Paraneoplastic neurological disorders

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ABSTRACT

Paraneoplastic syndromes are typical among middle aged to older patients and they most commonly present with cancers of the lung, breast, ovaries or lymphatic system (a lymphomas). Paraneoplastic syndromes are a group of rare disorders that are triggered by an abnormal immune system response to a cancerous tumor known as a “neoplasm.”

The most common cancers associated with paraneoplastic neurological disorders (PNDs) are breast, ovarian and lung cancer, but many other cancers have been linked to PNDs as well. PNDs are usually severe, often disabling, and often multifactorial. The cancers causing PND are often asymptomatic and sometimes occult. PND can affect any part of the nervous system. The symptoms and signs of paraneoplastic syndromes are diverse, but certain features are common. Many patients with paraneoplastic syndromes have antibodies in their serum and cerebrospinal fluid. Paraneoplastic syndromes can be due to a number of causes including hormones or other biologically active products made by the tumor, blockade of the effect of a hormone, autoimmunity, immune-complex production, and immune suppression.

The identification of antibodies and their target neural antigens has substantially advanced our ability to make an early diagnosis and has led to the concept that PNDs are immune mediated. The cytotoxic T-cells play a major role in the pathogenesis of PND. Paraneoplastic neurological disorders, which often precede the diagnosis of the tumor by months, may be present in about 1% of carcinoma patients. Dramatic and tragic disease accompanies the presence of antibodies to discrete portions of the nervous system collected under the term paraneoplastic syndromes.

Key words: paraneoplastic neurological disorders, immunity, antibodies

Paraneoplastic syndromes refer to a large group of complications and medical problems in patients who suffer from cancer. The term paraneoplastic comes from the Greek roots para (alongside or near), neo (new), and plastic (being formed or shaped), and thus means “beside a new formation, or cancer.” The term paraneoplastic syndrome refers to symptoms or signs resulting from damage to organs or tissues that are remote from the site of a malignant neoplasm or its metastases.
Sometimes the symptoms of paraneoplastic syndromes show even before the diagnosis of a malignancy (1,2).

Paraneoplastic syndromes can affect most organs and tissues. Body systems that may be affected by paraneoplastic syndromes include neurological, endocrine, cutaneous, renal, hematologic, gastrointestinal, and other systems (3). The most common manifestations of paraneoplastic syndromes are cutaneous, neurological, and endocrine disorders (4). The symptoms and signs of paraneoplastic syndromes are diverse, but certain features are common (TABLE 1).

These disorders typically affect middle-aged to older people and are most common in individuals with lung, ovarian, lymphatic, or breast cancer. Most or all paraneoplastic neurologic disorders are immune mediated. Neurological disorders that are mediated immunologically by a plasma-membrane-directed effector antibody. Some of these disorders are believed to occur when cancer-fighting antibodies mistakenly attack normal cells in the nervous system.

Paraneoplastic neurological disorders are the manifestation of a multifaceted immune response initiated by multiple onconeural antigens that are presented to the immune system as the result of tumor cell death. Paraneoplastic disorders are cancer-associated conditions that cannot be explained by a tumor’s direct invasion of tissue, or by its treatment or consequences.

Not all cancers cause paraneoplastic syndrome. A paraneoplastic disorder may affect only one part of the nervous system, such as the cerebellum, or multiple areas at once. Paraneoplastic syndromes are rare, affecting fewer than 1 percent of patients with cancer (2).

Paraneoplastic neurological disorders (PNDs) are remote effects of systemic malignancies that affect the nervous system. The term PND is reserved for those disorders that are caused by an autoimmune response directed against antigens common to the tumour and nerve cells.

Symptoms of paraneoplastic neurological disorders may include ataxia (difficulty with walking and balance), dizziness, nystagmus (rapid uncontrolled eye movements), difficulty swallowing, loss of muscle tone, loss of fine motor coordination, slurred speech, memory loss, vision problems, sleep disturbances, dementia, seizures, sensory loss in the limbs (5).

The subacute presentation of most patients with paraneoplastic autoimmunity initially mimics common disorders such as stroke, a peripheral neuropathy, or multiple sclerosis.

