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Neoplasm Related Encephalopathies

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1. Introduction

Encephalopathy is a common clinical syndrome in cancer patients. The underlying causes of cancer related encephalopathies are various and mostly non-specific, such as metabolic disturbances as seen in critically ill patients. Electrolyte disturbances, hypoxia, hyperammonemia, thiamine deficiency and toxic reactions are all possible causes of encephalopathy in cancer patients. Structural lesions such as brain metastasis or venous thrombosis can evoke intracranial hypertension, also inducing a clinical picture resembling encephalopathy.

However, next to these non-specific causes of cancer related encephalopathy, there are also uncommon but highly specific encephalopathic syndromes related to malignancies and their treatments. In this chapter, we discuss encephalopathy associated with these uncommon clinical syndromes.

Paraneoplastic neurological syndromes (PNS) are clinical syndromes caused by non-metastatic manifestations of neoplasm outside the nervous system. PNS can be immune-mediated, and in those cases an association with circulating anti-neuronal antibodies and cytotoxic T-cells, in combination with specific tumours, can be made.

In non-immune mediated PNS, encephalopathy can be induced by tumour products such as hypertensive encephalopathy in patients with aldosterone-producing adenoma. Encephalopathy can also be the result of a depletion of substrate by direct competition between the central nervous tissue and the tumour, e.g. carcinoid encephalopathy.

In addition to these paraneoplastic neurological syndromes, we will present two typical cancer treatment related neurological conditions causing encephalopathy: PRES (posterior reversible encephalopathy syndrome) and PML (progressive multifocal leukoencephalopathy).

Pathophysiological mechanisms will be discussed, as well as associated clinical symptoms, prognosis and possible treatments.

2. Paraneoplastic neurological syndromes

PNS are unusual presentations of cancer, occurring in 1 per 10 000 patients with malignancies. Clinically well defined immune-mediated PNS account for 10% of all non-

metastatic neurological complications with cancer. However, the percentage of patients with malignancies presenting with peripheral neuropathy or muscle weakness is much higher.

About 3-5% of patients with small-cell lung cancer (SCLC), 15-20% of patients with thymoma and about 10% of patients with plasma-cell dyscrasias develop PNS. In patients with cancer of the breast or ovary, prevalence is well below 1% (Darnell & Posner, 2003).

In 2/3 of patients, PNS will precede the diagnosis of malignancy. Identification of the PNS may allow tumour diagnosis when the tumour is small, localised and more responsive to treatment. Therefore, it is very important to recognize PNS with their various clinical presentations and subsequently start screening for malignancy when PNS is suspected.

Clinical presentations of PNS are various and include peripheral symptoms as well as central signs (Table 1). Peripheral symptomatology includes neuropathy, myasthenia and muscle weakness, whereas central signs are heterogeneous and include ataxia, visual disturbances, epilepsy, dysphagia and changes in mental state.

PARANEOPLASTIC SYNDROMES OF THE NERVOUS SYSTEM
<u>Paraneoplastic syndromes of the central nervous system</u> <ul style="list-style-type: none">• Paraneoplastic cerebellar degeneration• Paraneoplastic encephalomyelitis (limbic encephalitis, brainstem encephalitis, myelitis)• Paraneoplastic opsoclonus-myoclonus-ataxia• Paraneoplastic chorea• Paraneoplastic Stiff-man syndrome• Paraneoplastic necrotizing myelopathy• Motor neuron syndromes (ALS; subacute motor neuronopathy)
<u>Paraneoplastic syndromes of the peripheral nervous system</u> <ul style="list-style-type: none">• Subacute sensory neuronopathy• Autonomic neuropathy• Acute sensorimotor neuropathy• Polyradiculoneuropathy (Guillain-Barré)• Brachial neuritis• Chronic sensorimotor neuropathy• Sensorimotor neuropathies associated with plasma cell dyscrasias• Vasculitic neuropathy• Neuromyotonia
<u>Paraneoplastic syndromes of the neuromuscular junction and muscle</u> <ul style="list-style-type: none">• Lambert-Eaton myasthenic syndrome• Polymyositis/Dermatomyositis• Acute necrotizing myopathy• Cachectic myopathy• Carcinomatous neuromyopathy• Carcinoid myopathy

Table 1. Immune Mediated Paraneoplastic Syndromes of the Nervous System (Dalmau et al., 2007)

The more common PNS are syndromes of the peripheral nervous system and neuromuscular junction: Lambert-Eaton myasthenic syndrome (LEMS) which affects 3% of patients with SCLC and myasthenia gravis, occurring in 15% of patients with thymoma.

Paraneoplastic encephalomyelitis is the PNS of the central nervous system most frequently seen.

Tumours which are commonly involved in PNS of the central nervous system express neuro-endocrine proteins (e.g. small-cell lung cancer (SCLC)), affect organs with immunoregulatory proteins (e.g. thymoma) or contain mature or immature neuronal tissue (e.g. teratoma).

Tumours originating from tissue producing immunoglobulins (e.g. lymphomas) are more commonly involved in PNS of the peripheral nervous system (Dalmau & Rosenfield, 2008).

As mentioned above, circulating antibodies against the expressed tumoural proteins can be associated with PNS. Different antibodies can be associated with the same PNS and inversely, the same antibody can be associated with different clinical syndromes (Voltz, 2002). Moreover, several PNS may co-occur in the same patient, particularly if the underlying tumour is SCLC.

The detection of antibodies in serum or cerebrospinal fluid confirms the clinical diagnosis of a paraneoplastic syndrome and allows early identification of an underlying tumour. However, the failure of finding antibodies does not exclude a diagnosis of PNS and inversely, antibodies have been detected in patients without PNS, e.g. anti-Hu antibodies (in low titres) in patients with SCLC can be present without any neurological symptoms (Nath & Grant, 1997).

Next to immune mediated PNS, there are also non-immunologic mechanisms that can be involved in PNS. Cytokines and hormones produced by tumours can induce an encephalopathy. Another yet uncommon cause of encephalopathy involves the competition between the tumour and nervous tissue for a specific substrate, e.g. carcinoid tumours and tryptophan. This very rare and particular picture will be described further in this chapter.

2.1 Pathogenetic mechanism of immune-mediated PNS

The identification in 1985 of anti-neuronal antibodies in the serum of patients with non-metastatic neurological complications of cancer, led to the hypothesis that paraneoplastic neurological syndromes are immune-mediated (Voltz, 2002). Antibodies against neuronal antigens have since then been extensively described.

The central and peripheral nervous system are considered to be low immunogenetic systems, since the presence of the blood/brain barrier means that antigens which are localised in the cerebrospinal fluid do not normally induce an immune response. Aberrant expression of neuronal antigens by a tumour outside this barrier, can lead to an immunological response which breaches the blood/brain barrier, as such inducing a possible influence on the central and peripheral nervous system.

Before a disorder can be considered to be antibody mediated, several criteria have to be fulfilled (Koch's postulates, as cited in Sutton & Winer, 2002):

1. The reactivity of the antibody with the antigen results in antigen loss and/or neuronal loss, inducing the clinical phenotype.

2. A passive transfer of the immunoglobulins of an affected patient to an animal should induce the clinical phenotype.
3. Immunotherapy that leads to a reduction of antibody titres should be associated with clinical improvement or at least stabilisation of the symptomatology.
4. Immunization of an animal with the purified antigen leads to the development of an antibody response, resulting in the clinical phenotype.

In the group of onconeural antibodies, only the antibodies reacting against VGCC (voltage-gated calcium channel) and mGluR1 (metabotropic glutamate receptor) have met the above mentioned criteria and can be considered to be pathogenic antibodies, e.g. anti-VGCC antibodies inducing the Lambert-Eaton Myasthenic Syndrome. However, the anti-VGCC antibodies found in paraneoplastic cerebellar degeneration are not found to be pathogenic, whereas anti-GluR1 antibodies are the cause of the cerebellar degeneration in patients with Hodgkin's disease (Sutton & Winer, 2002).

Anti-VGCC antibodies and anti-GluR1 antibodies are antibodies reactive to antigens on the cell surface of neurones. Up till now, none of the antibodies acting against an intracellular neuronal antigen are found to be pathogenic.

In post-mortem findings of patients with PNS and antibodies against intracellular targets, the finding of infiltration of T-cells in the affected central nervous tissue has opened the possible role of a cytotoxic T-cell mediated immune response.

This pathway includes T-cell immune responses that probably act against the target antigens of the circulating antibodies. E.g. Hu antigen-specific T-cells have been identified in blood and cerebrospinal fluid of patients with circulating anti-Hu antibodies. Support for this additional T-cell mediated mechanism includes the difficulties in treating these disorders with strategies directed at the humoral immune response (Dalmau & Rosenfield, 2008).

This pathogenesis has been confirmed in the development of paraneoplastic encephalomyelitis in patients with SCLC and a positive anti-Hu antibody serology.

It remains to be investigated whether cytotoxic T-lymphocytes against the Yo-antigen are responsible for the paraneoplastic cerebellar degeneration (Sutton & Winer, 2002).

Thus, antibodies seem to be in most cases a marginal phenomenon opposed to a causing factor. The importance of detecting the antibody remains however essential, as screening for malignancies can be specified and the prognosis of the PNS can be formulated.

2.2 Antineuronal antibodies

Antineuronal antibodies belong to a group of heterogeneous antibodies, which tend to present a diversity of clinical symptoms.

