

# **Immunological Basis of Neurological Diseases, A Review**

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## **ABSTRACT**

Clinical neurology has been traditionally considered as an academic speciality in which the specialist regurgitates his/her knowledge of neurology without being able to do much for the patient. This attitude is no longer acceptable. Surge of information and discoveries in neurosciences within the last two decades translated into therapeutic interventions which is literally life saving in some occasions. Neuroimmunology, without a doubt, has been in the forefront of such discoveries. Just a few decades ago immunology of the nervous system was of little interest because brain was thought to be an immunologically "privileged" organ i.e. inaccessible to cellular and humeral immunity. Today, however, clinical neurologists deal with neurological problem with immunological basis on a daily basis. This article tries to review such diseases and their current therapeutic strategy proceeded by an introduction to CNS immunity. Multiple sclerosis, as one of the most common CNS disease with immunological basis, has been given more attention because of the growing number of affected people in Iran.

**Key words: Immunology, Neurological disease, Autoimmune diseases**

## **IMMUNOLOGICAL CHARACTERISTICS OF THE NERVOUS SYSTEM**

Brain defence is essentially dependent on systemic immunity. It was initially thought that the brain was inaccessible to systemic cellular and humeral immunity. This was based on the observations in which transplantation of sarcoma into the rat brain was not rejected by the host (1). In addition,

presence of brain-blood barrier, separating CNS from systemic immunological system and lack of lymphatic system in CNS were in support of such assumption. However, recovery after viral encephalomyelitides, evidence of inflammatory response to CNS infections and inflammations (i.e. increase protein level and lymphocytosis in CSF) and development of experimental allergic encephalomyelitis (EAE) as an animal model of central demyelinating disorder caused serious doubt in our initial understanding of immunology of CNS.

Lack of lymphatics, and presence of brain-blood barrier are distinctive features, which would limit cellular and humeral immunity within the CNS. The brain-blood barrier is an advanced extension of the epithelial cells interspersed with pericytes around which a continuous covering is provided by the extended foot process of type 1 astrocytes and microglial processes (2). Tight junctions between epithelial cells and dense population of mitochondria characterizes the brain-blood barrier ultrastructure.

Development of epithelial cells to form brain-blood barrier is essentially induced by astrocytes (3). The brain-blood barrier is highly permeable to water and lipid soluble molecules, but it prevents passage of solutes into the CNS. Glucose and some proteins enter through the brain-blood barrier with their specific carriers but other molecules like immunoglobulins and complements cannot pass this barrier. Choroid plexus follows similar rules with additional features which allows CSF production.

As far as cellular immunity is concerned only previously activated T cells can cross the brain-blood barrier. These activated T cells can be identified in the CSF during systemic immune response without CNS involvement (4). The mechanism of T cell passage through the brain-blood barrier appears to be similar to that of any other organ (5).

The brain-blood barrier is less competent in some areas of the CNS, these includes hypothalamus, area postrema, periventricular areas and spinal and cranial nerve roots (2,6,7). This might explain why lymphocytes are normally seen in the CSF of normal individuals (8). These normally occurring T cells leave CNS via channels ultimately draining through the cribriform plate into the postnasal space and thence the cervical lymphatics (9).

HLA expression is normally absent in CNS with an exception of microglia which expresses Class II MHC molecules, i.e. they are CD4+. Three types of macrophages have been described in the CNS; first type is immunologically inactive and is found in deep brain structures, second type is found in

perivascular regions and expresses Class II MHC, and the third type is engaged in active phagocytosis with the damaged area. The latter is thought to be originated from systemic circulation (10,11). This means that microglia with Class II MHC is capable of presenting antigen to lymphocytes for antibody production. However, in vivo study shows that even when microglia are induced to express MCH class II they can only present antigen to activated lymphocytes. Professional antigen presentation occurs in the cervical lymphatics, however it is not clear if in human body CNS antigens and lymphocytes drain to this area (9). The current opinion is that CNS immunological reaction is initiated by antigen presentation outside of the CNS. Interestingly it appears that CNS lymphocytes undergo apoptosis rather than leaving via CSF or blood vessels.

