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Paraneoplastic neurological disorders

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Introduction

Paraneoplastic neurological disorders are diseases of the nervous system that occur as a remote effect of malignant neoplasms and that are not due to infiltration of the nervous system by neoplastic tissue. These disorders have been described in association with a wide variety of neoplasms, with the lung, ovary and breast being common sites of origin. There is increasing evidence that paraneoplastic neurological disorders are due to an autoimmune attack on specific regions of the nervous system triggered by the aberrant expression of neuronal antigens by the neoplasm (Posner, 1992). Many regions of the nervous system can be involved, either in isolation or in combination, and this involvement determines the clinical features. The following paraneoplastic neurological syndromes have been described: subacute sensory neuronopathy (Denny-Brown, 1948), the Lambert–Eaton myasthenic syndrome (Eaton & Lambert, 1957), subacute cerebellar degeneration (Brain & Wilkinson, 1965), paraneoplastic motor neurone disease (Brain, Croft & Wilkinson, 1965; Henson, Hoffman & Urich, 1965), brainstem encephalitis (Henson et al., 1965), limbic encephalitis (Corsellis, Goldberg & Norton, 1968), opsoclonus and myoclonus (Brandt et al., 1974), the visual paraneoplastic syndrome (Grunwald et al., 1987), dysautonomia (Veilleux, Bernier & Lamarche, 1990), the stiff-man syndrome (Ferrari et al., 1990; Folli et al., 1993) and cochleovestibular dysfunction (Gulya, 1993). At least some of these syndromes can occur on an autoimmune basis in the absence of any detectable neoplasm. As the Lambert–Eaton myasthenic syndrome and the stiff-man syndrome commonly occur in the absence of an associated neoplasm, they are dealt with in separate specific chapters (Chapters 10 and 6, respectively).
Clinical features

Because of the diversity of clinical syndromes, the clinical features of the paraneoplastic neurological disorders will be discussed separately for each syndrome.

Subacute sensory neuronopathy

This disorder is most commonly seen in association with small cell carcinoma of the lung, but may also occur with a wide variety of other neoplasms, including breast cancer (Horwich et al., 1977; Chalk et al., 1992). The incidence of subacute sensory neuronopathy in small cell lung cancer is about 1% (Elrington et al., 1991). A similar disorder can develop in association with primary Sjögren’s syndrome (Malnow et al., 1986; Griffin et al., 1990; see Chapter 13) or may occur in the absence of any detectable associated disease (Kaufman, Hopkins & Hurwitz, 1981). Paraneoplastic subacute sensory neuronopathy may become manifest before or after the diagnosis of the associated neoplasm. Typically the syndrome comprises the subacute onset of pain, paraesthesiae, dysesthesiae and numbness in the limbs commencing distally and spreading proximally and sometimes involving the trunk and face (Denny-Brown, 1948; Horwich et al., 1977; Chalk et al., 1992). Physical examination reveals loss of light touch, pain and temperature sensation, and severe impairment of joint position sense and vibration sense. Sensory ataxia and areflexia are also characteristic features. Strength is preserved. In one series, about half of the patients had associated autonomic, cerebellar or cerebral abnormalities (Chalk et al., 1992). Electrophysiological studies are useful in confirming the selective sensory involvement. Examination of the cerebrospinal fluid (CSF) usually reveals an elevated protein level and sometimes a mononuclear pleocytosis (Horwich et al., 1977).