Two groups can be separated: antineuronal antibodies formed in the presence of a malignancy, i.e. paraneoplastic or onconeural antibodies (table 2), while the other group is often but not always associated with neoplasm (table 3).

The majority of antibodies can be detected using indirect immunofluorescence. A confirmation test using Western blot against recombinant antigen is an additional value (Sutton & Winer, 2002).

Antibody	Paraneoplastic neurological syndrome	Associated tumours
Anti-Yo (APCA1)	Paraneoplastic cerebellar degeneration (PCD)	Ovarian cancer, breast cancer
Anti-Hu (ANNA1)	Subacute sensory neuronopathy Encephalomyelitis Autonomic dysfunction PCD Limbic encephalitis	Small-cell lung cancer (SCLC)
Anti-CV2 (CRMP5)	Chorea Sensory neuronopathy Sensorimotor neuropathy Encephalomyelitis PCD Limbic encephalitis	SCLC, thymoma, germ-cell tumours of testis
Anti-Ri (ANNA2)	Brainstem encephalitis Opsoclonus-Myoclonus-Ataxia syndrome PCD	Breast cancer, ovarian cancer, SCLC
Anti-Ma (1&2)	Limbic/mesodiencephalic/ hypothalamic encephalitis	Breast cancer, germ-cell tumours of testis
Anti-amphiphysin	Stiff-person syndrome Encephalomyelitis	Breast cancer SCLC
Anti-Tr (PCA-Tr)	PCD	Hodgkin’s disease
Anti-ANNA3	Various PNS of the CNS	SCLC
Anti-PCA2	Various PNS of the CNS	SCLC
Anti-Zic	PCD	SCLC
Anti-mGluR1	PCD	Hodgkin’s lymphoma

Table 2. Well characterized onconeural antibodies (APCA: anti-Purkinje cell antibody, ANNA: anti-neuronal nuclear antibody, CRMP: collapsin response mediator proteins, mGluR: metabotropic glutamate receptor) (Dalmau et al., 2007)

Antibody	Paraneoplastic neurological syndrome	Associated tumours
Anti-NMDAR	Encephalitis	Ovarian teratoma
Anti-VGKC	Limbic encephalitis neuromyotonia other	Thymoma, SCLC, other
Anti-VGCC	LEMS PCD	SLCL
Anti-AchR	Myasthenia Gravis	Thymoma
Anti-nAchR	Subacute pandysautonomia	SCLC, other
Anti-GAD	Stiff-person syndrome cerebellar ataxia limbic encephalitis other	Thymoma, other

Table 3. Antibodies that occur with and without malignancy (NMDA: N-methyl-D-Aspartic acid receptor, VGKC: voltage-gated potassium channel, VGCC: voltage-gated calcium channel, AchR: acetylcholine receptor, nAchR: neuronal acetylcholine receptor, GAD: glutaminic acid decarboxylase, LEMS: Lambert-Eaton myastenic syndrome) (Dalmau et al., 2007)

2.2.1 Anti-Yo antibody (APCA-1 = anti-Purkinje cell antibody type 1)

Clinical associations

Anti-Yo antibodies are mostly clinically accompanied by a paraneoplastic cerebellar degeneration (>50%).

Tumour associations

Most patients are women and associated tumours are almost exclusively gynaecologic (47% ovarian, 13% endometrial and tubal carcinoma) or breast cancers (25%). Some patients with SCLC, various adenocarcinomas, transitional cell carcinoma of the bladder or lymphoma have been described (Gozzard & Maddison, 2010).

Antigen

The Yo-antigens belong to a family of DNA binding proteins. The expression of the antigens is limited to the cytoplasm of Purkinje cells. Anti-Yo antibodies recognize 2 antigens: a cytoplasmatic protein called CDR62 (cerebellar degeneration-related 62kDa protein) and a minor cytoplasmatic protein of 34 kDa, named CDR34.

Three genes have been cloned (cdr 1-3). Cdr1 encodes the 34 kDa protein while Cdr2 encodes the CDR62 protein that specifically binds to c-Myc thereby downregulating its activity. Disruption of this interaction by anti-Yo antibodies may increase c-Myc activity, leading to apoptosis of Purkinje cells (Dalmau & Rosenfield, 2008; Nath & Grant, 1997; Voltz, 2002).

However, different studies have demonstrated T-lymphocytes in the leptomeninges, brain stem and medulla, without lymphocytic infiltration or signs of inflammation in the cerebellar cortex in patients with a later stage of the cerebellar degeneration (Sutton & Winer, 2002). It is proposed that the loss of the Purkinje cells represent a final “burn out” stage of a cell-mediated immune process (Voltz, 2002). This hypothesis is supported by the presence of T-lymphocytes in the cerebellar cortex of a patient, who died 4 months after onset of the cerebellar symptomatology (Sutton & Winer, 2002).

2.2.2 Anti-Hu antibody (ANNA-1 = anti- neuronal nuclear antibody type 1)

Clinical associations

As anti-Hu antibodies react with antigens localized in the nucleus of every neuronal cell, anti-Hu antibodies can cause a variety of PNS of the central and peripheral nerve tissue (table 2): paraneoplastic limbic encephalitis, paraneoplastic cerebellar degeneration, paraneoplastic encephalomyelitis and subacute sensory neuronopathy.

Identification of anti-Hu antibodies at a concentration greater than 1/500 in cerebrospinal fluid is highly sensitive for a PNS of the central nervous system, typically limbic encephalitis or paraneoplastic encephalomyelitis.

Tumour associations

80%-93% of patients with anti-Hu antibodies will have SCLC (Gozzard & Maddison, 2010; Nath & Grant, 1997). Extrathoracic tumours in association with anti-Hu antibodies include neuroblastoma (50%) and prostate cancer (Titulaer et al, 2011).

Antigen

Anti-Hu antibody reacts with a neuronal nuclear antigen that belongs to a family of RNA binding proteins.

There are 4 antigens which are recognized by anti-Hu antibodies: HuD, HuC, HuR and Hel-N1. HuD, HuC and Hel-N1 are expressed in terminally differentiated neurons, whereas HuR is expressed in all proliferating cells (Sutton & Winer, 2002). HuD, HuC and Hel-N1 are expressed by all SCLC's.

Immunologic associations

Patients with paraneoplastic syndromes and anti-Hu antibodies may develop concurrent antibodies to other onconeural antigens. They include anti-CV2 (CRMP5), anti-amphiphysin, anti-Ri, anti-VGCC and anti-Zic4 antibodies.

2.2.3 Anti-Ri antibody (ANNA-2 = anti-neuronal nuclear antibody type 2)

Immunocytochemistry of serum or CSF shows an anti-neuronal nuclear antibody which is identical to the ANNA-1 antibody on immunocytochemical criteria. With western blotting, a different banding pattern can be seen, distinguishing this antibody from ANNA-1.

Clinical associations

This antibody has mostly been described in patients with opsoclonus-myoclonus-ataxia with SCLC as underlying tumour. Associated PNS can be paraneoplastic cerebellar degeneration (Gozzard & Maddison, 2010).

Tumour associations

Next to SLCL, other underlying neoplasms can be malignancies of breast, ovary and bladder (Darnell & Posner, 2003; Gozzard & Maddison, 2010).

Antigen

The antigen recognized by anti-Ri antibodies is a protein belonging to a family of RNA-binding proteins, mainly expressed in the nervous system. There are 2 Ri-antigens: Nova-1 and Nova-2, widely expressed within the central nervous system.

Recent pathological and functional MRI findings suggest that the disinhibition of the fastigial nucleus of the cerebellum is involved, causing the clinical picture. However, it remains unclear why this structure is most susceptible to the toxicity of the anti-Ri antibody, whilst the inflammatory process is seen in the entire central nervous system (Dalmau & Rosenfield, 2008; Sutton & Winer, 2002).

2.2.4 Anti-CV2 antibodies (=Anti-CRMP5 antibodies)

Clinical associations

Patients can manifest with different clinical syndromes. Sensorimotor neuropathy and paraneoplastic cerebellar degeneration are most commonly found. Less frequent are limbic encephalitis, encephalomyelitis and LEMS.

Tumour associations

The tumour most commonly found in patients with anti-CV2 antibodies, is SCLC (60%-77%). Further, thymoma (7%) and neoplasm of the uterus need to be excluded (Voltz, 2002).

Antigen

The target of anti-CV2 antibodies is a family of ~66 kDa proteins that are mainly expressed in the nervous system called CRMP for Collapsin Response Mediator Proteins. In the adult brain, the expression of CRMPs is dramatically down-regulated. However, they remain expressed in structures that have been shown to retain capacity of differentiation and also in a subpopulation of oligodendrocytes. In the peripheral nervous system CRMPs are expressed in a subset of sensory neurons and Schwann cells.

Immunologic associations

Patients with paraneoplastic syndromes and anti-CV2 antibodies may develop concurrent antibodies to other onconeural antigens. They include anti-Hu, anti-amphiphysin, anti-Ri, and anti-Zic4 antibodies.

2.2.5 Anti-Ma antibodies

The Ma proteins (Ma1, Ma2 and Ma3) belong to a family of brain-testis-cancer proteins. Ma1 and Ma2 antigens are expressed in the testis and in neurons. The highest level of expression of Ma antigens is seen in the neurons of the limbic structures, tegmental nuclei and cerebellar dentate nucleus. Aberrant expression of Ma antigens are seen in other malignancies, such as breast cancer (Sutton & Winer, 2002; Voltz, 2002).