Neurologic symptoms generally develop over a period of days to weeks and usually oc-
cur prior to the tumor being discovered. Symptoms of paraneoplastic syndromes of the nervous system usually appear when cancer is still in its early stages, often before you even know you have cancer.

A particularly devastating form of paraneoplastic syndromes is a group of disorders classified as paraneoplastic neurological disorders (PNDs) (1). These paraneoplastic disorders affect the central or peripheral nervous system and they are degenerative (3).

Paraneoplastic neurological disorders (PND) are remote effects of systemic malignancies that affect the nervous system.

Neurological manifestations of malignant diseases are common, disabling, and often multifactorial. The cancers causing paraneoplastic neurologic disorders are often asymptomatic and sometimes occult, it is the neurologic symptoms that take the patient to the doctor (5).

The combination of an indolent tumor and severe neurologic disability suggests effective antitumor immunity coupled with autoimmune brain degeneration. The neurologic disorder usually appears before the cancer has been identified. The term PND is reserved for those disorders that are caused by an autoimmune response directed against antigens common to the tumor and nerve cells (6).

The incidence of PND depends of the criteria used for the diagnostic. A PND should be diagnosed in a patient with cancer only after investigations have ruled out other possible causes.PND can affect almost any part of the nervous system (7).

Pathogenesis of the disease is more likely to be due to a cellular immune response than a direct action of the antibodies. T-cells are likely candidates for involvement in this cell-mediated mechanism (8).

Paraneoplastic syndromes include Lambert-Eaton myasthenic syndrome, stiff-person syndrome, encephalomyelitis, myasthenia gravis, cerebellar degeneration, limbic or brainstem encephalitis, neuromyotonia, opsoclonus, and sensory neuropathy.

Standard investigations including blood tests, MRI scanning, CSF analysis, and clinical neurophysiological testing are rarely helpful in confirming that a patient has a PND (9).

The finding of a formally characterized paraneoplastic autoantibody, or a combination of several, is an important guide to the underlying tumor pathology.

In general, paraneoplastic syndromes may be present in the patient before a diagnosis of cancer is made, or, as stated earlier, may be present at the time the patient is first diagnosed with cancer. Paraneoplastic neurological syndromes (PNS) are remote effects of cancer that are not caused by invasion of the tumor or its metastases. The diagnostic criteria for PNS were standardised in 2004.

If the central nervous system is involved, the tests should include cerebrospinal fluid (CSF), analysis for inflammatory cells, protein, evidence of intrathecal IgG synthesis and autoantibody profile.

The finding of CSF pleocytosis supports the diagnosis of an autoimmune inflammatory process and the paraneoplastic autoantibody profile in CSF may be informative.

If the patient has a past history of cancer, the antibody profile may on one hand mandate a search for recurrent cancer or on the other hand direct a search for a different primary malignancy.

The autoantibodies are classified by their reactivity with predominantly nuclear, cytoplasmic, or plasma-membrane components of cells in the central or peripheral nervous system.

Paraneoplastic neurological syndrome should only be defined by the well-characterised paraneoplastic autoantibodies (PNAs) (anti-Hu, anti-Ri, anti-Yo, anti-Ma2, anti-CV2 (CRMP-5) and anti-amphiphysin). The most frequent antineuronal antibody in paraneoplastic sensory neuronopathy is anti-Hu. High titer anti-Hu antibodies are associated with paraneoplastic encephalomyelitis and paraneoplastic sensory neuronopathy (PEM/SN). Low titer anti-Hu antibodies are strongly associated with SCLC and, in children, with neuroblastoma. Low titer anti-Hu antibodies in SCLC and neuroblastoma patients are not associated with paraneoplastic neurological disease. Patients with anti-Ma2 antibodies tend to be young (22-45 years of age) (7). The nomenclature of PNAs is confusing because different names have been promoted by different authors. CRMP-5-IgG and amphiphysin antibody have been fully characterized at the molecular level and have unambiguous western blot and immunostaining patterns of reactivity. In recent years increasing evidence came up for an autoimmune etiology of paraneoplastic polyneuropathies (PNP). However, the pathogenesis of these PNP is still not clear (10).
A paraneoplastic syndrome is a disease or symptom that is the consequence of the presence of cancer in the body, but is not due to the local presence of cancer cells. These phenomena are mediated by humoral factors (by hormones or cytokines) excreted by tumor cells or by an immune response against the tumor. Immunologic factors appear important in the pathogenesis of PNS because antineuronal autoantibodies and T-cell responses against nervous system antigens have been defined for many of these disorders. The immunologic response is elicited by the ectopic expression of neuronal antigens by the tumor. These events render those cell accessible to attack by activated T cells which readily cross the blood-brain barrier (11).