Subacute cerebellar degeneration

Subacute cerebellar degeneration is most commonly seen in association with small cell carcinoma of the lung, gynaecological cancers (especially of the ovary or breast) and Hodgkin’s disease (Brain & Wilkinson, 1965; Hammack et al., 1992), but may also occur with other malignancies, including carcinoma of the colon (Tsukamoto et al., 1993). When it occurs in Hodgkin’s disease, it is more common in men and has a younger age of onset than when associated with other malignancies (Hammack et al., 1992). Paraneoplastic subacute cerebellar degeneration may become clinically evident either before or after detection of the malignancy. The typical clinical pattern is the subacute evolution (over weeks to months) of truncal and limb ataxia and dysarthria (Brain & Wilkinson, 1965; Hammack et al., 1992). The ataxia can become so severe that the patient has difficulty sitting up in bed. Nystagmus, particularly downbeat nystagmus, may occur, but is often absent. Subacute cerebellar degeneration is often accompanied by evidence of involvement of other regions of the nervous system (Brain & Wilkinson, 1965). Examination of the CSF often reveals an elevated protein level and a lymphocytic pleocytosis (Peterson et al., 1992). Computerized tomography or magnetic resonance imaging may reveal cerebellar atrophy, particularly in the later stages (Peterson et al., 1992). Although spontaneous improvement may occur (Hammack et al., 1992), the disorder is usually irreversible.

Paraneoplastic motor neurone disease

A lower motor neurone syndrome with or without upper motor neurone involvement may occur in association with malignancy, particularly that of the lung (Brain et al., 1965; Dhib Jalkut & Liwocz, 1986). This paraneoplastic disorder may also be accompanied by clinical evidence of involvement of other regions of the nervous system (Henson et al., 1965), but when it occurs in the absence of such involvement it resembles idiopathic motor neurone disease. There is evidence that the latter may sometimes have an autoimmune basis (see Chapter 10).

Brainstem encephalitis

Paraneoplastic brainstem encephalitis occurs particularly in association with lung cancer and manifests itself in ophthalmoplegia, bulbar palsies, vertigo and nystagmus (Henson et al., 1965). It may also be accompanied by clinical involvement of other regions of the nervous system. Baloh et al. (1993) have recently reported a novel brainstem syndrome occurring in patients with prostatic carcinoma and consisting of a loss of voluntary horizontal saccadic eye movements and severe persistent muscle spasms of the face, jaw and pharynx together with mild unsteadiness of gait.

Limbic encephalitis

Limbic encephalitis occurs particularly in conjunction with small cell carcinoma of the lung (Brierley et al., 1960; Corsellis et al., 1968; Bakheit, Kennedy & Behan, 1990), but also with other tumours, such as thymoma (McArldle & Millingen, 1988; Ingenito et al., 1990), carcinoma of the testis (Burton et al., 1988) and carcinoma of the colon (Tsukamoto et al., 1993). Characteristically, the disorder is manifested by the onset over several
months of a marked disturbance of affect, such as severe anxiety or depression, and of a selective impairment of recent memory (Corsellis et al., 1968; Bakheit et al., 1990). Hallucinations and epilepsy may also occur. The clinical picture may resemble that of schizophrenia (Frommer et al., 1993). Clinical involvement of other regions of the nervous system may accompany the picture of limbic encephalitis (Tsukamoto et al., 1993). Examination of the CSF often reveals a mononuclear pleocytosis and an elevated protein level, while electroencephalography may demonstrate paroxysmal activity and/or slow waves over one or both temporal lobes (Corsellis et al., 1968). On magnetic resonance imaging there may be abnormal high-signal intensity in the medial temporal lobes on T2-weighted scans followed by the development of temporal lobe atrophy on T1-weighted scans (Dirr et al., 1990; Kodama et al., 1991).