Different neurological syndromes can be associated. Logically, mostly paraneoplastic limbic encephalitis and paraneoplastic encephalomyelitis are seen.

2.2.6 Anti-amphiphysin antibodies

The antigen is a protein located in synaptic vesicles and may have a role in vesicle endocytosis. This antibody is found in patients with Stiff-person syndrome, encephalomyelitis and subacute sensory neuronopathy. The underlying tumour can be breast cancer, as well as SLCL (Titulaer et al, 2011; Voltz, 2002).

2.2.7 Anti-Tr antibodies

This antibody has similarities with the anti-Yo antibody but can be differentiated by a typical immunohistochemical staining pattern of the molecular layer of the cerebellar cortex, in combination with staining of the Purkinje cell layer. Clinical presentation is a cerebellar degeneration. The associated tumour is Hodgkin lymphoma (Sutton & Winer, 2002; Voltz, 2002).

2.2.8 Antibodies that occur with and without malignancy

Anti-VGCC antibodies (anti-voltage gated calcium antibodies)

This antibody is mostly associated with LEMS. In 50% of patients with LEMS and anti-VGCC antibodies, SCLC is found. Rarely, patients present with a paraneoplastic cerebellar degeneration.

Anti-NMDAR antibodies (anti-N-Methyl-D-Aspartic acid receptor antibodies)

These antibodies are found in young women with a teratoma of the ovary. Clinically, patients present with a limbic encephalitis in combination with psychiatric symptoms and autonomic dysfunction. The neurological symptomatology can reverse after treatment of the tumour, as well as after immunotherapy.

Anti-Zic antibodies

This antibody has a low frequency. A variety of neurological symptoms can occur, with cerebellar ataxia due to paraneoplastic cerebellar degeneration most frequently seen. Underlying tumour is SCLC.

Anti-mGluR1 receptor antibodies

This metabotropic glutamate receptor antibody reacts with the mGluR1 receptor on the surface of Purkinje cells. There is an association with Hodgkin's lymphoma. Clinical presentation is a cerebellar syndrome (Darnell & Posner, 2003).

Anti-VGKC antibodies (anti-voltage gated potassium channel antibodies)

Patients with a positive serology for this antibody present typically with neuromyotonia. A PNS of the central nervous system occasionally seen is limbic encephalitis, commonly evolving to a less focalized encephalitis. Underlying tumours are SCLC and thymoma (Titulaer et al, 2011).

Anti-GAD antibodies (anti-glutaminic acid decarboxylase antibodies)

This antibody has a well known association with Stiff-Person Syndrome. Recently patients with paraneoplastic cerebellar degeneration or limbic encephalitis were described. This antibody is frequently found in patients with insulin-dependent diabetes mellitus. When a paraneoplastic mechanism is suspected, patients should be screened for a thymoma.

2.3 Immune-mediated paraneoplastic syndromes of the central nervous system

As 2/3 of PNS precede the diagnosis of malignancy, it is important to recognize the clinical picture and to start an appropriate screening for neoplasm.

Several features are shared by most PNS of the CNS. The clinical presentation is a fast accumulation of symptoms of central nervous system involvement, evolving over weeks and severely disabling the patient.

MRI findings are non-specific and can show normal findings, relative atrophy of specific regions (e.g. cerebellum) or regional Gadolinium-enhancing lesions. In cerebrospinal fluid, mostly signs of inflammation or immune-mediated mechanisms are withheld: moderate lymphocytic pleocytosis (30-40 white blood cells/mm³), increased protein concentration (50-100 mg/dl), high IgG index and CSF-specific oligoclonal bands (Darnell & Posner, 2003).

Because of the low prevalence of PNS, the PNS Euronetwork published diagnostic criteria for PNS (table 4) (PNS Euronetwork, 2002; Titulaer et al, 2011).

Diagnostic Criteria for Paraneoplastic Neurological Syndromes	
Definite PNS	
1.	A classical syndrome and cancer that develops within five years of the diagnosis of the neurological disorder.
2.	A non-classical syndrome that resolves or significantly improves after cancer treatment without concomitant immunotherapy, provided that the syndrome is not susceptible to spontaneous remission.
3.	A non-classical syndrome with onconeural antibodies (well characterised or not) and cancer that develops within five years of the diagnosis of the neurological disorder.
4.	A neurological syndrome (classical or not) with well characterised onconeural antibodies (anti-Hu, Yo, CV2, Ri, Ma2, or amphiphysin), and no cancer.
Possible PNS	
1.	A classical syndrome, no onconeural antibodies, no cancer but at high risk to have an underlying tumour.
2.	A neurological syndrome (classical or not) with partially characterised onconeural antibodies and no cancer.
3.	A non-classical syndrome, no onconeural antibodies, and cancer present within two years of diagnosis.

Table 4. Diagnostic Criteria for Paraneoplastic Neurological Syndromes (Graus et al, 2004)

2.3.1 Paraneoplastic cerebellar degeneration

Although one of the best known PNS, paraneoplastic cerebellar degeneration is rare, occurring in 0,2% of patients with cancer.

The clinical presentation is typical. The progression of a paraneoplastic cerebellar degeneration is fast, leaving the patient severely disabled after a small number of weeks.

Patients start complaining of vertigo, dizziness and nausea, followed by ataxia which makes it difficult to walk and to perform activities in daily living. As disease progresses, nystagmus develops causing blurry vision, and dysarthria and dysphagia may occur.

About 20% of patients present with mild cognitive deficits (Gozzard & Maddison, 2010).

Initially MRI is normal. However, subsequent MRI scans during the course of the disease, show a progressive cerebellar atrophy. Initial fluoro-deoxy-glucose PET can show cerebellar hypermetabolism. The findings in cerebrospinal fluid are compatible with an immune mediated or inflammatory process (Gozzard & Maddison, 2010).

Differential diagnosis includes viral cerebellitis, toxic cerebellitis, alcohol-related vitamin deficiency induced cerebellitis and Creutzfeldt-Jakob disease (CJD) (Dalmau et al, 2007).

In the differential diagnosis with CJD, it is important to consider that 12% of patients with PNS of the CNS have 14-3-3 protein in the CSF whereas high titres of this protein in cerebrospinal fluid are typically found in CJD.

In patients with paraneoplastic cerebellar degeneration, a range of antineuronal antibodies can be detected in serum and in cerebrospinal fluid. Some are specifically related to

cerebellar involvement, whereas others are non-specific and might reflect a tumour-induced immune response. Dependent on the associated antibody, the clinical course, prognosis and survival may differ (Voltz, 2002).

Most frequently, anti-Yo antibodies are seen, with ovarian cancer or breast cancer as underlying pathology. This PNS occurs consequently more in middle aged women. Median survival of anti-Yo positive patients with breast cancer is 100 months, whereas anti-Yo positive patients with ovarian malignancies survive 22 months.

When small-cell lung cancer is found, anti-Hu antibodies are present in 23-40% of patients with paraneoplastic cerebellar degeneration. Median survival is 9 to 12 months (Voltz, 2002).

41% of patients will develop anti-VGCC (voltage-gated calcium-channel) antibodies. These antibodies are also present in Lambert-Eaton myasthenic syndrome.

Anti-Tr antibody, associated with Hodgkin's lymphoma, is another highly specific antibody. The patients are usually young men and the diagnosis of PNS often follows the diagnosis of lymphoma (Nath & Grant, 1997).

Rarely other antibodies are found, such as antibodies against collapsing-response mediator protein 5 (CRMP or CV2), amphiphysin or antineuronal nuclear antibody 3 (ANNA3).

The neuropathological hallmark of the paraneoplastic cerebellar degeneration is extensive loss of Purkinje cells in association with atrophy of granular and molecular layers. Microglial proliferation is seen in combination with astrogliosis. More specific, in the beginning of the disease T-cell infiltration in leptomeninges and in cerebellar cortex can be found. As the disease progresses, lymphocytic infiltration diminishes and gliosis develops (Dalmau et al, 2007; Nath & Grant, 1997; Sutton & Winer, 2002).

2.3.2 Paraneoplastic encephalomyelitis

Paraneoplastic encephalomyelitis (PEM) has a strong association with the anti-Hu antibody (Titulaer et al, 2011). In 75% of patients with a positive serology, an underlying SCLC is found. Other antibodies less frequently associated with PEM are anti-CV2 (CRMP5) and anti-amphiphysin.

This PNS includes a variety of neurological syndromes, the clinical picture being the result of the variable anatomic involvement. The regions which are frequently involved are the hippocampus, lower brain stem, spinal cord and dorsal root ganglia (Gozzard & Maddison, 2010). The diversity of neurological dysfunction reflects the fact that anti-Hu antigens, the target of the autoimmune dysfunction, are expressed in all central and peripheral neurones (Sutton & Winer, 2002).

Most frequently, patients present with symptoms suggestive of subacute sensory neuronopathy, followed by limbic encephalitis, brain stem encephalitis and myelitis.

Patients present often with a symptomatology of one of the above mentioned regions, which eventually, as disease progresses, evolves into a multifocal neurological syndrome (PNS Euronetwork, 2002).

As limbic encephalitis is part of this clinical picture often accompanied with an encephalopathic syndrome, this will be discussed further.

