Paraneoplastic neurological syndromes (PNS) are rare, but severely debilitating complications of cancer. These disorders are a non-metastatic phenomenon and are considered to have an immune-mediated aetiology. In 1964 Wilkinson first identified complement-fixing antibodies in the serum of four individuals with cancer who were also affected by sensory neuropathy and proposed that:

"the tumour in a patient with sensory neuropathy may contain antigenic determinants not present in other tumours, and that these determinants are shared by some constituent of the central nervous system (CNS). An immune reaction against such tumour determinants might then incidentally cause damage to the CNS".1

This hypothesis has proved to be correct since it has subsequently been confirmed that tumours from affected individuals aberrantly express neuronal antigen. However, neuronal antigens are frequently expressed by tumours that are not complicated by PNS and the effector mechanisms that result in neurological dysfunction have not been defined in the majority of instances. A more comprehensive explanation on the current theories of the immunopathogenesis of PNS can be found elsewhere2,3 and the focus of this article is to summarise diagnostic and therapeutic aspects in the clinical investigation and management of PNS.

Diagnosis of paraneoplastic neurological syndromes

In two-thirds of cases affected individuals will present with a neurological syndrome prior to diagnosis of the associated malignancy. PNS are a clinically heterogeneous group of disorders with subacute sensory neuropathy (+/- encephalomyelitis), cerebellar dysfunction (+/- brainstem syndrome) and limbic encephalitis being the most frequently encountered disorders. However, virtually every neurological syndrome from Parkinsonism to gastrointestinal dysmotility syndromes has been reported as a paraneoplastic complication of cancer.

When presented with a patient with an unexplained neurological disorder there are often obvious clues in the history to suggest that a neurological syndrome has a paraneoplastic aetiology. For example, a history of smoking and weight loss is typically indicative of an associated lung cancer. Nevertheless, in other cases there is frequently nothing in either the history or examination to alert the investigating physician to the presence of an underlying malignancy, notably even disseminated ovarian malignancy in patients presenting with a subacute cerebellar syndrome can frequently be asymptomatic at the time of presentation with neurological dysfunction. Furthermore, conventional imaging modalities often provide equivocal results and therefore, a definitive diagnosis often rests upon the detection of “paraneoplastic anti-neuronal antibodies” within the serum of affected individuals.

Routine laboratory testing for paraneoplastic anti-neuronal antibodies initially involves testing of patient serum using anti-neuronal antibody present within serum binds antigen within monkey cerebellum

**Figure 1:** a. Human serum is incubated on monkey cerebellum, after washing off any unbound antibodies, antibody with specific binding to neuronal antigen is detected using a FITC-conjugated secondary antibody that can be visualised under a fluorescence microscope. b. APCA-1 - antibody binds to a Purkinje cell cytoplasmic antigen - confirmed as anti-Yo antibody by western blot against recombinant antigen. c. ANNA-1 - antibody binds to an antigen that predominantly located in the neuronal nucleus, but is absent from the nucleolus. Some cytoplasmic staining is also observed. Antibody confirmed as anti-Hu by western blot against recombinant antigen. (Figures b and c reproduced from Advanced Atlas of Autoantibody Patterns with permission, courtesy of Professor AR Bradwell, Department of Immunology, University of Birmingham)
indirect immunofluorescence (or immunohistochemistry) (figure 1a). Since paraneoplastic antibodies react with antigens that in most cases are specifically expressed in neurological tissues (the Ma1 antigen is additionally expressed in the testis) an appropriate neurological tissue (eg monkey cerebellum) is probed using patient serum and anti-neuronal antibody reactivity is detected using a labeled secondary anti-human antibody that allows visualisation of specific antibody binding. The tissue distribution of target antigen determines the pattern of antibody binding observed on indirect immunofluorescence. For example, APCA-1 is an acronym for anti-Purkinje cytoplasmic antibody (figure 1b) and ANNA-1 is anti-neuronal nuclear antibody (figure 1c). However, the gold standard for the confirmation of paraneoplastic antibody specificity detected using indirect immunofluorescence is western blot of the patient serum against defined recombinant neuronal antigen. The majority of paraneoplastic antigens observed by immunofluorescence methods have been identified by using serum from patients with PNS to screen cerebellar cDNA libraries: the nomenclature preferred by most investigators for paraneoplastic antibodies refers to the target antigen (eg Hu, Yo, Ri); antigens being named according to the first two letters of the surname of the patient whose serum was used to screen the cerebellar cDNA library and define the antigen.4