Opsoclonus and myoclonus

A syndrome of opsoclonus (‘dancing eyes’), truncal and limb myoclonus, and ataxia may occur in children with neuroblastoma (Brandt et al., 1974), and in adults with cancer, particularly small cell carcinoma of the lung (Anderson et al., 1988a). Opsoclonus is defined as the occurrence of involuntary, arrhythmic, large-amplitude, multidirectional, conjugate saccadic eye movements without an intersaccadic interval. The syndrome is characterized by the acute onset of vertigo, nausea, vomiting, opsclosus, truncal and limb myoclonus, truncal and (to a lesser extent) limb ataxia, and encephalopathy (Brandt et al., 1974; Anderson et al., 1988a). The truncal ataxia often becomes so severe that the patient is unable to stand or sit without support. The encephalopathy is manifested by apathy, lethargy and confusion, and may progress to stupor or coma. Unlike most other paraneoplastic neurological syndromes, the course is often remitting and relapsing (Anderson et al., 1988a). CSF examination may reveal a lymphocytic pleocytosis, a mild elevation of the protein level, and the presence of oligoclonal immunoglobulin (lg) bands. Electro-oculography allows accurate definition of the involuntary eye movements. Patients with this syndrome differ clinically from those with the more common paraneoplastic cerebellar degeneration by the predominance of truncal over limb ataxia, the presence of opsoclonus and myoclonus, the absence of severe dysarthria and a tendency for remission (Anderson et al., 1988a). A similar opsoclonus–myoclonus syndrome can occur in children without detectable neuroblastoma (Kinsbourne, 1962) and can occur in adults without malignancy as an acute self-limited disorder following a respiratory or gastrointestinal infection (Baringer, Sweeney & Winkler, 1968).

Other paraneoplastic neurological syndromes

The Lambert–Eaton myasthenic syndrome, which can occur in association with small cell carcinoma of the lung (Eaton & Lambert, 1957), and the stiff-man syndrome, which can occur with Hodgkin’s disease (Ferrari et al., 1990) and breast cancer (Folli et al., 1993), are discussed in detail in Chapters 10 and 6, respectively. Other paraneoplastic neurological syndromes include: the visual paraneoplastic syndrome, which occurs in association with small cell carcinoma of the lung and results in binocular visual loss (Grunwald et al., 1987); cochleovestibular dysfunction, which has been observed accompanying other paraneoplastic neurological syndromes (Gulya, 1993); and dysautonomia manifested by orthostatic hypotension, abnormal pupillary reflexes, hyperhidrosis, urinary retention, constipation, impotence, cardiac arrhythmias, hypothermia and sleep apnoea (Veilleux et al., 1990; Dalmau et al., 1992b). Posterior uveitis may also occur in association with paraneoplastic neurological involvement (Antoine et al., 1993). A severe impairment of gastrointestinal motility with intestinal pseudo-obstruction, gastroparesis and oesophageal dysmotility can occur in patients with small cell lung cancer with or without other autonomic dysfunction (Chinn & Schaffler, 1988; Sodhi et al., 1989; Lennon et al., 1991). Turner et al. (1993) found subclinical cardiovascular autonomic dysfunction in 80% of patients with Hodgkin’s disease or non-Hodgkin’s lymphoma at the time of presentation, and suggested that this was due to a paraneoplastic syndrome.

Neuropathology

The typical neuropathological features of the paraneoplastic neurological disorders are neuronal loss, neuronal pyknosis, neuronophagia, microglial nodules (or nodules of Nageotte in the dorsal root ganglia), meningeal lymphocytic infiltration, perivascular lymphocytic cuffing, parenchymal infiltration with lymphocytes and macrophages, and astrocytic gliosis (Denny-Brown, 1948; Henson et al., 1965; Brain & Wilkinson, 1965; Corsellis et al., 1968; Horwich et al., 1977). The distribution of these changes varies with the clinical syndrome. Thus, the dorsal root ganglion is the main site in subacute sensory neuronopathy (Denny-Brown, 1948; Horwich et al., 1977); the cerebellar Purkinje cell layer in subacute cerebellar degeneration (Brain & Wilkinson, 1965); the anterior horn cells of the spinal cord in paraneoplastic motor neurone syndromes (Henson et al., 1965; Brain et al., 1965); the lower brainstem nuclei in brainstem encephalitis (Henson et al., 1965; Baloh et al., 1993); the limbic grey matter (hippocampal formation,
amygdaloid nucleus, and the cingulate and orbital cortex) in limbic encephalitis (Corsellis et al., 1968); and the retinal ganglion cell layer in the visual paraneoplastic syndrome (Grunwald et al., 1987). The paravertebral sympathetic ganglia, brainstem grey matter and spinal cord are among the sites of involvement in dystautonomia (Veilleux et al., 1990; Dalmau et al., 1992b). In intestinal pseudo-obstruction and gastroparesis the pathological changes are found in the myenteric plexus (Chinn & Schuffler, 1988; Chu et al., 1993). The neuropathological basis of the opsoclonus-myoclonus syndrome is unknown (Anderson et al., 1988a). Involvement of the limbic grey matter, the lower brainstem nuclei, the anterior horn cells of the spinal cord and the dorsal root ganglia often occur together in various combinations (Henson et al., 1965); these combinations are often referred to as 'paraneoplastic encephalomyelitis'.