CSF studies may show pleocytosis and elevated protein levels. MRI brain scans are mostly normal. However, hyperintense T2-weighted lesions in brainstem, thalamus and hippocampus can be seen. Lesions are rarely contrast enhancing.

Extensive neuronal loss is seen in the affected brain regions: hippocampal sclerosis, gliosis in brainstem, spinal cord and dorsal root ganglia.

2.3.3 Paraneoplastic limbic encephalitis

This clinical syndrome is seen in 0.3% of cancer patients (Nath & Grant, 1997). Patients tend to be of middle age with no sex predilection. Patients develop mood and sleep disturbances, seizures, hallucinations and short term memory loss. This cognitive decline can eventually lead towards dementia (Voltz, 2002).

Electro-encephalographic findings often include epileptic foci, mostly in one or both temporal lobes, next to generalized slow wave activity. In 70 to 80% of patients, hyperintense foci in the medial part of one or both temporal lobes are seen on MRI fluid-attenuated inversion recovery (FLAIR) and T2-weighted sequences. Gadolinium contrast enhanced lesions are rare. Fluoro-deoxy-glucose PET often shows hypermetabolism of the medial parts of the temporal lobes and often precedes MRI findings. In cerebrospinal fluid, findings suggest inflammation (Gozzard & Maddison, 2010).

Differential diagnoses of limbic encephalitis include viral encephalitis, prion diseases and auto-immune non-neoplastic encephalopathies (Voltz, 2002).

Neuropathological findings can be summarized as an inflammation of the structures of the limbic system. Perivascular lymphocytic infiltration is seen, in combination with microglial proliferation and reactive gliosis. Immunological staining with anti-Hu shows strong staining of neuronal nuclei in central and peripheral nervous tissue with sparing of nucleoli. Cytoplasm is weakly stained. There is no staining of systemic tissue (Nath & Grant, 1997).

Tumours most frequently involved are SCLC, testicular germ-cell malignancies, thymoma, teratoma or Hodgkin's lymphoma. Dependent on the antibody which is found in serum and cerebrospinal fluid, subtyping of limbic encephalitis is recommended (Dalmau & Rosenfield, 2008).

Anti-NMDA receptor antibodies and anti-VGKC antibodies act against proteins that are exposed on the cell surface from e.g. hippocampus. Patients with a positive serology for those antibodies, respond well to immunotherapy, whereas patients who are positive for antibodies acting against antigens localised on the cytoplasmatic side of the cell (e.g. amphiphysin) or localised in the cytoplasm or nucleus (e.g. GAD, Hu), respond less or not to immunotherapy.

Limbic encephalitis with antibodies to intracellular antigens

In about 1 of 2 patients with anti-Hu antibodies SCLC and limbic encephalitis, the clinical picture starts with the symptomatology of limbic encephalitis but evolves eventually into a more widespread encephalitis, often in combination with myelitis.

Patients can present with anti-CRMP5 (anti-CV2) antibodies. In those cases, the clinical picture can be dominated by optic neuritis and myelitis, whereas symptoms suggestive of

encephalitis are less explicit. SCLC and thymoma are tumours most commonly involved. The combination of optic neuritis and myelitis resembles a diagnosis of Devic's syndrome (neuromyelitis optica).

Anti-Ma2 antibodies are associated with limbic encephalitis in combination with involvement of the hypothalamus and brainstem. Clinical presentation is variable and can start with hypersomnolence, cataplexy, narcolepsy, REM sleep disturbances, hormonal deficits or hyperphagia. Involvement of the mesencephalon causes vertical gaze palsy, orofacial and jaw dystonia. Differential diagnosis has to be made with Whipple's disease.

Anti-Ma2 antibodies in males younger than 50 years should trigger a screening program for testicular germ-cell tumours. In older patients, SCLC or breast tumours have to be excluded.

Many patients with germ-cell tumours of the testes and anti-Ma2-associated encephalitis benefit from orchiectomy and immunotherapy. In 35% of patients, neurological signs improve.

Limbic encephalitis with antibodies to neuronal cell-surface antigens

The two main clinical syndromes associated with these antibodies are typical limbic encephalitis and encephalitis with psychiatric symptoms, hallucinations and peripheral nerve hyperexcitability, amongst other signs of autonomic dysfunction.

Antibodies act against the voltage-gated potassium channels.

About 30% of patients with anti-VGKC antibodies have tumours, of which SCLC and thymoma are most prevalent.

The CSF of those patients shows less inflammation, less pleiocytosis and lower protein concentration compared to other PNS.

80% of patients respond to immunotherapy.

Patients with anti-NMDA-receptor antibodies are usually young and female. Symptomatology starts with headaches, memory deficits, epileptic seizures and psychiatric behavioural symptoms. As the disease progresses, autonomic disturbances are seen, leading to supported ventilation or pace-making.

About 65% of the patients have a malignancy. Underlying tumour is mostly a (cystic) ovarian teratoma. Immunotherapy in combination with treatment of the tumour results mostly in neurological improvement.

2.3.4 Paraneoplastic opsoclonus-myoclonus-ataxia syndrome

Opsoclonus is the abnormal movement of the eyes consisting of chaotic, involuntary conjugated saccades with horizontal, vertical and torsional components and without intersaccadic interval. Myoclonus is most often present as myoclonic jerks in limbs and trunk. Occasionally, encephalopathy or cerebellar ataxia is present.

Clinical symptoms often have an acute onset and may fluctuate in the development of the PNS. Rarely, it resolves spontaneously.

Opsoclonus-myoclonus-ataxia syndrome can occur in combination with infections, metabolic disturbances, toxic factors as well as in combination with neoplasm.

MRI is usually normal. CSF may show mild inflammatory changes, mostly B-lymphocyte pleiocytosis and oligoclonal bands (Gozzard & Maddison, 2010). EEG may be normal or demonstrate generalized slow activity, without epileptic discharges.

Paraneoplastic opsoclonus-myoclonus-ataxia syndrome is seen in 3 patients groups.

In children, this clinical syndrome is seen in combination with neuroblastoma in 50% of cases. There is no corresponding antibody identified.

In adult female patients, the tumour most commonly found is cancer of ovary and breast. The associated antibody is anti-Ri.

In adult patients who are anti-Ri antibody negative, the underlying tumour is SCLC. A positive serology for anti-Hu and an association with anti-Ma2 has been described in patients with SCLC and opsoclonus-myoclonus-ataxia syndrome (Voltz, 2002).

Recent immunological findings however have demonstrated the presence of antibodies against postsynaptic or cell-surface antigens. Those antibodies, present in the serum of children with neuroblastoma, react with the cell surfaces of cerebellar granular neurons and neuroblastoma cells (Dalmau et al, 2007).

Neuropathology shows a mild perivascular and interstitial lymphocytic infiltration, in combination with a relative loss of Purkinje cells and loss of neurons in the dentate nucleus.

Immunohistochemistry pattern of anti-Ri include strong staining of only central nervous system neuronal tissue, sparing of nucleoli, weak cytoplasmatic staining and no staining of systemic tissues (Nath & Grant, 1997; PNS Euronetwork, 2002).

2.4 Treatment of PNS

There is no standard of care for PNS of the central nervous system. Moreover, in the vast majority of cases, PNS are refractory to any form of treatment.

Clinical experience suggests that treatment and removal of the causing factor, i.e. the tumour is necessary to stabilise or improve symptomatology. Adjuvant corticosteroids, intravenous immunoglobulin therapy, plasma exchange, cyclophosphamide and tacrolimus have not substantially improved the neurological outcome. (Dalmau & Rosenfield, 2008).

In children with paraneoplastic opsoclonus-myoclonus syndrome, the clinical picture often responds, however only partially, to treatments such as corticosteroids, intravenous immunoglobulin, plasma exchange, cyclophosphamide or rituximab. Symptom relapses can occur during transient illnesses (e.g. viral infections). In adults, paraneoplastic opsoclonus-myoclonus syndrome is less responsive to immunotherapy. Stabilisation or improvement is only seen in patients with cured or controlled malignancies. Rarely, spontaneous remission of neurological symptoms can occur in patients with opsoclonus-myoclonus-ataxia syndrome. (Nath & Grant, 1997).

2.5 Non-immune mediated paraneoplastic encephalopathies

As previously mentioned, non-immune mediated encephalopathies can be provoked by a whole spectrum of etiological factors such as metabolic disorders, electrolyte disturbances

and excessive production of certain hormones or proteins, elicited by cancer or not. Some specific clinical entities have been described. Neuro-endocrine tumours can synthesize biologically active substances, such as hormones, growth factors or cytokines, which can induce non-immune mediated encephalopathy. For instance, pheochromocytoma, paraganglioma or tumours of the adrenal gland can cause hypertensive encephalopathy through production of vaso-active peptides (Kaltsas et al., 2010).

A peculiar form of non-immune mediated encephalopathy has been described in carcinoid tumours where competition arises between the tumour and the nervous tissue for a specific substance called tryptophan. Active production of serotonin by the carcinoid tumour causes depletion of tryptophan leading to neuronal dysfunction. Associated neurological disorders include carcinoid myopathy and carcinoid encephalopathy. Other mechanisms of carcinoid encephalopathy have also been proposed such as excessive production of serotonin in the brain by CNS metastasis, fulminant hepatic metastasis and aberrant secretion of ACTH of CRH by carcinoid tumours (Lapeire et al., 2010). Treatment of carcinoid encephalopathy is mainly focused on controlling the tumour although more 'targeted' treatment such as oral tryptophan substitution or serotonin receptor antagonism have proved their use in case reports.

