

# Inflammatory Disease of the CNS III: Sarcoidosis and Non-neoplastic Diseases Associated with Neoplasia

In contrast to the previous articles on the neuropathology of organism-related disorders, this article deals with inflammatory diseases that are not, as far as it is known, due to infections, but are most likely mediated by aberrant immune host reactions. Neurosarcoidosis should be regarded as a granulomatous, probably hyperimmune, inflammatory disorder, whereas paraneoplastic syndromes are associated with the presence of a variety of tumour-related antibodies and give rise to a wide range of clinical presentations.

## Neurosarcoidosis

Sarcoidosis is an inflammatory granulomatous disorder affecting virtually all organs, particularly the lungs. The nervous system, both central and peripheral, is involved in 5-15% of patients.<sup>1</sup> Ante-mortem diagnosis is possible only in 50% of cases.

It occurs world-wide, in all races, both sexes and at all ages (usually between 20 and 40 years) and is considered the second commonest respiratory disease in young adults after asthma. Its prevalence has been estimated at 50/100000 and it is most common among Black North Americans and in northern Europe.<sup>2</sup>

Although the aetiology of sarcoidosis remains unknown, there are data supporting the role of environmental factors in genetically susceptible individuals, who would respond with an unusually strong Th1-immune reaction.<sup>2</sup> The lymphocytes taking part in the reaction are phenotypically CD4 helper and produce cytokines. Possible environmental factors include infections (in particular *Mycobacterium tuberculosis*) as well as exposure to various chemicals (pesticides and insecticides), pine pollen, silica, talc, metal dusts and artificial fibres. The existence of a few clusters of disease within families further supports a genetically-related mechanism.

## Clinical syndromes

Neurosarcoidosis can present with various clinical forms, depending on its localisation and speed of progression.<sup>1</sup> As a general rule, the course is slow, with relapses and remissions. On the other hand, less frequently, the disorder can progress to death within a few weeks. Clinically, neurosarcoidosis can present with involvement of the cranial, or peripheral, nerves, meningitis, diffuse brain or spinal lesions responsible for seizures, psychiatric symptoms or various forms of paralysis.<sup>3</sup>

1. The form with involvement of single or multiple cranial nerves carries the best prognosis and the facial nerve is the most commonly affected.<sup>1</sup> Involvement of the optic nerve can be uni- or bilateral and chronic progressive, responding poorly to steroids, or acute and with a good response. Papilloedema is a relatively common complication, particularly in young women. Heerfordt's syndrome, suggestive of sarcoidosis and involving the cranial nerves, most commonly the facial, is characterised by uveitis, swelling of the parotid gland and fever. On the other hand, peripheral neuropathy is definitely rare and can affect large or, more commonly, small, including autonomic, fibres.

2. Meningitis may appear in acute or chronic forms. When localised to the basal regions, it accounts for

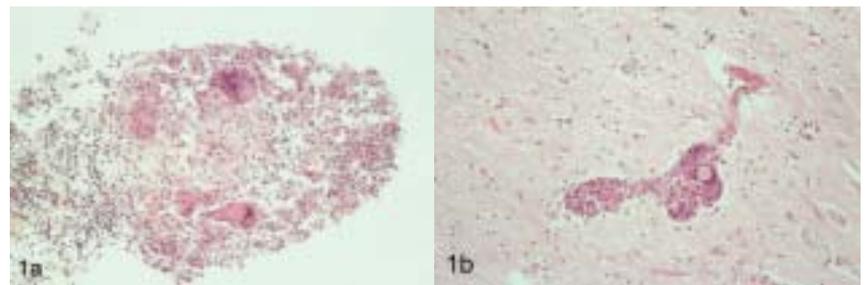
involvement of the cranial vessels. Acute forms respond favourably to steroid treatment; the chronic variant may recur. Hydrocephalus can result from obstruction of the foramina by the inflammatory process.