The analysis of humoral and cellular immune responses in cancer patients, had indicated for a long time that cancer specific antigens do indeed exist and are recognized by the immune system of the tumour bearing host (12). It is not yet known how a peripheral immune response initiated against the tumor leads to upregulation in the nervous system of major histocompatibility (MHC) class I proteins that display these antigenic peptides on the surface of neurons and glia.

Identification of the antibodies allows the PNS to be defined, which can otherwise be difficult.

The characterisation of the onconeural antigens varies significantly. However, in most cases the antigens have been identified and their respective genes have been cloned and sequenced.

Studies are directed at developing tests that detect the presence of antibodies. Most paraneoplastic neurological disorders reflect nervous system-specific autoimmune attack initiated by onconeural antigens released to peripheral lymphoid tissues from an unsuspected primary or recurrent neoplasm (3).

In most cases, autoimmune neurological disorders that are recognized today as

<table>
<thead>
<tr>
<th>PNA</th>
<th>Neuronal autoantigen(s)</th>
<th>Immunocytochemical staining pattern</th>
<th>PND</th>
<th>Tumour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Hu (ANNA-1)</td>
<td>35 and 40 kDa neuron specific RNA binding proteins</td>
<td>All neuronal nuclei including myenteric plexus weaker, cytoplasmic staining</td>
<td>PEM, PCD, PSN</td>
<td>SCLC, other carcinomas</td>
</tr>
<tr>
<td>Anti-Ri (ANNA-2)</td>
<td>55 and 80 kDa RNA neuronal binding protein</td>
<td>All CNS neuronal nuclei with nucleolar sparing, not DRG neurones (in contrast to Hu)</td>
<td>POM, PCD, BE</td>
<td>Breast, SCLC, gynaecological</td>
</tr>
<tr>
<td>ANNA-3</td>
<td>170 kDa</td>
<td>Purkinje-cell cytoplasm and nucleus renal glomerular podocytes</td>
<td>LE, PCD, PSN</td>
<td>SCLC oesophageal</td>
</tr>
<tr>
<td>Anti-Yo (PCA-1)</td>
<td>34 and 62 kDa DNA binding, gene transcription regulators</td>
<td>Purkinje cell cytoplasm and axons</td>
<td>PCD, peripheral neuropathy (rare)</td>
<td>Breast and gynaecological oesophageal</td>
</tr>
<tr>
<td>Anti-PCA 2</td>
<td>280 kDa</td>
<td>Purkinje-cell cytoplasm and other neurones</td>
<td>PEM, PCD, LEMS</td>
<td>SCLC</td>
</tr>
<tr>
<td>Anti-Ma 1</td>
<td>40 kDa</td>
<td>Nucleus</td>
<td>BE, PCD</td>
<td>Lung cancer</td>
</tr>
<tr>
<td>Anti-Ma 2 (Ta)</td>
<td>41.5 kDa</td>
<td>Nucleus perikaryon</td>
<td>LE, BE</td>
<td>Testicular cancer</td>
</tr>
<tr>
<td>Anti-Tr</td>
<td>Unknown Antigen</td>
<td>Purkinje cell cytoplasm, fine granular staining in molecular layer, all nuclei of CNS</td>
<td>PCD</td>
<td>Hodgkin’s disease</td>
</tr>
<tr>
<td>Anti-mGluR1</td>
<td>Metabotropic glutamate receptor</td>
<td>Purkinje cell cytoplasm</td>
<td>PCD</td>
<td>Hodgkin’s climbing fibres disease</td>
</tr>
<tr>
<td>Anti amphiphysin</td>
<td>128 kDa synaptic vesicle protein</td>
<td>Presynaptic nerve terminals of CNS</td>
<td>SPS, PEM</td>
<td>Breast, SCLC</td>
</tr>
<tr>
<td>Anti-VGKC</td>
<td>Voltage gated potassium channel</td>
<td>Peripheral nerve</td>
<td>Neuromyotonia</td>
<td>Thymoma, SCLC</td>
</tr>
<tr>
<td>Anti-VGCC</td>
<td>Voltage gated calcium channel</td>
<td>Pre-synaptic neuromuscular junction</td>
<td>LEMS, PCD, SCLC</td>
<td></td>
</tr>
<tr>
<td>Anti-AChR</td>
<td>ACh receptor</td>
<td>Post-synaptic Neuromuscular junction</td>
<td>MG</td>
<td>Thymoma</td>
</tr>
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</table>