3. Cancer treatment related encephalopathies

As the treatment modalities of cancer evolve, the side effects subsequently follow. Already decades ago, cytotoxic agents were linked with the development of encephalopathies and with the more recently developed targeted therapies the number of case reports regarding cancer treatment related encephalopathies is rising.

Cancer treatment related encephalopathies can be divided into two groups. On one hand we have toxic encephalopathies, of which posterior reversible encephalopathy syndrome or PRES is an uncommon yet characteristic cliniconeuroradiological syndrome. The second group comprises encephalopathies induced by opportunistic infections with progressive multifocal leukoencephalopathy or PML being most reported and investigated.

3.1 Posterior reversible encephalopathy syndrome (PRES)

3.1.1 Definition of PRES

In 1996, Hinchey et al. were the first to describe a syndrome characterized by similar cliniconeuroradiological findings in a group of patients with different clinical settings (Hinchey et al., 1996). They suggested the term 'reversible posterior leukoencephalopathy syndrome' (RPLS) given the reversibility of the abnormalities and the typical localization of white-matter lesions in the posterior occipital-parietal regions of the brain.

Afterwards, many critical remarks were postulated on the term RPLS. First of all, some case reports described the development of intracranial hemorrhage as complication with subsequent permanent sequelae or even fatal outcome, suggesting that not all RPLS are 'reversible' (Schwartz, 1996). Secondly, although in most patients the posterior regions were involved, other brain regions were also often affected. Thirdly, the term leukoencephalopathy is too restrictive since the white-matter lesions were frequently accompanied with cortical involvement.

Since then, many other terms were proposed like ‘hypertension encephalopathy’ (HTE), ‘occipito-parietal encephalopathy’ (Pavlakis et al., 1997) or ‘potentially reversible encephalopathy syndrome’ (Narbone et al., 2006). Casey et al. first used the term ‘posterior reversible encephalopathy syndrome’ or PRES (Casey et al., 2000). Although ‘posterior’ and ‘reversible’ are still present, the term PRES became generally accepted and systematically used. A possible explanation for this acceptance is that in time, it became apparent that with a prompt diagnosis and treatment, PRES is reversible in almost every patient. In addition, using the term ‘posterior’ does not exclude other regions to be involved but merely depicts the fact that occipito-parietal abnormalities are the most common feature on neuro-imaging.

3.1.2 Clinical presentation

PRES normally emerges gradually over a few days but can also have an acute, sudden onset. Mild to severe hypertension is a common feature in 70 to 80% of patients with PRES. Other typical clinical symptoms include headache, nausea/vomiting, seizures and visual disturbances (table 5). Seizures may start focally and evolve into generalized attacks or even status epilepticus. Quite often, seizures are the first presenting symptom of PRES. Many forms of visual changes have been reported ranging from a blurred vision to complete cortical blindness.

Next to the typical symptoms, many patients with PRES suffer from an altered mental status with confusion and diminished concentrating ability. Lethargy is common, sometimes worsening into stupor or even coma. Other neurological aberrations, like dysarthria and ataxia, have also been associated with PRES.

Clinical symptoms of PRES
<u>Typical:</u> Hypertension Headache Nausea/vomiting Seizures Focal Tonic-clonic/generalized Status epilepticus Visual disturbances Blurred vision Hemianopsy Visual neglect Cortical blindness
<u>Other:</u> Confusion Attention deficit Lethargy Stupor Coma Ataxia Dysarthria

Table 5. Clinical symptoms of PRES

3.1.3 Etiology

The name PRES was given to common cliniconeuroradiological findings in patients with very divergent underlying pathologies as summarized in table 6. All these clinical conditions induce a form of ‘systemic toxicity’, making the patient vulnerable for developing PRES.

With regard to cancer treatment, PRES was mostly seen after the administration of high-dose (combination) chemotherapy for hematologic malignancies. However, PRES has also been reported in patients treated with a single chemotherapeutic agent like cisplatin, gemcitabine or cytarabine. Moreover, the newer ‘targeted therapies’ like the monoclonal antibody bevacizumab and the tyrosine kinase inhibitors sorafenib and vandetanib have recently been linked with the development of PRES (Broniscer et al., 2010; Glusker et al., 2006; Govindarajan et al., 2006).

Clinical conditions associated with PRES
<u>Frequently:</u> Preeclampsia/eclampsia Infection/sepsis/shock Post-transplantation (allo-BMT, solid organ transplantation) Immune suppression (cyclosporine, tacrolimus) Cancer therapy (combination chemotherapy, single agent, targeted therapy) Auto-immune diseases (systemic lupus erythematosus, scleroderma, Wegener’s disease, etc.)
<u>Miscellaneous (not limited):</u> Hypomagnesemia Hypercalcemia Hypocholesterolemia Intravenous immunoglobulin Guillain-Barré syndrome Ephedra overdose Tumor lysis syndrome Triple-H therapy Hydrogen peroxide Dimethyl sulfoxide stem cells Dislysis/erythropoietin Corticosteroid treatment

Table 6. Clinical conditions associated with PRES

3.1.4 Pathophysiology

The pathophysiological mechanism behind PRES still remains a matter of debate.

When PRES was initially described, the hypodense parietal-occipital regions on CT imaging prompted investigators to suggest that ischemia was the causative factor of the observed abnormalities. The hypothesis was that the ‘systemic disease’ of the patient elevates the blood pressure which is counteracted by an auto-regulatory vasoconstriction in the brain, leading to reduced blood flow, ischemia and subsequent vasogenic edema.

As more cases were described and more research was performed, a new hypothesis was proposed based upon the hypertension/hyperperfusion theory. This hypothesis stated that PRES was the result of acute and severe hypertension beyond the autoregulatory limits, leading to a breakthrough of the blood-brain barrier, hyperperfusion, capillary bed injury, fluid leakage and vasogenic edema (Bartynski, 2008b, Staykov and Schwab, 2011). Different animal studies supporting the hypertension/hyperperfusion theory and the success of immediate anti-hypertensive treatment in clinical setting strengthened the belief in this more recent hypothesis.

However, several remarks have been posted questioning the reliability of this mechanism. For instance, hypertension is not or only mildly present in about 25% of patients with PRES, certainly not reaching the upper limits of autoregulation (Bartynski, 2008b, Staykov and Schwab, 2011). Secondly, solid evidence of hyperperfusion is scarce. Thirdly, the results from animal studies can not merely be extrapolated to humans. In patients with PRES, hypertension is induced by a 'systemic process/disease' while in animal studies hypertension is induced in healthy animals (Bartynski, 2008b and Staykov, 2011). At last, more advanced imaging techniques like cerebral angiography and MR angiography showed unexpectedly an inverse relation between the severity of hypertension and the extent of brain edema (Bartynski and Boardman, 2008).

In addition, as our knowledge of PRES expands, new insights in the pathophysiological mechanisms arise, pointing towards the older vasoconstriction-hypoperfusion theory. For example, all the well-known underlying pathologies (table 6) show activation of the cellular immune system, production of inflammatory cytokines and endothelial activation and injury, leading to a vasculopathy with vasoconstriction, hypoperfusion and subsequent ischemia as possible outcome (Bartynski, 2008b). It is clear that more investigations in this area are needed to elucidate this complex subject.

3.1.5 Diagnosis

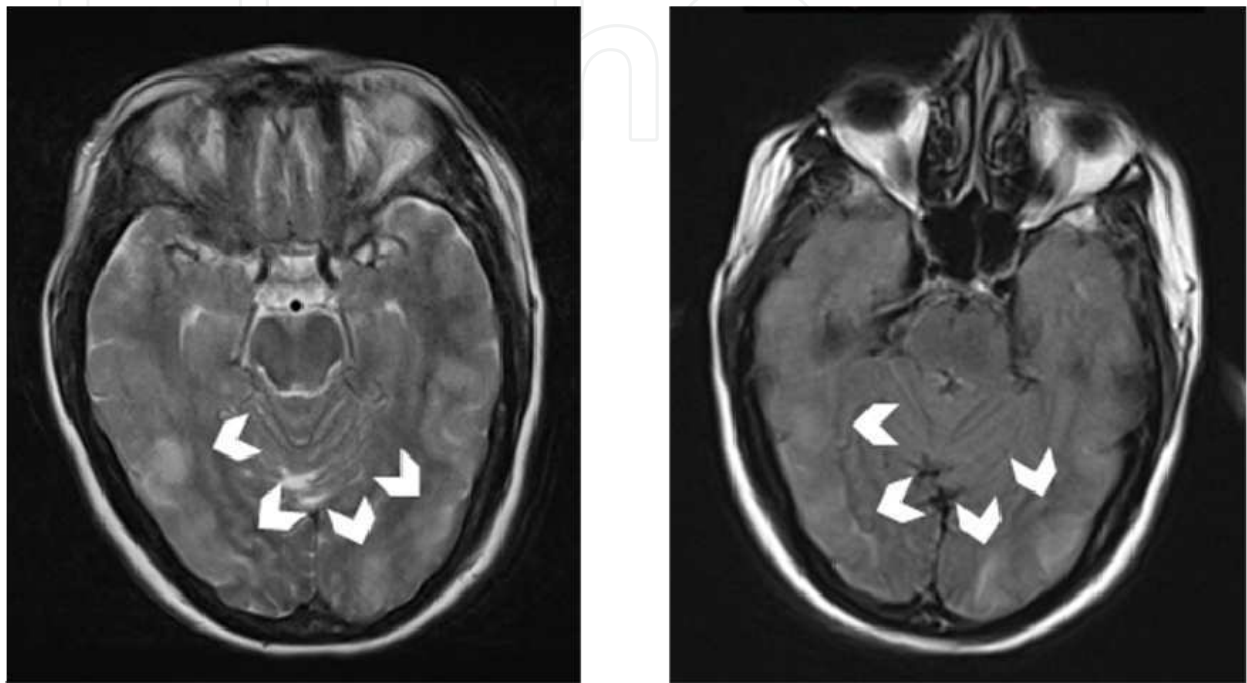
The diagnosis of PRES is mainly based upon the combination of typical clinical symptoms and specific abnormalities on brain imaging.