3. Brain involvement results from the presence of smaller or, more rarely, larger granulomas in the extra-subdural localisation or within the brain tissue itself;<sup>4</sup> resulting symptoms are similar to those of any other space-occupying lesion with the same localisation. The most common brain localisation is in the hypothalamus and pituitary gland, resulting in endocrine disturbances. Granulomas can extend to the vessels, resulting in granulomatous angiitis and cerebral infarcts from vascular obstruction.
4. Spinal sarcoidosis may present as arachnoiditis, extra- or intra-medullary lesions, the latter being an extremely rare complication. Unfortunately granulomas in this location cannot be distinguished clinically and radiologically from neoplasms. Patients can present with a transverse myelopathy or radicular or cauda equina syndromes.
5. Neurosarcoidosis may be responsible for the appearance of seizures or psychiatric conditions.

## Neuropathology

Microscopic diagnosis requires the presence of the sarcoid granuloma. In its active stage, it shows a core of epithelioid and multinucleated giant cells (Fig. 1a), surrounded by B and T lymphocytes, mononuclear cells and fibroblasts. A chronic granuloma is characterised by fewer T cells. A feature distinguishing this from tuberculous granuloma is an area of central necrosis, typically present in the latter. Admittedly a small necrotic centre can be seen also, albeit uncommonly, in sarcoidosis. However, in this case it does not present the caseous appearance seen in tuberculosis.

Granulomas, localised predominantly in the leptomeninges, may extend to the intraparenchymal perivascular spaces and to the brain tissue (Fig 1b). They may be confluent and form tumour-like masses surrounded by an astrocytic reaction. Involvement of the ventricles is known. Granulomatous vasculitis with the possibility of vascular complications has already been mentioned above.



**Figure 1: Sarcoidosis**

(a) Sarcoid granuloma of the leptomeninges. Note its central core of epithelioid cells, the peripheral halo of small inflammatory cells, the multinucleated giant cell and the absence of any necrosis (H&E). (b) Granulomas of variable size may be seen within the brain parenchyma; small ones may be circumscribed to the perivascular spaces (H&E).

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**Laboratory diagnosis, neuroradiology and treatment**

The diagnosis of sarcoidosis can be established according to the criteria laid down by Baughman et al.<sup>5</sup> 1) presence of a granulomatous lesion not showing tuberculous, mycotic or neoplastic features or any other causes in a patient with clinical signs supporting this disease; 2) in the absence of biopsy, a diagnosis of bilateral hilar adenopathy on chest X-ray, erythema nodosum, uveitis and maculo-papular skin lesions support this diagnosis.

Neuroradiology and CSF abnormalities do not provide the best diagnostic support for neurosarcoidosis as their findings are non-specific. The latter shows pleocytosis, high protein content and, in some instances, mildly decreased glucose levels. Kveim and diagnostic support may be provided by Mantoux tests and hypercalcaemia.

Treatment consists of steroids or, if steroid sparing agents are required or steroids are contraindicated, then cytotoxic drugs may be needed.<sup>3</sup>

**Paraneoplastic neurological syndromes**

The term paraneoplastic neurological syndromes (PNS) encompasses a number of uncommon disorders associated with systemic malignancies. The definition of PNS requires that malignancies should not invade, compress or metastasise to the nervous system to produce their neurological effects. The identification of these disorders dates to the first half of the past century.<sup>6</sup> A breakthrough<sup>7</sup> consisted in the identification in the serum and CSF of patients with PNS of auto-antibodies reacting both with the tumours and the central nervous system.

The incidence of these syndromes, first estimated at around 25 to 66%, was subsequently established between 0.31 and 1%.<sup>8</sup>

