neurological symptoms and signs after the cancer treatment appear to be firm arguments supporting a causal link between tumour and neurological disorder. The standard laboratory work-up has, to date, contributed little to understanding of the association. The cerebrospinal fluid has usually been normal, although protein levels have occasionally been high or intrathecal immunoglobulin synthesis present, and tests for onconeural antibodies have been negative (10,22).

Rare combinations of tumours and motor neuron disease

A link between lung cancer and MND predates the identification of Hu antibodies, with reports of ALS symptoms leading to the discovery of cancer, in most cases lung cancer. A striking example, published by Mitchell and Olczak, concerned a 54-year-old male who, over a six-month period, developed symptoms typical of ALS and was then diagnosed with a pulmonary adenocarcinoma (23). Surgical removal of the tumour prompted immediate regression of fasciculations and return to near-normal motor function over six months, suggesting that the motor symptoms were induced by a paraneoplastic syndrome (23).

Exceptional cases of ALS combined with kidney cancer have been reported (24,25). Review of these cases nonetheless casts doubt on whether a PNS could be at play. One patient, a 59-year-old male whose symptoms began with fasciculations and muscle weakness in the upper limbs, was found to have a kidney tumour during work-up for the MND. While the neurological signs improved after removal of the tumour and regressed at the time a second tumour was discovered in the other kidney, the absence of onconeural antibodies and the dearth of clinical findings confirming the diagnosis of ALS make it difficult to exclude other causes of the weakness (25). In contrast, one case reported by Evans et al. showed improvement in objective tests along with signs of MND following nephrectomy, consistent with a paraneoplastic aetiology (24).

Strategy

PNS are rare (3) and there is currently little evidence to suggest that patients with the symptoms of typical ALS should be systematically screened for onconeural antibodies (13,26) or a paraneoplastic syndrome. Screening for a PNS is, however, justified in two specific instances (Table II):

- Predominantly UMN forms of MND in females aged 50 years and above who are at risk for breast cancer (10,14,21,22).
- Patients with ALS that has atypical features such as young age at onset, presence of neurological signs affecting systems other than motor neurons and, especially, acute or subacute progression (9,10,11,14).
In these cases, a search for onconeural antibodies and whole-body 18 fluorodeoxyglucose-PET scan are the best screens for malignancy (27,28). Priority is given to treatment of any cancer found in association with ALS (29). No therapeutic strategy has been proved effective for the treatment of PNS, but immunomodulating or immunosuppressant agents can be tried and appear effective in some patients (29), especially those with definite or possible PNS (7,29).

It should be noted that the presence of onconeural antibodies does not ensure that the MND results from a paraneoplastic syndrome. Diagnosis of a PNS depends on an established link between the identified antibody and tumour, and detailed exploration of neurological symptoms whose course is modified by that of the underlying cancer (30).

Finally, it is important to bear in mind that the typical age of onset of many of the cancers described here and of ALS overlap; the two diseases may arise concomitantly.

**Does paraneoplastic ALS exist?**

Paraneoplastic forms of ALS or other motor neuron diseases should be entertained when 1) the course of the MND mimics that of the tumour; 2) a link can be established between an identified onconeural antibody and tumour; and 3) inflammatory infiltrates are found in the anterior horn of the brain at autopsy.

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