A laboratory work-out can give an indirect hint towards PRES by detecting thrombocytopenia, schistocytes and an increased serum lactate dehydrogenase (LDH) caused by endothelial injury which almost always accompanies PRES (Bartynski, 2008a; Staykov and Schwab, 2011).

Affected brain regions can be recognized by a hypodense signal on CT-scan but an MRI of the brain with fluid-attenuated inversion recovery (FLAIR) is the gold standard for the diagnosis of PRES because of its higher accuracy in detecting all affected areas (Casey et al., 2000). A pattern of symmetrical edema of the parietal-occipital regions is most frequently seen on neuro-imaging (Picture 1), but involvement of the frontal lobes, basal ganglia, brain stem and cerebellum have also been reported (Bartynski, 2008a; Hinchey et al., 1996; Staykov and Schwab, 2011).

Focal aberrations can be present along with the symmetrical edema but in absence of the latter, the diagnosis can be quite difficult. Three major patterns of PRES were proposed by Bartynski, namely a holohemispheric watershed pattern, a superior frontal sulcus pattern

and a dominant parietal-occipital pattern. These three typical patterns were seen in 99 of 136 patients with PRES. The other patients showed a partial or asymmetric variation of one of these major patterns (Bartynski and Boardman, 2007). Awareness of these different patterns is of great importance for a quick diagnosis and treatment, subsequently leading towards a better outcome.



Picture 1. An example of NMR imaging in PRES: hyperintense signal (white arrowheads) on T2-weighted (left) and FLAIR (right) images of symmetrical affected parieto-occipital regions.

MR diffusion weighted imaging (DWI) with calculation of the apparent diffusion coefficient (ADC) may have an additional value in distinguishing a vasogenic edema (in PRES) from a cytotoxic edema (infarction), especially given the differences in treatment strategies (Doelken, 2007).

Cerebral angiography (CA) and MR angiography (MRA) commonly show signs of diffuse or focal vasoconstriction (with sometimes a typical string-of-beads appearance) and vasculopathy (Bartynski and Boardman, 2008). MR perfusion mostly reveals a reduced blood flow in the affected areas (Bartynski, 2008a; Brubaker et al., 2005).

MR spectroscopy describes reduced N-acetylaspartate:choline and N-acetylaspartate:creatinine ratios suggesting neuronal, axonal or synaptic dysfunction (Bartynski, 2008a; Pavlakis, 1997; Staykov and Schwab, 2011). The presence of lactate in PRES accompanied by vasoconstriction is suggestive for ischemia (Bartynski, 2008a; Staykov and Schwab, 2011). It is clear that information and results obtained from the more recent and advanced imaging techniques like CA, MRA, MR perfusion and others are more in favor of the old vasoconstriction/hypoperfusion theory.

3.1.6 Treatment

Patients with PRES should be treated in a (neuro)critical care unit with close hemodynamic monitoring and the opportunity for intubation and ventilation in case of severe decrease in mental state. Cornerstone in the treatment of PRES is removing the causative pathology or drug. Specifically in cancer, the responsible chemotherapeutic agent(s) or targeted therapy should be reduced or even completely stopped when possible. About 75% of patients will present with a mild to severe elevated blood pressure which needs to be corrected with anti-hypertensive drugs. Nitroglycerine however should be avoided as it has been reported to aggravate the cerebral edema in PRES (Finsterer, 2003, as cited in Staykov and Schwab, 2011). In case of seizures or status epilepticus, benzodiazepines are given in the acute phase followed by long-term anti-convulsive therapy. Controversy remains about the duration of the anti-convulsive therapy. In some cases the treatment was successfully stopped after a few days, others continued the drugs for a couple of months. Seizures in pregnant women with eclampsia can be treated with magnesium sulfate.

3.1.7 Prognosis

As can be derived from the 'R' in the term PRES, this syndrome is usually completely reversible in a few days to weeks. A prompt diagnosis and correct treatment are therefore imperative. Sequellae however can arise, even with adequate treatment. Ischemia, parenchymal hemorrhage and epilepsy are possible complications of PRES with long-term consequences and a detrimental effect on quality of life (Staykov and Schwab, 2011).

Reoccurrence of PRES has been reported anecdotally (Sweany et al., 2007). In cancer patients the question remains if the causative drug can safely be reintroduced after recovery from PRES. Many case reports describe a successful completion of the planned treatment scheme suggesting that the cancer treatment is an evoking but not sole causative factor in cancer treatment related PRES.

3.2 Progressive multifocal leukoencephalopathy (PML)

3.2.1 Introduction

Progressive multifocal leukoencephalopathy is a demyelinating disease of the white matter of the human brain. In 1958, Astrom et al. were the first to utter the term progressive multifocal leukoencephalopathy after their experience of similar clinical, neurological and pathological findings in two patients with chronic lymphocytic leukemia and one patient with Hodgkin's lymphoma (Astrom et al., 1958). At that time, the underlying cause of the disease was unknown. A few years later, electron microscopy of the brain lesions associated with PML revealed intranuclear particles in the oligodendrocytes which were later identified as virions derived from a papovavirus.

Eventually, more than ten years after the first description of PML, Padgett et al. were able to culture the virus out of a brain lesion in human fetal glial cells (Padgett et al., 1971). They named it the JC virus (JCV) according to the initials of the donor patient and it was later characterized as a human polyomavirus.

More recently, next to PML, other neurological disorders have been associated with JCV, namely JC virus granule cell neuronopathy, JC virus encephalopathy and JC virus

meningitis (Tan and Koralnik, 2010). JCV is even thought to play a role in different types of brain tumors, gastro-intestinal cancers and lung cancer, although its contribution to the development of these cancers remains unraveled.

3.2.2 Clinical manifestation

The brain lesions associated with PML are asymmetric and variable in size, subsequently leading to a variety of possible clinical symptoms. In contrast with PRES, PML is characterized by a subacute onset of symptoms, gradually progressing over weeks to months.

Signs of subcortical dementia with cognitive impairment are a common feature and often the first symptoms indicating the development of PML (Major, 2010). Motor dysfunctions often accompany the cognitive problems and can range from walking difficulties and deranged coordination to ataxia and hemiparesis (Major, 2010; Brew et al., 2010). Visual changes are also frequently reported with hemianopsia being the most prevalent one. Seizures have been described in about twenty percent of PML cases and can be expected if the lesions are in close contact with the cortex (Brew et al., 2010).

Other possible symptoms are headaches, dysarthria, aphasia and abulia (Lima et al., 2010).

As the disease progresses, the patient gradually develops global impairment eventually leading to death if treatment fails.

3.2.3 Etiology

Infection with the JC virus is imperative for the possible development of PML but the JC virus on its own is not enough to cause this neurological disorder. The presence of a predisposing immunocompromising condition is also an absolute necessity.

Until the 1980's, PML was a rare neuropathological disease mostly associated with hematological malignancies and systemic inflammatory disorders (Brew et al., 2010). With the outbreak of the AIDS pandemic in the mid-1980's, the incidence of PML rose spectacularly to a 50-fold increase. AIDS became the most important predisposing factor for developing PML, being present in about 3% of HIV-1 positive individuals (Major, 2010).

More recently, new case reports of PML arose from a rather unexpected corner, namely the treatment of patients with immunomodulatory drugs, with the monoclonal antibodies natalizumab, efalizumab and rituximab as best described entities. The first cases of PML were seen in 2005 in different phase III trials where patients received natalizumab for the treatment of multiple sclerosis (MS) or Chron's disease (Kleinschmidt-DeMasters and Tyler, 2005; Langer-Gould et al., 2005 and Van Assche et al., 2005 as cited in Berger et al., 2009 and Weissert, 2011). Diagnoses of PML in patients treated with efalizumab for psoriasis or with rituximab for lymphoproliferative disorders followed but to a lesser extent than natalizumab.

Each monoclonal antibody has its specific immunomodulatory characteristics (Berger et al., 2009) possibly providing the reason why some monoclonal antibodies are more frequently associated with PML than others. In addition, the disorder requiring immunomodulatory therapy can also be a predisposing condition for developing PML making it difficult to

assess the real influence of the therapy on the incidence of PML. For example, rituximab is used for the treatment of lymphoproliferative disorders and both are linked with PML.