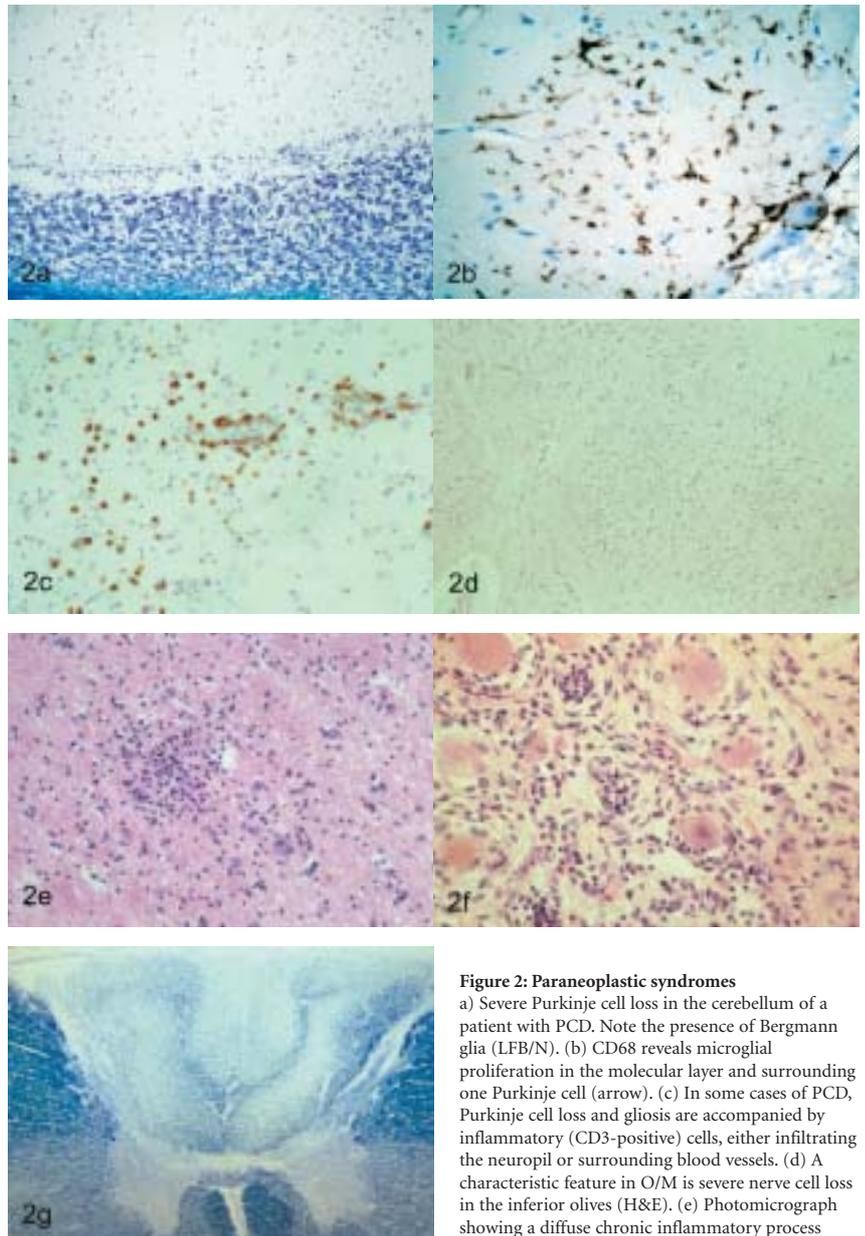
When considering paraneoplastic disorders, the following points should be taken into consideration:

1. correlation between the type of neoplasm and the neurological syndrome is not absolute;
2. in some syndromes both gross and histological abnormalities may be absent;
3. they may become clinically manifest before, or at the same time as the discovery of the neoplasm;
4. their outcome is almost invariably fatal.

For the purpose of this review, these syndromes are classified according to their pathological appearance. They can involve 1) the CNS; 2) the peripheral nervous system; 3) both these systems; 4) the neuromuscular junction (see table).