Although some investigators argue that paraneoplastic anti-neuronal antibodies can be identified by their characteristic pattern of staining observed on indirect immunofluorescence alone it is now apparent that several antibodies of different specificity react with target antigens, which have a similar distribution. For example, APCA-1, PCA-2, and anti-Tr each react with a Purkinje cell cytoplasmic antigen. Failure to define the appropriate antibody specificity by western blot may lead to formulation of an inappropriate plan of investigation, since not only does identification of paraneoplastic antibodies within the serum of a patient presenting with an apparently idiopathic neurological syndrome define the paraneoplastic aetiology of the disorder, but knowledge of the antibody specificity can assist the physician in the search for the underlying tumour (table one). There are a number of other issues in the interpretation of paraneoplastic antibody results that are potential traps to the unwary. Firstly, paraneoplastic antibodies are only detected in 40% of PNS cases. Secondly although paraneoplastic antibodies are a specific marker for an underlying malignancy the HuD antigen, a marker of subacute sensory neuropathy and encephalomyelitis, is expressed by all small cell lung cancers (SCLC) and approximately 15% of SCLC patients will harbour low-titre (<1:500) anti-Hu antibodies in the absence of neurological dysfunction. Interestingly this subgroup of patients is more likely to have limited disease stage, complete response to therapy and longer survival.5

In patients that are seropositive for paraneoplastic antineuronal antibodies and in seronegative patients in whom a paraneoplastic neurological syndrome is suspected, a number of studies have now been able to demonstrate the usefulness of [18F] fluoro-2-deoxyglucose positron emission tomography (FDG-PET) when conventional imaging techniques are negative or provide equivocal results. In a study of 43 patients suspected of having a PNS in whom no tumour was identifiable by conventional imaging or bronchoscopy, a hypermetabolic focus suggestive of malignancy was identified in 16 cases. Although a false-positive scan was obtained in a patient with Guillain-Barre syndrome and negative studies were observed in two patients with anti-Hu antibodies, thereby alluding to some limitations of this investigation modality, FDG-PET is generally proving to be a valuable tool in the tumour diagnosis of patients suspected to have a PNS. Recent advances that acquire and fuse FDG-PET and CT data sets will further assist in precisely defining the anatomical site of malignancy.

**Treatment of patients with paraneoplastic neurological syndromes**

In the two-thirds of patients that present with a neurological syndrome prior to diagnosis of malignancy it is clearly imperative to establish tumour diagnosis, and in those patients in whom a diagnosis of cancer is already established the onset of the neurological syndrome may coincide with disease recurrence. Therefore the onset of a PNS should prompt rapid investigation and instigation of appropriate anti-tumour therapy as soon as possible. In addition to treatment of the underlying malignancy in some cases successful tumour

**Table 1: Some paraneoplastic anti-neuronal antibodies and their clinical associations**

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Also termed</th>
<th>Antigen</th>
<th>Neurological syndrome</th>
<th>Associated tumours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Hu</td>
<td>ANNA-1</td>
<td>HuD</td>
<td>Paraneoplastic encephalomyelitis/ subacute sensory neuropathy</td>
<td>Small cell lung cancer (80%) Neuroblastoma</td>
</tr>
<tr>
<td>Anti-Yo</td>
<td>APCA-1</td>
<td>cdr 62, 34 Purkinje cytoplasmic</td>
<td>Cerebellar degeneration</td>
<td>Ovary-gynaecological Breast</td>
</tr>
<tr>
<td>Anti-Ri</td>
<td>ANNA-2</td>
<td>Nova1,2</td>
<td>Brainstem-cerebellar (Opsoclonus ~ 50%)</td>
<td>Breast (50%)</td>
</tr>
<tr>
<td>Anti-Ma1</td>
<td>Ma1,2</td>
<td>Neuronal nuclear</td>
<td>Brainstem-cerebellar</td>
<td>Various</td>
</tr>
<tr>
<td>Anti-Ma2</td>
<td>Anti-Ta</td>
<td>Ma2</td>
<td>Brainstem-cerebellar/limbic</td>
<td>Testis</td>
</tr>
<tr>
<td>Anti-Tr</td>
<td>Purkinje cytoplasmic</td>
<td>Cerebellar</td>
<td>Hodgkins</td>
<td></td>
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<tr>
<td>Anti-GluR</td>
<td>Glutamate receptor</td>
<td>Cerebellar</td>
<td>Hodgkins</td>
<td></td>
</tr>
<tr>
<td>Anti-retinal</td>
<td>Recoverin Photoreceptors</td>
<td>Retinopathy</td>
<td>Small cell lung cancer</td>
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</tbody>
</table>
treatment is associated with beneficial effects on the neurological syndrome. This is illustrated by a study in which 51 patients with small cell lung cancer (SCLC), subacute sensory neuropathy/encephalomyelitis and anti-Hu antibodies received conventional SCLC treatment with 26 receiving additional immunotherapy to treat their neurological syndrome. Stabilisation of neurological symptoms was witnessed in 70% and complete response to tumour therapy was the only predictor of stabilisation of neurological symptoms. Even more striking results have been observed in the treatment of limbic encephalitis associated with testicular cancer and anti-Ma antibodies, with one study reporting complete resolution and partial response of neurological symptoms in seven patients with anti-Ma antibodies. Notably the improvement observed in all six cases with testicular cancer correlated with a complete response to tumour therapy. 