Next to monoclonal antibodies, several anti-neoplastic and immunosuppressive therapies like methotrexate, cyclophosphamide, carboplatinum/gemcitabine, fludarabine and mycophenolate mofetil have been reported as causative agents for PML (Brew et al., 2010; Palmieri et al., 2010).

3.2.4 Pathophysiology

The pathophysiological mechanism behind PML is complicated and until now not fully elucidated. However, to some degree there is a consensus about the major steps that need to be fulfilled for the development of PML (table 7). These steps include: primary infection with JCV, period of latent infection, reactivation of JCV and eventually invasion into the brain (Brew et al., 2010; Major, 2010; White and Khalili, 2011).

Primary infection:

A primary infection with the JC virus is indispensable for the possible development of PML. Primary infection occurs mainly in the childhood but continues into middle age. JCV is a hemagglutinating virus and hemagglutination inhibition assays were able to detect JCV antibodies in 50-90% of adults (Taguchi et al., 1982 and Walker and Padgett, 1983 as cited in White and Khalili, 2011). The route of transmission is believed to be inhalation of the virus with infection of the tonsils or ingestion of contaminated water or food and uptake of the virus by the gastro-intestinal tract. A primary infection usually occurs without symptoms while some organs stay behind with latent infection.

Period of latency:

Based upon detection of JCV in urine and the presence of JCV DNA in tissue of PML and non-PML patients, at least 3 organs are believed to harbor latent infection: the kidney, the bone marrow and lymphoid tissues like the tonsils, spleen, B-lymphocytes and CD 34+ hematopoietic cells (Major, 2010; White and Khalili, 2011).

Molecular and genetic characterization of JCV found in these tissues and cells led to the discovery of two different types, namely archetype JCV and prototype JCV. The difference between these two types is the appearance of rearrangements in the non-coding control region (NCCR) of the virus leading to a neurotropic prototype JCV (Berger et al., 2009).

Based upon these findings, following hypothesis was put forward: archetypal JCV is responsible for the primary infection, possesses a normal NCCR and is not able to infect human glial cells. During latency, rearrangements in the NCCR occur leading to the more aggressive, neurotropic prototype JCV. This hypothesis was supported by the intriguing observation of possible latency in B-cells, possessing all the necessary machinery for gene rearrangement (Berger et al, 2009). Moreover, the fact that PML remains a rare entity despite the high prevalence of JCV-infection points towards the necessity of this genetic alteration.

Of note, controversy remains regarding the brain as possible site of latency. Although prototype JCV-DNA has been found in normal non-PML brain tissue (White and Khalili, 2011), some investigators question the possibility of the brain as a functional latency site

given the rarity of PML and the unlikeliness of establishing a long-term latency without inflammatory consequences during viral clearance (Major, 2010).

Reactivation of JCV:

The most popular theory is reactivation of JCV in peripheral blood mononuclear cells causing hematogenous dissemination of the virus across the body with B-lymphocytes having the ability to cross the blood-brain barrier (Berger et al., 2009; Brew et al, 2010; White and Khalili, 2011).

An alternative model was proposed by White and Khalili where extracellular cytokines cause a reactivation of latent JCV in the brain (White and Khalili, 2011). In both models, reactivation and active replication of JCV is only possible in light of a reduction in immunosurveillance (as described in partim etiology).

Invasion of the brain:

Regardless of the 2 different models, eventually, activated neurotropic JC virus is present in the brain and has the capability of infecting oligodendrocytes and astrocytes, leading to cell lysis and further spreading of the virus to adjacent cells. Lysis of oligodendrocytes causes demyelination, a process responsible for the typical clinical and neuroradiological features of PML.

Proposed stages of PML development
<u>Primary infection</u> Initial JCV infection, mainly in childhood or adulthood, through inhalation (tonsils) or ingestion of contaminated food or water (gastro-intestinal system)
<u>Latent infection</u> Establishment of latent infection in kidneys, bone marrow and lymphoid tissues (brain as functional site of latent infection remains controversial) Rearrangement in the non-coding control region of JCV (within B-cells) leading to a neurotropic JCV strain
<u>Reactivation</u> Failed immunosurveillance in the periphery Reactivation of JCV in PBMCs with hematogenous dissemination through the whole body and crossing the blood-brain barrier via B-cells
<u>Brain infection</u> Entry of neurotropic JCV into the brain (via B-cells) Establishment of productive infection of oligodendrocytes Failed immunosurveillance in the brain

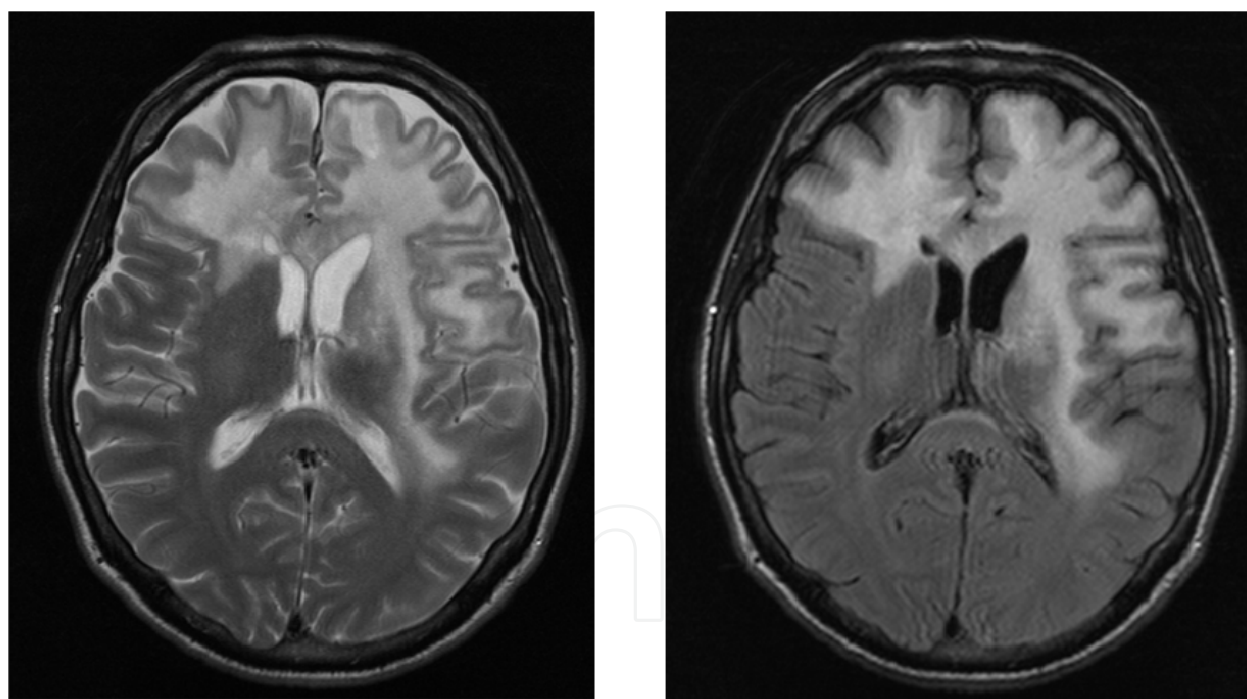
Table 7. Proposed stages of PML development

3.2.5 Diagnosis

The diagnosis of PML is based on typical clinical manifestations, specific neuroradiological findings and detection of JCV-DNA in the cerebrospinal fluid (CSF).

A brain CT scan shows low-density lesions in the subcortical white matter with no mass effect and no contrast enhancement. MRI of the brain has proven its superiority to CT scanning in documenting the number and extent of the lesions (Post MJ et al., 1986 as cited in Major et al., 1992) and in detecting the lesions in the initial stages of the disease (Shah et al., 2010).

PML mainly presents itself on MRI as single or asymmetric multifocal white matter lesions, enlarging and becoming confluent as the disease progresses. The lesions are typically hypointense on T1- and hyperintense on T2-weighted and FLAIR images compared to the normal white matter (Picture 2) (Shah et al., 2010). There usually is no mass effect, no edema and no gadolinium enhancement. However, gadolinium enhancement is frequently seen in natalizumab treated patients as documented in 43% of cases (Calabrese et al., 2007 and Clifford et al., 2010 as cited in Brew et al., 2010). Involvement of the parieto-occipital white matter, corpus callosum and posterior fossa is commonly seen while lesions restricted to the cerebellum, brainstem or pyramidal tract are also possible. Involvement of the spinal cord is rare, certainly in the beginning of PML, and when present alternative causes should be considered first. Although PML is known for its white matter lesions, involvement of the grey matter has been detected in up to 50% of patients with PML (Mark AS and Atlas SW, 1989 as cited in Shah et al., 2010).