**Table 1 Classification of Paraneoplastic neurological syndromes**

1) Involving the CNS	<ul style="list-style-type: none"> <li>• Paraneoplastic cerebellar degeneration</li> <li>• Opsoclonus-myoclonus</li> <li>• Retinopathy</li> </ul>
2) Involving the peripheral nervous system	<ul style="list-style-type: none"> <li>• Sensory-motor neuropathy</li> <li>• Autonomic neuropathy</li> </ul>
3) Involving both systems	<ul style="list-style-type: none"> <li>• paraneoplastic encephalomyelitis/</li> <li>• sensory neuropathy</li> </ul>
4) Involving the neuromuscular junction	<ul style="list-style-type: none"> <li>• Lambert-Eaton myasthenic syndrome (LEMS)</li> </ul>



**Figure 2: Paraneoplastic syndromes**

a) Severe Purkinje cell loss in the cerebellum of a patient with PCD. Note the presence of Bergmann glia (LFB/N). (b) CD68 reveals microglial proliferation in the molecular layer and surrounding one Purkinje cell (arrow). (c) In some cases of PCD, Purkinje cell loss and gliosis are accompanied by inflammatory (CD3-positive) cells, either infiltrating the neuropil or surrounding blood vessels. (d) A characteristic feature in O/M is severe nerve cell loss in the inferior olives (H&E). (e) Photomicrograph showing a diffuse chronic inflammatory process involving the grey matter (H&E).

(f) Similar changes are seen in affected dorsal root ganglia. Note one nodule of Nageotte replacing a disappeared neurone (H&E). (g) Degeneration of dorsal root fibres following dorsal root ganglion cell loss in paraneoplastic ganglionitis results in pallor of the dorsal columns of the spinal cord (LFB/N).

**Clinico-pathological subtypes of paraneoplastic disorders****Paraneoplastic cerebellar degeneration (PCD)**

The neurological disorder usually precedes the discovery of the neoplasm, is characterised by incoordination of gait, dysarthria and often nystagmus. Though associated with any type of malignancy, gynaecological tumours are the commonest, followed by lung tumours (especially small cell) and lymphomas of the Hodgkin type.

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Macroscopically, the cerebellum may appear globally atrophic. The salient histological finding is a severe Purkinje cells loss (Fig. 2a) with preservation of baskets. There may be axonal swelling, microglial proliferation (Fig. 2b), hyperplasia of the Bergmann glia and decreased numbers of granule cells. Degeneration may be associated with lymphocytic infiltration of the leptomeninges and perivascular spaces (Fig. 2c).

*Paraneoplastic opsoclonus-myoclonus (O/M)*

It occurs in association with neuroblastoma in children and with a number of tumours in adults. Patients present with ataxia and myoclonus of the head, palate, trunk, limbs, head and diaphragm. Although it occurs only in 2% of the children with neuroblastoma, 50% of those with this disorder have neuroblastoma.

Neuropathological changes go from being completely absent in some patients, to complete loss of olivary neurones in others (Fig. 2d) and the presence of small inflammatory cells in the periaqueductal grey matter.

*Paraneoplastic retinopathy*

It is a rare disorder characterised by a triad of symptoms: severe photosensitivity, scotomatous visual loss and attenuation in calibre of the retinal arterioles. The commonest neoplasm (90%) is small cell cancer of the lung, followed by melanoma, breast and prostate carcinoma and uterine sarcoma.

Changes of the eye include diffuse degeneration of photoreceptor cells with relative sparing of cones, almost complete cell loss of the outer molecular layer and presence of melanin-laden macrophages in the outer retinal layer. The other retinal layers and the optic nerve are preserved.

*Peripheral neuropathy*

Denny-Brown (1948)<sup>9</sup> established the relationship between peripheral neuropathy and carcinoma; although the incidence of this syndrome is difficult to establish.<sup>8</sup> The majority of patients with this syndrome have lung cancers; however GI tract, breast, uterus and prostate may also be implicated.

Clinically, peripheral neuropathies are subdivided into sensory, sensory-motor and autonomic, mixed forms being more common than pure ones.

Neuropathological changes include axonal degeneration, segmental demyelination, sometimes with onion bulb formation. A perivascular lymphocytic component

may extend to the dorsal root ganglia (DRG). Discrete degeneration of the DRG and posterior columns and anterior horn cells has been reported.