**Immunopathology of the lesions in the nervous system**

**Characteristics of the inflammatory infiltrate in the nervous system**

Immunohistochemical studies in patients with paraneoplastic encephalomyelitis and sensory neuropathy have shown that the perivascular inflammatory infiltrates are composed mainly of B cells and CD4+ T cells with some CD8+ T cells and macrophages, while the interstitial inflammatory infiltrates consist predominantly of CD8+CD11b- (reportedly cytotoxic) T cells, although CD4+ T cells, macrophages and occasional B cells are also present (Graus et al., 1990; Yoshioka et al., 1992; Jean et al., 1994). Neurons do not express class I or class II major histocompatibility complex (MHC) antigens, although satellite cells in the dorsal root ganglia express HLA-DR in both patients and controls (Graus et al., 1990; Yoshioka et al., 1992). By incubating tissue sections with biotinylated HuD neuronal antigen (see below), Szabo et al. (1991) have demonstrated HuD-reactive B lymphocytes in the brain of a patient with a paraneoplastic neurological disorder. Interestingly, a predominance of CD8+ T cells has also been observed in the dorsal root ganglion inflammatory infiltrate of a patient with subacute sensory neuropathy due to primary Sjögren's syndrome (Griffin et al., 1990), suggesting that a similar mechanism may be responsible for the neuronal destruction in this syndrome and in the paraneoplastic one.

**Localization of antibody in the nervous system**

IgG bound to neurones has been demonstrated in situ in patients with paraneoplastic neurological disorders and with circulating anti-Hu anti-

bodies (Graus et al., 1990; Brashears et al., 1991; Dalmau et al., 1991). Dalmau et al. (1991) found that the amount of anti-Hu IgG relative to total IgG was higher in some areas of the brain than in the serum and CSF. The anti-Hu IgG within the nervous system is predominantly of the IgG1 isotype and to a lesser extent of the IgG2 and IgG3 isotypes (Jean et al., 1994). There is also a minor degree of complement deposition within the nervous system parenchyma (Jean et al., 1994). Binding of Ig to neurones in situ has been demonstrated in patients with small cell lung cancer and circulating anti-neuronal antibodies in the absence of clinical evidence of a paraneoplastic neurological disorder, but not in cancer patients without circulating anti-neuronal antibodies (Drüöck et al., 1992). Immune deposits have also been found in the retina of a patient with the visual paraneoplastic syndrome (Grunwald et al., 1987).

**Immunological findings in the peripheral blood**

Anti-neuronal antibodies can be demonstrated in the sera of patients with paraneoplastic neurological disorders. Different antibodies have been defined according to their specificities and will be discussed separately below. The antibodies have been called 'anti-Yo', 'anti-Hu' and 'anti-Ri' after the first two letters of the last names of patients with the respective antibodies.

**Antibodies against Purkinje cell cytoplasm (anti-Yo antibodies)**

Antibodies against Purkinje cell cytoplasm (anti-Yo antibodies) are present in the sera of patients with subacute cerebellar degeneration and gynaecological cancer (mainly ovarian and breast) but not in normal healthy controls or patients with other paraneoplastic neurological disorders or other neurological diseases (Greenlee & Brashear, 1983; Jaeckle et al., 1985; Peterson et al., 1992). Generally, they are not present in patients with subacute cerebellar degeneration associated with other malignancies. These antibodies are also present in some patients with gynaecological cancer without clinical evidence of cerebellar degeneration, although they are absent in the majority of such patients (Greenlee & Brashear, 1983; Brashear et al., 1989). Therefore, serum anti-Yo antibodies are a specific marker for gynaecological cancer (Peterson et al., 1992). Their presence in patients with cerebellar dysfunction should prompt a careful search for such an underlying malignancy.