## **IMMUNOLOGY OF DEMYELINATING DISORDERS**

Multiple sclerosis and Guillain-Barre syndrome are most common demyelinating diseases of central and peripheral nervous system respectively. Clinical aspects of these conditions are beyond domain of this article and attempts will be made to concentrate mainly on the immunological aspects. Other related syndromes are optic neuritis, transverse myelitis, neuromyelitis optica, acute necrotising myelitis (Foix-Alajuanine syndrome), acute disseminated encephalomyelitis, Marburg's disease, Balo's concentric sclerosis, Schilder's diffuse sclerosis, combined peripheral and central demyelination (See also notes added in proof).

### **Immunological basis of multiple sclerosis**

Multiple sclerosis is thought to be a T cell disease (12). This is evidenced by presence of activated T cells in MS plaques, fluctuation of peripheral T lymphocytes in MS patients, presence of Class II MHC antigens and induction of a MS-like syndrome (EAE) by inoculation of activated T cells in rat. For example, increase proportion of activated T lymphocytes and level of IL-2 and TNF are consistent findings in CSF of MS patients (13). The ratio of CD4+ to CD8+ cells in CSF of MS patients is 2:1, which is higher than that of the blood. In addition, proportion of naïve T cells (CD45RA+) are less but memory T cells (CD45RO+ and CD29+) are more in CSF than in the blood (14). Various HLA associations have been described for MS. In Iran, HLA A3, A11 and B7 (15), DRB1\*1503, DQA1\*0102, DQB1\*0602 (16) and HLA-A24, HLA-DR2, HLA-DR15 (17) association have been reported. In European countries HLA class II DRB1\*1501-DQA1\*0102-DQB1\*0602 have been recognised (18). DR1, DR7, and DR11 in Europeans, and DRB1\*15021, DQA1\*0103 and DQB1\*0601 in

Iranians have been found to be protective against multiple sclerosis (16,18). No specific antigen/antibody has been identified as a causative agent in multiple sclerosis, however there are evidences of presence of activated T cells specific for Myelin basic protein, proteolipid protein, myelin-associated glycoprotein and myelin-oligodendrocyte glycoprotein (19).

The immunopathogenesis of MS probably starts with T lymphocytes being activated in the periphery. This is most likely to be upon introduction of an antigen carried by a contagion, like a common virus. Depending on the host genetic composition, an idiosyncratic immunological cascade begins. The antigen mimics oligodendrocyte-myelin epitope (20) and cause a specific antibody to be produced.

In the second phase, which probably occurs much later, a viral infection reactivates similar immune response but this time some of the previously activated T cells traverse the blood brain barrier as part of normal T cell traffic and enters the CNS. Macrophages and microglia, which express Class II MHC antigen, present unknown target self-antigen to the T cell receptors, which attach to the activated T cell within the perivascular CNS parenchyma (21,22). This initiates a focus of inflammation, which cause further activation of immune response within the CNS. The inflammation causes release of cytokines, which in turn, up-grades expression of adhesion molecules on circulating lymphocytes and blood-brain barrier endothelia. This directly increases the permeability of the barrier, causing increased binding and migration of the inflammatory cells into brain parenchyma, in addition to an influx of humeral immune mediators, culminating the formation of a perivascular hypercellular infiltrates.

Oligodendrocytes and myelin damage is contingent upon this T cell-dependent cascade of events. However, myelin damage can occur without destruction of oligodendrocyte. In such circumstances the damage is reversible. On the other hand, accumulation of the cellular and humeral immune mediators, which is responsible for myelin damage, may be impossible to resolve. At early stages of inflammation even oedema would be enough to cause myelin dysfunction. Of course in many cases restoration of blood-brain barrier integrity leads to recovery of oligodendrocytes and return of myelin production and function. Animal studies showed that antibodies directed against oligodendrocyte-myelin surface components are important for targeting damage, activating complements and opsonizing for macrophages/microglia attack. There are also evidences of non-specific toxic elements like cytokines, free radicals, oxidants, TNF- $\alpha$ , lymphotoxin, nitric oxide and myelin-degrading protease (23,24,25). Eventually the

damaged myelin sheath is engulfed and removed by the microglia following which astrocytes invade, hypertrophy occurs and proliferate, and the classical gliotic oligodendrocytopenic demyelinated plaque formed.