*Paraneoplastic encephalomyelitis/sensory neuropathy (EM/SN)*

The disorder appears in association with any form of carcinoma; however a bronchial carcinoma of the small cell type was detected in 77% of the patients.<sup>10</sup>

The pathological process underlying this syndrome is of a polioencephalomyelitis (Fig. 2e) in the central and a ganglioradiculoneuritis (Fig. 2f) in the peripheral nervous system with neuronal cell loss and microglial hyperplasia and reactive gliosis. As symptoms vary, according to the distribution of the lesions, the following clinicopathological forms have been defined:

1. Limbic encephalitis presents with hallucinations, abnormal behaviour, fits and loss of recent memory. Pathological changes are seen in the hippocampus, cingulate gyrus, pyriform cortex, frontal orbital region of the temporal lobe, insula and amygdala.
2. Brain stem encephalitis can pose considerable diagnostic problems with other disorders involving the brain stem, in particular vascular and motor neurone disease, MS, infectious and inflammatory disorders and intrinsic tumours.
3. Myelitis presents as poliomyelitis involving both anterior and posterior horns and involving variable number of spinal segments. The existence of a pure form of motor neurone disease (MND) is debated;<sup>10</sup> however, the discovery of specific autoantibodies associated with MND suggests that further studies may shed light on this issue.
4. Ganglio-radicle neuritis and autonomic neuropathy may present in isolation or associated with lesions of the CNS. Involvement of the ganglia may be selective and symmetrical, or diffuse and result in degeneration of the dorsal columns of the spinal cord (Fig. 2g). Disappearance of DRG is accompanied by an increase of nodules of Nageotte; the remaining neurones may show cytoplasmic vacuolation, chromatolysis and nuclear shrinkage. Inflammation appears as diffuse

**Table 2**

Antibody	Clinical syndrome	Ca. most frequent	IHC	Western blotting	Antigen
Anti-Hu/ ANNA-1	EM/SN	Small, non-small lung Ca.	Staining of all neuronal nuclei; less perikarya	35-40 kDa	Neuron specific RNA binding proteins
Anti-Yo/ PCA-1	Acute/subacute cerebellar syndrome	Ovarian, breast, uterus	Purk cell cytoplasm, coarse	34 and 62kDa in Purkinje cells	DNA binding, gene transcription regulators
Anti-Tr	Slowly progressing cerebellar syndrome	Hodgkin's disease	Purkinje cell cytoplasm, coarse	No protein detected yet	Not known
Anti-Ri/ ANNA-2	O/M	Breast, small cell lung	All CNS nuclei	55 and 80 kDa protein NOVA	RNA-binding protein
Anti-amphiphysin	Stiff Person syndrome	Breast	Synapses of CNS neurones	128 kDa neuronal pr.	Amphiphysin in synaptic vesicles
Anti-VGCC	LEMS	Small cell lung Ca.	Presynaptic	VGCC	ACh release
Anti-Ta	Limbic encephalitis	Testicular Ca.	Nuclei, perikarya	40 kDa	Unknown

EM/SN - Paraneoplastic encephalomyelitis/sensory neuropathy • O/M - Paraneoplastic opsoclonus-myoclonus • LEMS - Lambert-Eaton myasthenic syndrome

lymphocytic infiltration or cuffing of the vessels and may extend to the roots.

#### Paraneoplastic syndromes and auto-antibodies

Although the role of antibodies in the pathogenesis of the various syndromes is still unclear (anti-Hu antibody was also detected in patients with Sjögren syndrome), their detection is a useful tool both in the diagnosis of the disorders and for giving clues in the search for the neoplasm. Table 2<sup>6</sup> provides a list of antigens and antibodies so far identified. Three antibodies (anti-Hu, -Yo and P/Q voltage-gated calcium channels – VCGG) have been observed in a large series of patients and their predictive clinical value is now well established.

#### Lambert-Eaton myasthenic syndrome (LEMS)

Patients with this disorder complain of weakness and fatigue, particularly in the proximal limbs, whereas ocular symptoms are less obvious than in myasthenia gravis and autonomic symptoms are present.<sup>11</sup>

Neuropathology is limited to the neuromuscular junction which shows reduced numbers and disorganisation of motor nerve terminal active-zone particles, probably representing calcium channels involved in the release of ACh.