Western blot analysis of purified Purkinje neurones has shown that the autoantibodies recognize at least two proteins: a major antigen of 62 kDa (CDR 62, cerebellar degeneration-related 62-kDa protein) and a minor
antigen of 34 kDa (CDR 34) (Cunningham et al., 1986). The gene encoding CDR 34 has been isolated and characterized and found to reside on the X chromosome (Dropcho et al., 1987; Furneaux et al., 1989; Chen et al., 1990). It is uniquely expressed in Purkinje cells of the cerebellum and has also been detected in tumour tissue from a patient with paraneoplastic cerebellar degeneration (Furneaux et al., 1989). Screening of a human expression library has also resulted in the isolation of cDNA clones encoding the major CDR 62 antigen (Fathallah Shaykh et al., 1991). Sequence analysis revealed the presence of leucine-zipper and zinc-fingers motifs in the predicted open reading frame, suggesting that the CDR 62 protein plays a role in the regulation of gene expression. In contrast to the minor antigen CDR 34, the recombinant CDR 62 antigen is highly reactive with anti-Yo sera and provides the basis for a simple diagnostic enzyme-linked immunosorbent assay for the presence of anti-Yo antibodies (Fathallah Shaykh et al., 1991). Interestingly, H.M. Furneaux et al. (1990) have found that the CDR 62 protein is expressed by gynaecological tumours from patients with paraneoplastic cerebellar degeneration but not by gynaecological tumours from patients without this neurological complication. They hypothesize that paraneoplastic cerebellar degeneration is a result of an immunological response directed against the Purkinje cell but provoked by the tumour-induced expression of the Yo antigen.

An antibody specifically reacting against Purkinje cell cytoplasm, but in a different, more diffuse pattern than that obtained with anti-Yo antibodies, has been found in the sera of some patients with paraneoplastic cerebellar degeneration and Hodgkin’s disease, but Western blotting has not identified a discrete Purkinje cell antigen (Hammack et al., 1992). Furthermore, non-anti-Yo antibodies reacting with Purkinje cell cytoplasm and recognizing 62-kDa or 110-kDa neuronal antigens have been detected in the sera of men with subacute sensory neuropathy without tumours (Nemni et al., 1993).

Antibodies against neuronal nuclei (anti-Hu antibodies)

Antibodies specifically reactive against neuronal nuclei, but not the nuclei of most other cells, (anti-Hu antibodies) are present in the sera of patients with subacute sensory neuropathy, or paraneoplastic encephalomyelitis (including limbic encephalitis, motor neurone dysfunction, cerebellar dysfunction, brainstem encephalitis and dysautonomia) and small cell lung cancer (Graus, Cordon-Cardo & Posner, 1985; Dick et al., 1988; Anderson et al., 1988b; Moll et al., 1990; Dalmau et al., 1990, 1992b; Lennon et al., 1991). They are predominantly of the IgG1 isotype and to a lesser extent of the IgG2 and IgG3 isotypes (Jean et al., 1994). The antibodies are also present, although at lower titre, in the sera of a minority of patients with small cell lung cancer without clinical evidence of a paraneoplastic neurological disorder. They are not present in normal healthy individuals. Furthermore, they are not usually present in cases of subacute sensory neuropathy associated with other cancers or occurring without malignancy (Anderson et al., 1988b) although they can be detected in some patients with primary Sjögren’s syndrome with or without sensory neuropathy (Moll et al., 1993). With the latter exception, the anti-Hu antibody is a specific marker for the paraneoplastic syndromes associated with small cell lung cancer; its detection in a patient not known to have cancer should prompt a careful search for this malignancy.