**TABLE 2.** Paraneoplastic autoantibodies (PNAs), relevant autoantigens, characteristic staining patterns, and associated paraneoplastic neuronal disorders (PNDs) and tumours (1, 13)
Paraneoplastic neurological disorders complicate relatively few types of cancer. The factors determining the occurrence of autoimmunity in the context of cancer are complex and only partly understood (4). These include genes influencing the patient’s immune responsiveness, a multitude of potential onconeural antigens and endogenous adjuvant molecules in individual neoplasms, as well as environmental and therapeutical modulating factors.

In a variety of paraneoplastic PNP-patients antineuronal autoantibodies have been described. Screening sera for PNAs is performed by either indirect immunofluorescence or immunoperoxidase staining on fixed cryosections of cerebellar tissue. Samples are screened at 1/50, higher titres are normally of clinical significance (12).

Neuronal nuclear or cytoplasmic autoantibodies serve as serological markers for cytotoxic CD8+ T-cell-mediated mechanisms. They reflect an immune response triggered by peptides derived from an intracellular nuclear or cytoplasmic onconeural protein that is expressed in both the tumour and the nervous system.

ACh, acetylcholine; BE, brainstem encephalitis; CNS, central nervous system; LE, limbic encephalitis; LEMS, Lambert-Eaton myasthenic syndrome; MG, myasthenia gravis; PCD, paraneoplastic cerebellar degeneration; PEM, paraneoplastic encephalomyelitis; PNA, paraneoplastic neuronal autoantibodies; PND, paraneoplastic neurological disorder; POM, paraneoplastic opsoclonus and myoclonus; PSN, paraneoplastic sensory neuronopathy; SCLC, small cell lung carcinoma; SPS, stiff person syndrome (13).

From a scientific point of view, characterisation of the antigens recognised by paraneoplastic antibodies has led to the identification of proteins that are important for the functioning of the nervous system and tumorigenesis (14).

Paraneoplastic anti-neuronal antibodies bind to antigens in Purkinje cells and other neurones. In most studies about paraneoplastic neuropathies the patients have been selected by detection of an antineuronal antibody, there are no bigger studies giving the frequency of antineuronal antibodies in all paraneoplastic neuropathy patients. The percentage of antineuronal antibody-positives ranges from 27-50% in different studies (15).

The anti-neuronal antibodies are also found in patients with neurological syndromes of unknown aetiology and occasionally in healthy individuals. The antigens are generally neuronal specific and their cellular location is both cytoplasmic and nuclear. Their presence should, therefore, not be taken as the only condition for defining the neurological syndrome as paraneoplastic (16).

However, paraneoplastic neuropathy can also be associated with anti-ANNA-3, anti-CV-2 or other antineuronal antibodies and most of these autoantibodies are not strongly associated with a distinct clinical type of neuropathy. Indirect immunofluorescence on cerebellar tissue is the initial screen for anti/neuronal antibodies and Western blots with cerebellar extracts are used to confirm the specificities (17).

The most common and widely investigated PNA is anti-Hu, also known as the anti-neuronal nuclear type-1 (ANNA-1). The Most of these patients have anti-Hu antibodies. The antigen recognised by ANNA-1 is Hu. In anti-Hu positive patients there is a high percent-age of pure sensory neuronopathy, but one can also find anti-Hu positive sensomotoric neuropathies (18).