#### Pathogenetic mechanism in paraneoplastic disorders

The role of antibodies in paraneoplastic disorders has been demonstrated conclusively only in Lambert-Eaton myasthenic syndrome.<sup>12</sup> These patients develop antibodies against the P/Q-type voltage gated calcium channels (VGCC) located at the pre-synaptic level of the neuromuscular junction. They block the entry of calcium necessary for the release of quanta of acetylcholine resulting in neuro-muscular weakness.

On the other hand, in some paraneoplastic disorders there is circumstantial evidence supporting a pathogenetic role for T-lymphocytes: 1) presence of intense inflammatory infiltrates of mononuclear cells including CD4 and CD8; 2) the presence of cytotoxic and memory helper T-cells; 3) the presence, within tumours of patients with paraneoplastic disorders, of MHC class I and II antigens.

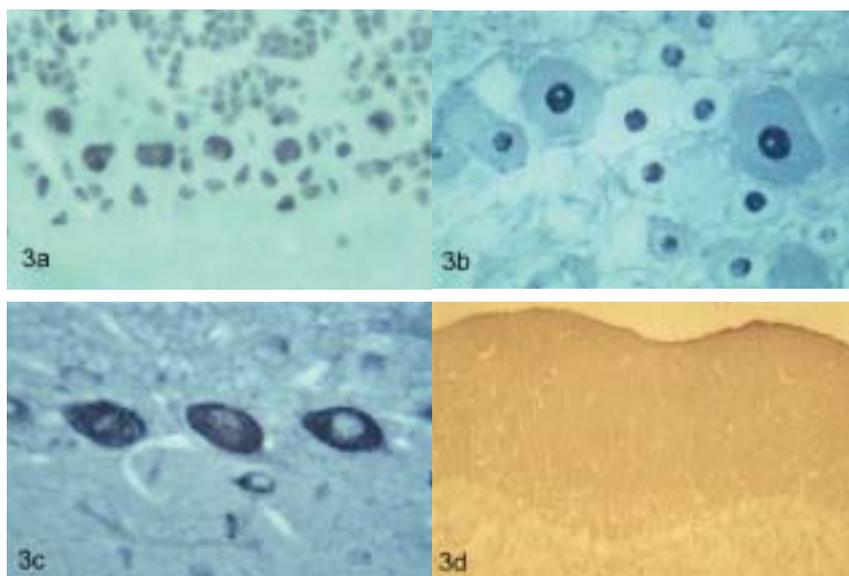
However, it is also possible that these disorders may result from non-immune mediated mechanisms. These include: 1) synthesis of hormone-like substances; 2) competition for substrate between the tumour and the nervous system; 3) secretion of cytokines by the tumour or by the inflammatory infiltrates.<sup>13</sup>

#### Treatment of paraneoplastic disorders

When the issue of the treatment of these disorders is considered<sup>6</sup> the following facts have to be taken into consideration:

1. In most of these patients in whom antibodies can be detected, the tumour is usually small and its progress follows a rather indolent course;<sup>14</sup>
2. Spontaneous regression has been described with small cell lung carcinoma in patients with antibodies<sup>15</sup> and neurological improvement without treatment has been reported.<sup>16</sup>

In paraneoplastic encephalomyelitis with cerebellar degeneration, disappointing results were obtained using various immunosuppressive strategies, such as steroids, plasmapheresis and intravenous immunoglobulins. On the other hand improvement of neurological symptoms



**Figure 3: Paraneoplastic syndromes**

a) & b) Nuclear staining by anti-Hu antibodies of cerebellar and dorsal root ganglion cells. c) Nuclei of Purkinje cells stained by anti-Yo antibody, which also stains nuclei of dorsal root ganglion cells. Only the former are stained by anti-Ri antibodies. d) Anti-amphiphysin antibody stains diffusely the cytoplasm of the cerebellar cortex.

has been obtained in LEMS or in O/M from the treatment of the underlying tumour or by the reduction of the antibody titre with plasmapheresis or intravenous immunoglobulins.

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