## IMMUNOTHERAPY FOR MULTIPLE SCLEROSIS

It should be made clear from the outset that there is no convincing evidence that use of any of currently available treatments would reduce progression of the disease and long term disability. Long term immuno-suppression using cyclophosphamide, azathioprine, cyclosporine A or corticosteroids are not fully supported by credible double blind, randomised control studies. Meta-analysis of azathioprine and cyclosporin A clinical trials show some evidence of reduction of disease progression, however side effects outweigh their effectiveness in long-term use (26). Intravenous immunoglobulins also delay disease progression but the effect is short lived (27,28). There

**Table 1. Connective tissue disorders and their antibodies  
(% shows percentile of cases which would have positive antibody)**

Disease	Antibody	Immunofluorescence pattern
Systemic Lupus Erythematosus	Anti ds-DNA (50%) Anti Ro (SS-A) (30%) Anti La (SS-B) (15%) Anti Sm (75%) Anti RNP (30%)	Rim ANA Speckled ANA Speckled ANA Speckled ANA Speckled ANA
Drug-induced lupus	Anti histone (97%)	Homogenous ANA
Sjögren syndrome	Anti Ro (SS-A) (75%)	Speckled ANA
Sjögren syndrome	Anti La (SS-B) (60%)	Speckled ANA
Systemic sclerosis	Anti Scl-70 (50%)	Speckled ANA
Mixed connective tissue disease	Anti RNP (95%)	Speckled ANA
Polymyositis/dermatomyositis	Anti PM-Scl	Nucleolar ANA
Systemic sclerosis	Anti centromere	Other cellular organelles
Rheumatoid arthritis	IgM (RF)	N/A

are small studies favouring use of plasma exchange in MS particularly in acute attack (29,30). The author has used this method on a few newly presenting patients with acute progressive demyelinating disease and observed dramatic improvement.

Although there is some evidence favouring use of methyl prednisolone in acute exacerbation of MS, data for long-term use is insufficient (31).

Currently long-term use of steroids for MS patients is strongly discouraged, however twice per year of pulse therapy with methylprednisolone (usually 1 gram daily iv for 3 days) is frequently used in acute relapse.

Beta interferon inhibits immune cell proliferation, alters cell trafficking, modifies antigen-presenting cell function, reduces interferon- $\gamma$  and TNF- $\alpha$  production. The efficacy of interferon on disease progression and the number of relapses in patients with relapsing remitting MS is modest within two years of follow up (32). The National Institute for Clinical Excellence (NICE) in England and Wales appraised the evidence on the clinical and cost effectiveness of azathioprine, IFN-beta, cladribine, cyclophosphamide, glatiramer, intravenous immunoglobulin (IVIg), methotrexate and mitoxantrone. They found that most of the study were unsatisfactorily performed and could not be taken as evidence for the effect of these drugs. They recommended more rigorous randomised control trials (33). In spite of NICE recommendation against use of beta-interferon, because of the political pressure, British government had to rule against NICE and approved funding for use of beta interferon. This is currently based on a shared fund basis in which the manufacturer would be paid the cost of treatment only if the long-term effects of ongoing trials is proved to be useful for the patients. Current criteria allow beta interferon to be used for relapsing remitting MS patients who have at least 2 relapses per year and can walk for at least 10 meters.