ANNA-3, AGNA-1/ANNA-4, PCA-2, and PCA-Tr antibodies were described generally based on their distinctive patterns of immunofluorescence staining. A specific protein antigen has not yet been defined in these instances, however, ANNA-3 and PCA-2 proteins are identifiable by neuronal and small-cell carcinoma Western blots. Most paraneoplastic antigens are located in the cytoplasm (e.g. Yo), or nucleus (e.g. Hu and R1 antigens of the cell, and a pathogenic role for the respective antibodies could not be demonstrated. In these disorders, indirect lines of evidence support the view that the cellular immune response against these antigens is responsible for the neurological damage. The paraneoplastic antibodies may, in these cases, be surrogate markers for T-lymphocyte activation.

In most cases of PND are associated with antibodies, the antigen has been identified (onconeural antigens: Hu, Ri, Yo were analysed by indirect immunofluorescence on frozen sections of primate cerebellum). The paraneoplastic Hu, Ri, Yo and VGCC (P/Q-type voltage gated calcium channel) antibodies were not detectable in these cancer patients. The specificity of anti-neuronal antibodies is indi-
cated by the staining pattern; however, it must be confirmed by a specific assay. This is best achieved by Western blot analysis (16).

Detection of certain antibodies identifies patients with specific clinical syndromes and tumours. These antibodies react with different intracellular and extracellular antigens, ranging from nuclear proteins (for example, Hu antigens). In anti-Hu positive patients with neuropathy have also been shown to have CD8+ cytotoxic T-cells in their blood and in the dorsal root ganglia. Detection of paraneoplastic antibodies is extremely helpful in diagnosing an otherwise unexplained and often rapidly progressive neurological syndrome as paraneoplastic. In most cases of paraneoplastic autoimmunity, the neuropathological findings are non-specific consisting of gliosis, neuronal loss microglial proliferation, and variable infiltrates of CD8+ T lymphocytes. However, in a recent study it was showed that IgG from PND patients have cytotoxic effects on cultured myenteric plexus (19).

In addition, the paraneoplastic antibodies may also direct the search for an underlying neoplasm. These disorders can be broadly conceptualised as being mediated immunopathologically by a plasma-membrane-directed effector antibody, or as being associated with neuronal or glial nuclear or cytoplasmic autoantibodies that serve as serological markers for cytotoxic CD8+ T-cell-mediated mechanisms. The mechanisms by which a peripherally generated humoral immune response might involve the central nervous system are largely unknown.

The autoantibody originally named generically as an anti-Purkinje cell cytoplasmic antibody (APCA) was later renamed arbitrarily by an independent group of authors as anti-Yo. The presence of anti-Yo antibodies in the serum of a woman with cerebellar symptoms is virtually conclusive evidence that she has paraneoplastic cerebellar degeneration and gynecologic, usually ovarian cancer. They are thought to arise as a result of aberrant expression of antigens, common to tumours and neurons. This leads to loss of tolerance and the induction of an immune response that acts with both tumour and normal neuronal tissue. Whether or not these antibodies are pathogenic is a moot point (17). The number of paraneoplastic antibodies is still growing, and at least seven of these can now be considered well characterized. Based on the clinical syndrome, the type of antibody, and the presence or absence of cancer, patients are classified as having a “definite” or “possible” PNS.

Paraneoplastic syndromes are thought to happen when cancer-fighting antibodies or white blood cells (known as T cells) mistakenly attack normal cells in the nervous system. There is evidence, that cytotoxic T-cells play a major role in the pathogenesis of central nervous system (CNS) PND. It was described the occurrence of tumour-specific cytotoxic T-cells reactive against the onconeural antigen cdr2, which is expressed in ovarian carcinoma and Purkinje cells. The T-cell receptor Vb chain has been found in CD8+ T-cells in the tumour and CNS of anti-Hu positive PND patients (7).

The presence of antigen-specific cytotoxic T cells in PNDs was clearly documented. There is increasing evidence that cytotoxic T cell mechanisms play a pathogenic role, although it has not yet been possible to reproduce an animal model of these diseases.

In PND, relatively high titers of the antibody in the cerebrospinal fluid (relative to total IgG) indicate that the antibody is synthesized within the brain, presumably by specific B cells that have crossed the blood brain barrier.

The relative roles of humorally mediated immunity (antibodies) and cellular immunity (T cells) in PNDs are unsolved. This uncertainty is complicated by the fact that different PNDs may have different underlying mechanisms (19).