The antibodies stain predominantly the neuronal nuclei, with sparing of the nucleioli, and with weaker staining of the neuronal cytoplasm. Western blot analysis of nuclear extracts of human and rat brain has revealed that the antibodies react with a closely arranged set of protein bands of 35–40 kDa (Graus et al., 1986; Dalmau et al., 1990). Using immunohistochemistry or Western blot analysis, Dalmau et al. (1992a) studied the expression of the Hu antigen in normal human tissues and in tumours of different histological types. They found that in normal tissues the Hu antigen was restricted to neurones (including those of the myenteric plexus), adrenal chromaffin cells and ganglion cells of the bronchus. With regard to tumours, the antigen was present in all small cell lung cancers, but not other lung cancers; it was not present in most other cancers, except for neuroendocrine-related cancers, especially neuroblastoma. Given that all small cell lung cancers express the Hu antigen, it is unclear why only a minority of patients with this cancer develop anti-Hu antibodies.

By screening a phage lambda cerebellar expression library, Szabo et al. (1991) have isolated a recombinant neuronal antigen (HuD) that is recognized by anti-Hu antibodies and that can be used to provide an unambiguous assay for these antibodies. In normal tissues, HuD mRNA is uniquely expressed in the nervous system. The HuD antigen is homologous to the Drosophila proteins Elav (embryonic lethal abnormal vision) and cup of potato, which are essential RNA-binding proteins expressed early during neuronal development (Szabo et al., 1991; Bellen et al., 1992). In view of this homology it is likely that HuD plays a role in neurone-specific RNA processing. Sakai et al. (1994) have isolated a hippocampal 38-kDa antigen (PLE21) that is also recognized by anti-Hu antibodies. This protein contains RNA recognition motifs and is highly homologous to the HuC antigen isolated by Szabo et al. (1991).

Anti-Ri antibodies

Patients with opsoclonus, ataxia and breast cancer have serum antibodies specifically directed against neuronal nuclei (Luque et al., 1991). Histologically these antibodies appear identical to anti-Hu antibodies, but
Western blot analysis with cerebral cortex neuronal extracts reveals that the protein antigens have a different molecular mass (55 kDa and 80 kDa) than the antigens recognized by anti-Hu antibodies (35-40 kDa) (Luque et al., 1991). Serum anti-Ri antibodies are not present in normal individuals. Generally they are not detected in patients with breast cancer without opsinclonus, although they have been found in some patients with breast cancer and ataxia in the absence of opsinclonus (Luque et al., 1991; Escudero et al., 1993). Furthermore, these antibodies have not been detected in the sera of patients with paraneoplastic opsinclonus associated with small cell lung cancer or neuroblastoma. While they are generally absent in patients with non-paraneoplastic opsinclonus (Luque et al., 1991), they have been detected in a patient with steroid-responsive opsinclonus–myoclonus in the absence of tumour (Droppo, Kline & Riser, 1993). Anti-Ri antibodies react with the tumours of patients with the respective antibodies and opsinclonus, but do not react with the breast cancers of those without anti-Ri antibodies (Luque et al., 1991). Therefore, the situation in anti-Ri paraneoplastic opsinclonus is similar to that in anti-Yo paraneoplastic cerebellar degeneration, where the antigen is present only in the tumours of those patients who develop the antibody response. It is different from the situation with anti-Hu antibodies and from the paraneoplastic Lambert–Eaton myasthenic syndrome, where the antigen appears to be present in all small cell lung cancers but where only a small proportion of patients mount an antibody response.

**Immunological findings in the cerebrospinal fluid**

Furneaux, Reich & Posner (1990) quantified the activity of anti-Yo and anti-Hu antibodies in simultaneously obtained samples of serum and CSF of patients with paraneoplastic neurological disorders. In the majority of patients the autoantibody activity per milligram of total IgG was substantially greater in the CSF than in the serum, indicating intrathecal production of these autoantibodies in the paraneoplastic syndromes. Plasmapheresis reduced the level of antibody in the serum without affecting that in the CSF in five of six patients. In patients with the anti-Ri paraneoplastic syndrome there is also evidence of intrathecal production of the anti-Ri antibodies (Luque et al., 1991).