Glatiramer acetate (Copaxone) is a novel preparation of synthetic peptides composed of four amino acids. Its mode of action has not been fully understood but it is known to induce suppresser T cells and competitively inhibits the effect of CNS myelin antigens. Controlled clinical trials have shown its effect on reducing both the relapse rate and the resultant disability which at its best would not be more than interferon-beta but probably has fewer systemic side-effects (34).

Campath-1H is a panleukocyte cytotoxic antibody (CDw52 specific) and causes rapid and long lasting depletion of CD4+ cells. It is administered after pre-treatment with methylprednisolone. It keep the patient in remission for one year but side effects may limits its use (35,36,37).

There are other experimental immunotherapies for MS currently under study. These include antiCD45, transforming growth factor- $\beta$ , interleukin 10, anti interleukin 12, anti TNF- $\alpha$  , anti- very late antigen-4 (VLA-4), rolipram (type IV phosphodiesterase inhibitor) and metalloproteinase inhibitors.

## NEUROSARCOIDOSIS

Neurosarcoidosis is a non-caseating epithelioid cell granulomatous disease. Respiratory system is the most common target for sarcoidosis but the nervous system can be involved exclusively. The most common sites are cranial nerves (II and VII in particular), cavernous sinuses, spinal cord, brain stem, meninges, hypothalamus and pituitary respectively in order of their occurrence (38,39). There is no specific diagnostic test. MRI scan with gadolinium usually shows enhanced high signal changes within the brain or spinal cord parenchyma as well as meningeal enhancement. Serum angiotensin-converting enzyme (ACE) is usually increased in systemic sarcoidosis with or without CNS involvement, however it is often normal in neurosarcoidosis. CSF ACE has even lower sensitivity and is often normal, however increased protein and lymphocytosis are useful evidences. Oligoclonal band can be positive. A thorough search for identification of sarcoidosis out of the CNS has to be carried out. Chest CT scan would be a useful investigation, but if negative gallium scan may prove useful. In some cases, the clinician may have to embark on tissue biopsy before immunosuppression is advised.

Mononuclear phagocytes including microglia predominates the involved tissue and forms appearance of giant cells. Macrophages express the calcium binding protein calgranulin Mac 387 (40). Epithelioid cells retain macrophage markers within granulomata and express MHC Class II molecules and act as antigen-presenting cells (41). Lymphocytes are also found in the granulomata. They are usually activated CD4<sup>+</sup> T cells particularly at the centre of the granulomata, in contrast to CD8<sup>+</sup> cells, which are usually located peripherally (42). Within the lesions a wide range of the cytokines are found. These include lymphocyte function-associated molecule (LFA), intracellular adhesion molecule -1, interleukin-1 and 2, interferon- $\gamma$  and tumour necrosis factor- $\alpha$  (43,44). Though the factors that initiates immunological processes leading to granulomatosis are not known, mycobacteria and herpes virus have been implicated (45,46).

## CONNECTIVE TISSUE DISEORDERS AND THE CNS

There are numerous publications on the immunological basis of this group of disorders. Table 1 summarises the immunological markers of connective tissue disorders.

## **RHEUMATOID ARTHRITIS**

Inflammatory neuropathies, in form of typical mononeuritis multiplex or less commonly peripheral neuropathy, have been reported to occur in up to 30% of seropositive patients (47). It may accompany a mild demyelinating peripheral neuropathy or a severe axonal mononeuritis which is usually associated with other vasculitic features. Up to 50% of cases suffer from entrapment syndromes, like carpal tunnel syndrome, at some stage of their disease. Autonomic neuropathy has rarely been identified.

In the CNS, atlanto-axial subluxation is the most important complication. This occurs as a result of destruction of the upper cervical spinal and the transverse ligament of the atlas, resulting in subluxation and pannus formation. This causes compression of the upper cervical cord which can result in quadriplegia.

Cerebral vasculitis and intracranial rheumatoid nodules are other CNS involvements. Rheumatoid cerebral vasculitis is rare and is usually associated with other features of RA. Whilst cerebral vasculitis may present with seizures or aseptic meningoencephalitis, intracranial rheumatoid nodules tend to be asymptomatic.