The discovery of paraneoplastic antineuronal autoantibodies resulted in the general belief that these are immune-mediated disorders triggered by aberrant expression of “onconeural” antigens in the tumour. Further support for this hypothesis comes from the fact that the target paraneoplastic antigens are expressed both in the tumour and in the affected parts of the nervous system. Furthermore, the paraneoplastic antibodies are synthesized intrathecally. A pathogenic role could, however only be proven for paraneoplastic autoantibodies directed against easily accessible antigens located at the cell surface. Examples of such antigens are the acetylcholine receptor (anti-AChR in myasthenia gravis), voltage gated calcium channels (anti-VGCC, in Lambert-Eaton myasthenic syndrome), voltage gated potassium channels (anti-VGKC, in neuromyotonia) and the metabotropic glutamate receptor (anti-mGluR1, in
paraneoplastic cerebellar ataxia.

Peripheral neuropathy is an occasional complication of systemic cancer, related either to the systemic effects of the tumor or, more often, to various neurotoxic, chemotherapeutic agents. Cancer-associated peripheral neuropathy is usually mild, axonal and at times painful, and affects mostly the small nerve fibres. It is frequently difficult to distinguish from the co-existing toxic neuropathy of chemotherapeutic drugs.

There is, however, a distinct sensory paraneoplastic neuropathy, the paraneoplastic sensory neuronopathy (PSN), which has a unique clinical picture and an autoimmune pathogenesis. PSN is most often associated with small cell lung cancer and, with breast cancer or other neoplasms. Laboratory studies show increased CSF protein, an axonal sensory neuropathy by electrophysiologic testing, and an axonal degeneration with rare mononuclear cell infiltrates in the nerve biopsy. PSN is a ganglionopathy (sensory neuronopathy) caused by involvement of the dorsal root ganglionic neurons (20).

The autoimmune nature of PSN is supported by the presence of specific IgG autoantibodies to the antigen Hu. The antibodies are present in almost all patients who have small cell lung carcinoma and, less often, in patients with other cancers. Anti-Hu antibodies may also be found in higher titers in the CSF, suggesting intrathecal synthesis (21).

The antigens of the Hu protein are present not only in the tumors of patients with PSN but also in the small cell lung cancer from patients without anti-Hu antibodies or neurologic disease. Further, low titers of anti-Hu antibodies can be seen in up to 20% of patients with small cell lung cancer without neurologic symptoms. This observation suggests that PSN may be the result of an autoimmune reaction against antigens shared by both the tumor cells and the dorsal root ganglionic neurons. The Hu protein may also be an antigenic target of CD4 Th1-type T cells, which may be involved in cell-mediated injury of the peripheral nerve. Although, the pathogenic role of anti-Hu antibodies has not been clearly established and cellular immunity may be important, these antibodies appear to be highly specific as markers to detect an occult small cell lung cancer in patients who present with sensory ataxic neuropathy (22).

The antigen of anti-Ma has been defined at the molecular level, but the antibody has not been well characterized immunohistochemically. Up to 40% of patients with cerebellar ataxia and lung cancer have anti-Ma2 antibodies. The additional Ma1 and Ma3 specificities are more common in older patients who tend to develop a wider range of cerebellar symptoms with more intense dysfunction (23, 24).

Anti-CV2 is predominantly associated with a mixed axonal and demyelinating neuropathy (25). Conditions affecting voltage-gated calcium or potassium channels (VGCC or VGKC) are frequently paraneoplastic. A link between paraneoplastic and genetic cerebellar ataxia is also illustrated by voltage-gated calcium channel antibodies (VGCC-Ab). VGCC-Ab, especially those directed against the P/Q type VGCC, are mainly associated with Lambert-Eaton myasthenic syndromes (LEMS). Studies have shown that the frequency of cerebellar ataxia in patients with LEMS is higher than that expected by chance, and that LEMS with ataxia is usually associated with cancer, VGCC-Ab against the P/Q type have also been found in patients with small cell lung cancer and PCA without LEMS, suggesting that VGCC could be associated with some cases of PCA. However, there is a new subset of similar diseases mediated by antibody to neuronal components cross-reactive with streptococcal components, the so-called PAN-DAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections). Autoantibodies directed at specific plasma-membrane ion channel proteins have been demonstrated to cause loss or dysfunction of muscle and neuronal acetylcholine receptors and neuronal calcium channels and potassium channels in both the peripheral nervous system and the central nervous system (14).