It remains to be established whether immunotherapy has any significant role to play in the treatment of neurological dysfunction in patients with PNS for several reasons. Firstly, PNS have been reported to improve spontaneously, although this is an infrequent observation. Secondly, PNS are rare disorders making it difficult to organise placebo-controlled, randomised, double-blinded trials. Finally, PNS are a heterogeneous group of disorders and may not all respond in the same way to a particular immunotherapy regimen. Nevertheless, there is a general consensus that immunomodulatory therapies are ineffective despite numerous case reports of neurological improvement following corticosteroids, ivlg, plasma exchange and cyclophosphamide. While one study has noted that administration of tacrolimus markedly reduced the number of activated T cells within the CSF and peripheral blood of three patients with paraneoplastic cerebellar degeneration, no significant arrest in progression of neurological disability was observed. 

The results of the largest trial of immunotherapy in PNS to date recently have been published. This well-designed prospective trial included 20 patients with PNS after exclusion of those patients that were neurologically stable, those with chronic indolent disease and those with long-standing neurological deficits considered to be irreversible. It was planned that all 20 patients receive a total of five plasma exchanges. The first treatment arm composed of 10 patients without evidence of active malignancy who were seropositive for paraneoplastic antibodies or had a cancer that did not require chemotherapy. This group was administered cyclophosphamide, however, in six out of 10 patients the six-month course could not be completed mainly due to profound leucopaenia. The second group of 10 patients received plasma exchange and standard chemotherapy. In total 10 of the 20 patients improved or stabilised with no significant differences between the two groups. The remaining patients’ neurological status worsened and four died prior to the six-month study endpoint. On the basis of this study it is difficult to evaluate the role of plasma exchange and it should be noted that four of the 20 patients failed to complete the planned five exchanges. 

My own practice is to administer plasma exchange to cases of limbic encephalitis in which dramatic improvements have been observed; otherwise patients receive a trial of ivlg.

**Prognosis of paraneoplastic neurological syndromes**

It is a devastating situation for patients to be faced with not only the prospect of cancer, but also progressive neurological dysfunction. Nevertheless, the previous section highlights that neurological deterioration might be arrested following successful tumour treatment. Furthermore, it is widely believed by investigators of PNS that affected patients have an improved tumour prognosis since it is thought that the immune response resulting in neurological dysfunction is also eliminating tumour cells aberrantly expressing neuronal antigen. This hypothesis of natural tumour immunity is based on some laboratory evidence and a number of clinical observations. For example, in one study of patients with anti-Hu antibodies a tumour could not be identified even with careful post mortem examination in 16.5% of cases. However, there are numerous ways that tumours can evade immune surveillance and the report of Keime-Guibert et al’ observed patients with subacute sensory neuropathy/encephalomyelitis and SCLC had a median survival similar to that observed in SCLC patients without neurological dysfunction. Nevertheless, a higher probability of survival of PNS cases at 30 months in this study indicates that there is a subgroup of subacute sensory neuropathy/encephalomyelitis patients with improved overall prognosis.

In patients with paraneoplastic cerebellar degeneration (PCD) and anti-Yo antibodies an underlying gynaecological malignancy carries a poor prognosis. The study of Rojas et al. included 18 patients with PCD and anti-Yo antibodies and in 15 metastatic disease was evident at presentation and tumour progression was the cause of death in just over half of the cases. Interestingly, patients with breast cancer had a significantly better prognosis than those with gynaecological malignancy and in my own series of eight anti-Yo associated PCD cases a similar improved prognosis was observed in patients with breast cancer. Furthermore, in support of the tumour immunity hypothesis metastatic breast cancer may occur in PCD patients in the absence of a detectable primary lesion even with five years of follow up.

**Conclusion**

Despite being rare neurological complications of cancer almost all neurologists and oncologists will encounter patients with PNS. PNS are typically subacute syndromes and most neurological deficits once established are irreversible. Since successful treatment of the underlying malignancy can arrest neurological deterioration it is important that the diagnosis of PNS is rapidly established and anti-tumour treatment initiated immediately. The more widespread availability of FDG-PET coupled to paraneoplastic antibody testing can significantly improve the speed of diagnosis, and considered application of test results can potentially have profound effects on patient morbidity, eg Rosnefeld et al reporting that a partial improvement in neurological function was observed in two patients with progressive neurological deterioration who underwent orchidectomy because of positive testing for Ma2 antibodies and “minimal abnormalities on testicular ultrasound”. 

**References**


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