## **SJÖGREN SYNDROME**

A wide range of neurological disorders has been reported in association with Sjögren syndrome. Trigeminal neuropathy is a classic presentation. Myositis and vasculitic sensory neuropathy are PNS complications. Seizure, stroke, meningo-encephalitis or increased intracranial pressure, as well as affective disorders and dementia may complicate Sjögren syndrome. These complications are not uncommon. Sjögren syndrome can mimic clinical and radiological features of multiple sclerosis and can present as transverse myelitis.

## **SYSTEMIC SCLEROSIS**

Trigeminal neuropathy, cranial neuritis, inflammatory myopathy, myelopathy, cerebral vasculitis and stroke have been described in systemic sclerosis. Severe hypertension as one of the complications of SS is an additional risk factor for stroke in these patients.



## MIXED CONNECTIVE TISSUE DISEASE

CNS involvement with MCTD is uncommon, however peripheral and central involvement which are described in other CTDs have been reported with MCTD, too.

## SYSTEMIC LUPUS ERYTHEMATOSUS

Neurological complication of SLE is common (up to 75%). Fits, optic neuritis, myelitis, stroke (arterial or venous), movement disorders (e.g. chorea and hemiballismus), ataxia, encephalopathy, meningo-encephalitis, cranial and peripheral neuropathies, headaches particularly migraine type, seizures, and cognitive impairment are all well recognised. Chorea, migraine, Strokes in form of arterial ischaemia or cerebral venous thrombosis, are associated with presence of anticardiolipin antibody and lupus anticoagulant. However, a population of patients with stroke who have ACA and LA do not meet the diagnostic criteria for SLE. SLE can present as primary progressive multiple sclerosis with similar MRI findings.

**Table 2: Neurology of gluten sensitivity (Ref. 56)**

Patients seen in the neurology clinic in Royal Hallamshire Hospital, Sheffield over a period of 8 years	131
Ataxia (four with myoclonus)	56
Sensorimotor axonal neuropathy	26
Mononeuropathy multiplex	15
Motor neuropathy (three MND-like picture on NCS/EMG)	10
Small fibre neuropathy	4
Mixed demyelinating/axonal neuropathy	2
Myopathies	8
White matter disease (with episodes of headache)	19
Stiffman syndrome	4
Neuromyotonia	1

Immunological mechanisms suggested for CNS involvement in SLE are;

- 1- Direct antibody-mediated effect, ACA binds to phospholipid in the endothelial cell membrane causing platelet aggregation and local thrombosis (48).
- 2- Deposition of anti-dsDNA antibody-antigen or ACA-cardiolipin immune complex in the blood vessels (49).

3- Chronic systemic inflammation associated with release of cytokines upregulating adhesion molecules causing vasculopathy (50,51).

Seronegative arthritic disorders like Behcet's disease, ankylosing spondylitis, Reiter's disease and even psoriasis can cause neurological problems. These are more in form of peripheral nerve disease, radiculopathies and cord compressions however epilepsy, white matter disease and vasculitis have also been described.

## **IMMUNOLOGY, GUT AND THE CNS**

### **Inflammatory bowel disease**

IBD like ulcerative colitis and crohn's disease are associated with neurological disorders. Up to 3% of patients with IBD develop neurological complications. The most common complication is cerebrovascular events, mostly in form of venous thrombosis, although arterial infarctions are well described. Cerebral vasculitis is rare but has been reported. Epilepsy and white matter diseases in the brain and spinal cord are other forms of neurological complication of IBD.