**Mechanism of neuronal destruction and/or dysfunction**

It is likely that the anti-neuronal antibodies that are present in the serum, CSF and nervous tissue in the paraneoplastic disorders play a role in the neuronal destruction that is characteristic of these disorders; however, this has not yet been definitely established. Greenlee, Parks & Jaecle (1993) found that anti-Hu antibodies from patients with paraneoplastic disorders produced specific lysis of rat cerebellar granule neurones in vitro in the presence of complement, as compared with controls using normal serum or heat-inactivated complement. More prolonged incubation of cultures with anti-Hu antibodies without complement also resulted in specific lysis, whereas incubation with normal serum or serum from neurologically normal patients with small cell lung cancer did not. These results indicate that anti-Hu antibodies may cause neuronal destruction in the absence of lymphocytes. On the other hand, attempts to transfer the neurological disorder by injecting anti-Hu antibodies into experimental animals have so far been unsuccessful (Dick et al., 1988; Szabo et al., 1991). Repeated intraventricular injections of anti-Yo IgG from a patient with paraneoplastic cerebellar degeneration into guinea pigs have failed to produce either clinical or histological evidence of cerebellar disease, despite the presence of IgG in the Purkinje cell cytoplasm of the recipients (Graus et al., 1991).

The CD8+ lymphocytes infiltrating the nervous system (Graus et al., 1990; Yoshioka et al., 1992) may also contribute to the neuronal elimination by acting as cytotoxic T cells. However, as neurones do not express class I MHC antigens (Graus et al., 1990; Yoshioka et al., 1992), it is difficult to explain how CD8+ cytotoxic T cells, which recognize antigen in the context of these MHC antigens, could specifically interact with the neurones. An alternative explanation is that some of the infiltrating CD8+ cells represent natural killer cells which might be targeted by their Fc receptors to antibody-binding neurones. Natural killer cells have been shown to mediate the destruction of sympathetic neurones in the superior cervical ganglia of rats treated with guanethidine (Hickey et al., 1992). However, Jean et al. (1994) did not find natural killer cells in the inflammatory infiltrates of patients with paraneoplastic encephalomyelitis.

While neuronal death is the cause of the clinical deficit in most of the paraneoplastic disorders, antibody-mediated dysfunction without neuronal death may be responsible for the manifestations of reversible central nervous system syndromes, for example opsinclonus–myoclonus, as in the case of the Lambert–Eaton myasthenic syndrome (see Chapter 10). The availability of recombinant neuronal antigens such as Yo and Hu may allow the production of animal models that will facilitate studies on the pathogenesis of the paraneoplastic neurological disorders.

**Effect of the immune response on the tumour**

Altman & Baezner (1976) observed that children with coincident opsinclonus–myoclonus and neuroblastoma had a much better prognosis for
survival than those without opsoclonus–myoclonus. They acknowledged that this might be partly explained by earlier tumour detection in the former group, because of the striking neurological symptomatology. However, as five of the seven patients with opsoclonus–myoclonus and advanced malignancy also exhibited long-term survival, they suggested that an immune response might be responsible for controlling the growth and spread of the tumour, as well as being responsible for the neurological syndrome. This hypothesis has been supported by the observation that patients with small cell lung cancer who have low-titre anti-Hu antibodies and no paraneoplastic neurological syndrome are more likely to have their tumour limited to the chest than patients without anti-Hu antibodies (Dalmau et al., 1990). Despite the fact that the presence of anti-Hu antibody appears to protect against death from the tumour, the median survival of patients with the associated paraneoplastic syndrome is similar to that of small cell lung cancer patients without the syndrome, because of the severity of the neurological disorder (Dalmau et al., 1992b). Interestingly, spontaneous tumour regression can occur in patients with small cell lung carcinoma, paraneoplastic neurological disease and anti-neuronal antibodies (Darnell & DeAngelis, 1993). This raises the possibility that the absence of identifiable tumour in some patients with ‘paraneoplastic’ neurological syndromes may be explained by immune-mediated elimination of the tumour cells. Anti-Hu IgG and anti-Hu B lymphocytes have been demonstrated in the tumour as well as in the brain in patients with paraneoplastic neurological disorders (Dalmau et al., 1991; Szabo et al., 1991).