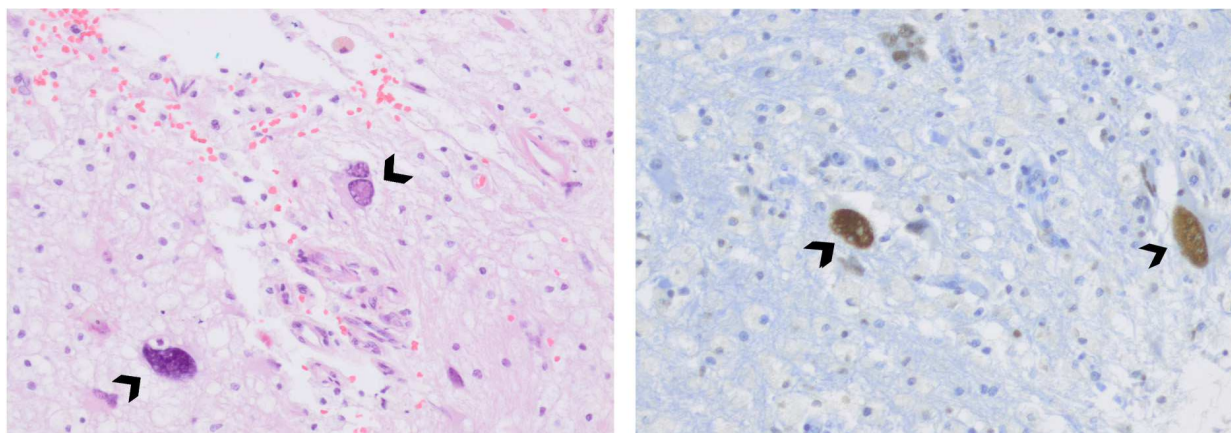
Picture 2. An example of NMR imaging in PML: hyperintense signal on T2-weighted (left) and FLAIR (right) images indicating asymmetric white matter lesions.

DWI MRI with ADC mapping provides additional information for characterizing the detected aberrations on MRI. A high signal on DWI with a low ADC value indicates regions with active infection as seen in new lesions and at the border of larger lesions while the center of these larger lesions usually have elevated ADC values (Brew et al., 2010 and Shah et al., 2010).

MR spectroscopy in PML may reveal a diminished N-acetylaspartate linked with neuronal loss and dysfunction, increased choline indicating demyelination, high lactate and lipid levels correlated with necrosis, and a temporary increase of myoinositol in evolving lesions (Brew et al., 2010 and Shah et al., 2010). None of these findings, however, are specific for PML and therefore can not be used for definitive diagnostic purposes.

Detection of JCV-DNA in CSF by PCR amplification is imperative for diagnosing PML. However, negative results do not simply exclude PML as JCV-DNA can still be undetectable in the beginning of the disease course. Moreover, the quality of JCV-DNA testing can variate substantially between different testing facilities. In case of a negative result and strong clinical and imaging evidence, a repeat lumbar puncture is recommended. If JCV-DNA remains undetected in the CSF, a stereotatic brain biopsy can be helpful. Although this is a highly invasive technique, it may often provide the necessary information for a correct diagnosis.

Histopathological features of PML are areas of demyelination. These lesions contain a moderate number of foamy astrocytes and only scant perivascular lymphocytes. Lymphocytic infiltration may be more common in HIV-positive PML and may be associated with a slightly better prognosis. A striking feature, particularly in older lesions, is the presence of very large astrocytes with bizarre, pleiomorphic nuclei. Viral inclusions are seen in the periphery of the foci of demyelination and are localized in the enlarged nuclei of oligodendrocytes (Brew et al., 2010; Ellison et al., 2004). JCV-DNA can be detected by in situ hybridization. Immunohistochemistry is often used to confirm diagnosis by revealing the presence of JCV antigen (Picture 3) (Brew et al., 2010; Major et al., 1992).



Picture 3. Hematoxylin-eosin stain (left) in a case of PML (magnification 200x) reveals foci of demyelination with macrophages and scattered glial cells showing hyperchromatic and atypical nuclei (arrows), sometimes with ground glass appearance. The diagnosis of PML is confirmed by immunostain for JC virus (right) in the affected nuclei (arrows).

3.2.6 Treatment

Although different agents with antiviral activity have been tried, there is no adequate treatment for PML as we speak.

Cytarabine was able to inhibit JCV replication in vitro but failed to show improvement of survival in randomized controlled trials (Hall et al., 1998 as cited in Brew et al., 2010).

Cidofovir, an antiviral agent against cytomegalovirus infection, was tested in different trials with HIV-positive PML patients and showed contradictory results in terms of survival or PML-related residual disability (Tan and Koralnik, 2011).

The discovery that JCV binds the 5-HT_{2A} receptor before infecting the cell led to the use of mirtazapine (a serotonin receptor blocker) as possible treatment for PML. However, the positive results from case reports have not been consolidated by large studies (Brew et al, 2010; Tan and Koralnik, 2011).

More recently, promising *in vitro* data were reported using the anti-malaria drug mefloquine. This led to the set up of a momentarily ongoing large clinical trial evaluating the use of mefloquine in the treatment of PML (clinicaltrials.gov, 2009).

With the lack of an effective antiviral agent the treatment of PML is mainly focused on improvement of the impaired immune status of the host. For cancer patients, this usually means reducing or even stopping the immunosuppressive agents allowing the immune system to recover with, hopefully, subsequent containment of the JCV infection.

In case of immunomodulatory monoclonal antibody associated PML, some specific characteristics should be considered. For example, natalizumab has a half-life of 11 days in the blood and even after immediate cessation of the drug, it still has biological activity for 3 months during which PML can further progress (Tan and Koralnik, 2011). Plasma exchange for quick removal of serum natalizumab has been tried but exposes the patient to a high risk of developing immune reconstitution inflammatory syndrome (IRIS) with possible fatal outcome (described in partim prognosis). Rituximab on the other hand, induces a long-term decrease in B-cells and has already cleared the circulation long before PML occurs. Thus, immediate cessation of the drug or plasma exchange are of no use in this situation.

Better understanding of the specific role of the different monoclonal antibodies in JCV reactivation and more knowledge regarding the development of IRIS during immune reconstitution will be necessary for a better management of immunomodulatory monoclonal antibody associated PML (Tan and Koralnik, 2011).

3.2.7 Prognosis

PML is a deleterious disease with mortality rates up to 90% within a few months when left untreated. However, if the immune response can be restored, survival significantly improves. A clinical neurologic recovery, contrast enhancement of PML lesions on neuro-imaging, high CD4⁺ T-lymphocyte count at disease onset and the appearance of JCV-specific CD8⁺ cytotoxic T-lymphocytes in the blood within three months of the diagnosis are considered positive prognostic factors (Berger et al., 1998; Marzocchetti et al., 2009). A high JCV-DNA load in CSF is considered a determinant of poor survival.

The outcome in long-term survivors of PML can range from complete recovery to sustained severe neurologic disabilities requiring institutionalization (Lima et al., 2010). Patients with small PML-lesions and a short symptom-to-diagnosis time appear to have a better outcome while involvement of the cerebellum or brainstem may indicate a worse prognosis (Brew et al., 2010; Lima et al., 2010; Vermersch et al., 2011).

Although reconstitution of the immune system is a key factor for a better survival in PML, it can be accompanied by an acute inflammatory reaction called immune reconstitution

inflammatory syndrome or IRIS, marked by a transient worsening of the neurological symptoms and contrast enhancement of the PML lesions on brain imaging. In severe cases of IRIS, edema with mass effect and brain herniation may occur with possible fatal outcome.

This might give IRIS a negative accent while in fact, development of IRIS in PML does not negatively influence PML survival and may even be potentially linked with prolonged survival and possible cure given the fact that IRIS actually reflects a (too) fast recovery of the immune system (Tan and Koralnik, 2011; Weissert, 2011).

Successful treatment of IRIS has been reported with high dose steroids to suppress the inflammation, although this remains controversial since these are also immunosuppressants with possible detrimental effects on the underlying immunocompromising diseases responsible for inducing PML in the first place (Tan and Koralnik, 2011).

4. Conclusion

Encephalopathy is a clinical syndrome, seen in many patients with underlying systemic diseases. In this chapter, we focused on uncommon clinical pictures presenting as an encephalopathy and discussed the causing pathophysiology.

As mentioned above, paraneoplastic neurological syndromes precede a diagnosis of malignancy in 60% of all cases, emphasizing that recognition of this syndrome may lead to early detection of an associated malignancy, with subsequent advantages in therapy response and prognosis.

Initially an auto-immune mediated pathophysiological mechanism was assumed, but the mechanisms of most paraneoplastic neurological syndromes could not be elucidated up till now. We hope that further research in this intriguing immune-neuro-oncological field will help understand the mechanisms of cancer and PNS and that manipulating the immune system can lead to tumour treatment and regression.

Although PRES and PML are rare diseases, recognizing these clinical entities can be of vital importance. Their prompt diagnosis and correct management not only positively influences the clinical outcome and survival but also reduces a possible decrease in the patients' quality of life which is already greatly impaired due to the seriousness of their underlying diseases. For both PRES and PML, predictive markers and a better understanding of the pathophysiological mechanisms could be useful in terms of prevention and more adequate treatment. Further research comprising these topics is ongoing.

With the fast changing world of cancer therapies, especially the targeted therapies, more reports of PRES and PML are expected but also new encephalopathies can arise. It is our responsibility to closely monitor patients during and after cancer treatment and to be vigilant for unexpected adverse events.

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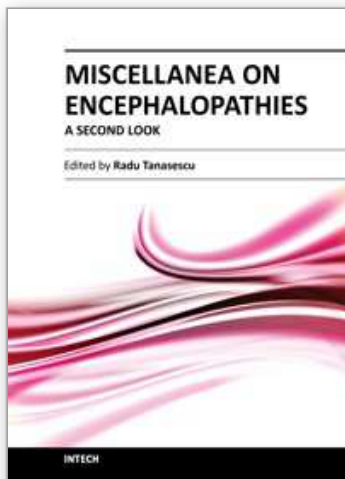
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