The discovery and characterisation of several paraneoplastic antibodies have allowed neurologists to diagnose puzzling neurological syndromes as paraneoplastic and to more easily identify tumours that are often small and occult.

Sabater et al report the identification of autoantibodies against protein kinase C (PKC)g in a patient with paraneoplastic cerebellar ataxia (PCA). They identified these antibodies in only one patient, but the data suggest that PKCg could have a role in PCA. Indeed, PKC is expressed at particularly high concentrations in the
Purkinje cells of the cerebellum, where it is believed to have an important role in signal transduction and synaptic transmission (26, 27).

Stiff person syndrome (SPS) is characterised clinically by axial and proximal lower limb stiffness and spasms, and electrophysiologically by continuous motor unit activity. This disorder is more commonly non-paraneoplastic and is associated with anti-GAD antibodies, but in a minority of cases it may be the presenting feature of breast cancer with anti-amphiphysin antibodies (1).

Blaes et al., found a subgroup of patients with sensomotoric neuropathy without antineuronal antibodies, but with high-titer antinuclear antibodies (ANA). Some of these patients showed a good response to immunosuppressive drugs. Blaes et. al., found an influence of the IgG fractions of some anti-Hu negative, but not anti-Hu positive patients, on intracellular signal transduction pathways, indicating a heterogeneous etiology of paraneoplastic neuropathies (28).

Despite the presumed autoimmune etiology of PNS, the results of various forms of immunotherapy have been disappointing, with some exceptions. Because paraneoplastic syndromes are considered to be immune-mediated two treatment approaches have been used: removal of the source of the antigen by treatment of the underlying tumor, and suppression of the immune response. For many paraneoplastic syndromes, the first approach is the only effective treatment. In the Lambert-Eaton myasthenic syndrome and myasthenia gravis, plasma exchange or intravenous immune globulin is usually effective in suppressing the immune response. If the disease is mediated by T cells, as is suspected in many central nervous system disorders, such as paraneoplastic cerebellar degeneration with anti-Yo antibodies or encephalomyelitis with anti-Hu antibodies, drug such as tacrolimus or mycophenolate mofetil may be tried.

Paraneoplastic syndromes may be useful as clinical indicators to evaluate the response of the primary cancer to the treatment. The course of the disorder is usually independent of the tumour, and neurological symptoms usually progress rapidly and then stabilize. Some disorders, such as the Lambert-Eaton myasthenic syndrome and myasthenia gravis, respond well to immunosuppression and subsequently to treatment of the underlying tumor. Most reports that describe an absence of response of the paraneoplastic syndrome to immunosuppression do not note an exacerbation of the tumor. (1).

Rapid detection and immediate treatment of the underlying tumor appears to offer the best chance of stabilizing the patient and preventing further neurological deterioration (11).

**CONCLUSION**

Paraneoplastic neurological disorders are the manifestation of a multifaceted immune response to a neoplasm.

Paraneoplastic syndromes can occur with any type of malignancy. Paraneoplastic syndromes of the nervous system are a group of rare disorders that develop in some people with cancer, most commonly in people with lung, breast or ovarian cancer. Paraneoplastic syndromes are rare disorders caused by substances that are secreted by a benign tumor, a malignant (cancerous) tumor, or a malignant tumor’s metastases. Despite their rarity, paraneoplastic syndromes have always intrigued neurologists. Currently, it is thought that most or all PNDs are immune-mediated. The evidence indicates that T-cell responses have an important role in PNDs.

Paraneoplastic neurological antibodies are markers for paraneoplastic neurological syndromes. They are found, at high titres, in both the serum and cerebrospinal fluid, and only IgG antibodies are considered to be clinically relevant. Multiple levels of the nervous system can be affected and multiple autoantibody markers may be detected at diagnosis or as neoplasm evolves over time. The antibodies are found in the serum of a significant proportion of patients with paraneoplastic neurological syndromes. Antibodies in PNDs react with the portion of the nervous system that is responsible for the clinical symptoms. Identification of anti-neuronal specific antibodies (PNAs) aids diagnosis of the neurological syndrome as paraneoplastic and alerts clinicians to undertake thorough examinations for tumors.
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