**Therapy**

In general, the clinical deficits in patients with the paraneoplastic neurological syndromes with underlying neuronal loss are irreversible, whereas syndromes without demonstrable neuronal loss such as paraneoplastic opsoclonus–myoclonus may spontaneously remit. In some instances of limbic encephalitis, clinical improvement has occurred following antineoplastic therapy or surgical removal of the tumour (Burton et al., 1988; Kaniecki & Morris, 1993; Tsukamoto et al., 1993), indicating either that neuronal loss was not responsible for the clinical manifestations or that any neuronal loss had been compensated for, perhaps by axonal sprouting. In some patients with paraneoplastic sensory neuronopathy, treatment of the neoplasm may halt progression of the neuronopathy but neurological improvement does not occur and most patients continue to worsen even when the tumour responds well to therapy (Chalk et al., 1992).

With the exception of the paraneoplastic Lambert–Eaton myasthenic syndrome (see Chapter 10), the paraneoplastic neurological disorders do not respond to plasmapheresis, corticosteroid or other immunosuppressant therapy (Peterson et al., 1992; Hammack et al., 1992; Dalmau et al., 1992b). Given the underlying neuronal loss, the most that could be expected from such therapy would be prevention of progression. By inhibiting the immune response against the tumour, immunosuppressive treatment may also allow the tumour to progress unless it is controlled by other therapy.

**Conclusions**

The hypothesis that paraneoplastic neurological syndromes are due to an autoimmune attack on the nervous system triggered by the aberrant expression of neuronal antigens by the neoplasm is supported by the following observations: lymphocytic pleocytosis in the CSF; lymphocytic infiltrate in the nervous system; circulating anti-neuronal antibodies that also react with the underlying tumour; intrathecal synthesis and localization of these autoantibodies in nervous tissue parenchyma; and (in one study) the lytic effect of anti-neuronal antibodies on neurones in vitro. Further studies are needed to determine the relative roles of T cells and antibodies in the pathogenesis of these disorders. At least some, and perhaps all, of these syndromes may occur on an autoimmune basis in the absence of any triggering neoplasm. Studies on the pathogenesis of the paraneoplastic neurological disorders may shed light on the pathogenesis of the corresponding non-paraneoplastic disorders. The availability of recombinant neuronal antigens should allow the development of animal models that will facilitate these studies.

**References**


PARANEOPlastic Neurological Disorders


Neurological complications of connective tissue diseases and vasculitis

PAMELA A. McCOMBE

Connective tissue diseases such as systemic lupus erythematosus can have neurological manifestations. Furthermore, systemic vasculitides can result in neurological disease (Sigal, 1987; Moore, 1989b) and some vasculitides are restricted to the nervous system (Dyck et al., 1987; Moore, 1989a; Crane, Kerr & Spiera, 1991). There are three possible means by which connective tissue diseases and vasculitides could be associated with neurological disorders. Firstly, the neurological complications of these conditions could be due to ischaemia secondary to vascular occlusion. Secondly, neurological complications could be due to a specific immune response directed against antigens in the parenchyma of the nervous system. Thirdly, neurological disturbance could result from a separate autoimmune neurological disorder occurring in an individual predisposed to autoimmune disease. This chapter reviews central nervous system (CNS) and peripheral nervous system (PNS) manifestations of connective tissue diseases and vasculitides, but does not attempt a comprehensive review of these systemic disorders.

Clinical features

Systemic lupus erythematosus

The neurological manifestations of systemic lupus erythematosus (SLE) are manifold (Johnson & Richardson, 1968; Feinglass et al., 1976; Futrell, Schultz & Millikan, 1992). There are strict criteria for the diagnosis of SLE (Tan et al., 1982) and these include the presence of neurological signs. In some patients, neurological symptoms and signs are the first manifestation of SLE (Tola et al., 1992). SLE is associated with a wide range of