### **Whipple's disease**

Whipple' disease was described by Whipple in 1919 (52) and is caused by *tropheryma whipplii*. Its neurological involvement is usually in form of white matter disease. Neurological presentation may proceed gastroenterological manifestations. It typically presents as a rapidly progressive dementia, seizure, ataxia, movement disorders, spasticity and/or rigidity and ophthalmoplegia. The clinical presentation depends on the part of brain which is affected by the organism. The most favourite site of involvement for the organism is upper brain stem, although it may be found in any other part of the CNS like hemispheres, hypothalamus and spinal cord. Isolated spinal cord involvement is extremely rare. The author has recently encountered such case (personal communication with Dr. Carl Clark, Birmingham University). Whipple's disease is curable and therefore has to be promptly diagnosed. The diagnosis is possible with detection of the organism in the CSF using PCR technique. In some cases biopsy of the brain or spinal cord might be necessary and justified. In such cases the author would suggest duodenal/gastric biopsy in the first instance, even if there is no history of GI symptoms.

## Coeliac disease

Coeliac disease is an immunologically mediated disorder which results from intolerance of gluten, a protein present in wheat and many other cereals (53). Although nutrient deficiencies caused by malabsorption due to coeliac disease can lead to neurological syndromes (e.g. B12 deficiency causing peripheral neuropathy), neurological syndrome of gluten-sensitivity is directly related to cross-matching antibodies against gluten proteins with CNS components like Purkinje cells (54). Neurological complications of coeliac disease have been known for many years but in the last decade a wide spectrum of neurological syndromes from peripheral neuropathy to

**Table 3: Classification of Vasculitis**

Vessel involved	Primary	Secondary
Large vessels	Giant cell arteritis Takayasu's arteritis	Aortitis with CTD Infections (e.g. syphilis)
Medium arteries	Classical polyarteritis nodosa Kawasaki disease	Infection (e.g. hepatitis B) SLE
Small vessels and medium arteries	Wegener's granulomatosis Churg-Strauss syndrome Microscopic polyangiitis	Sjögren, drugs, infection (e.g. HIV) Drugs (e.g. sulphonamides) Infection (e.g. hepatitis C)
Small vessels	Henoch-Schonleinpurpura Essential cryoglobulinaemia Cutaneous leukocytoclastic vasculitis	

dementia have been described in patients with immunological, but not necessarily histological evidence of coeliac disease in the duodenum (55). Table 2 shows a list of neurological syndromes reported from Sheffield group (56). This led to the development of the term "gluten-sensitivity" as an autoimmune systemic illness rather than coeliac disease as a gastroenterological disease.

The diagnosis of gluten-sensitivity is based on high titers of IgA or IgG antigliadin antibody, antiendomysial antibody, tissue transglutaminase and presence of HLAs DQ2, 8 or 1. Duodenal biopsy in neurological syndrome of gluten-sensitivity is informative in only 30% of cases. A common reason for underdiagnosis of neurological illness of gluten-sensitivity is lack of appreciation that IgG antigliadin antibody (AGA) is the most commonly found antibody (and not only IgA) and that GI symptoms are commonly absent. In a neurological context without gastrointestinal involvement,

high titers IgG AGA (rather than IgA) is often found. Presence of IgA AGA, AEMA, TTG are usually associated with gastroenterological involvement which is only present in a third of cases with neurological presentation. Recently anti-purkinje cell antibody has been detected in patients with gluten sensitivity ataxia and cerebellar atrophy (54).

In essence, any patient with peripheral neuropathy, ataxia or white matter disease (like MS) should have gluten-sensitivity screen unless the cause is apparent. The author has recently encountered a rare case of acute gluten-sensitivity panmyelitis in a young Asian lady who responded to a short course of high does intravenous methylprednisolone. The diagnosis was based on high titers of IgA-AGA, TTG and AEMA as well as histological proof of coeliac disease in the duodenal biopsy (57). Although no systematic study for the treatment of gluten-sensitivity neurology has been carried out, the author suggest use of high does iv methylprednisolone (1 gram daily for three days); for acute progressive gluten-sensitivity neurological syndrome followed by gluten-free diet might be useful. In chronic cases gluten-free diet should suffice. Antigliadin antibody is a good marker for disease monitoring, but the patient has to be under gluten-free diet for a few months before clinical and immunological improvements are seen.

### **Cerebral vasculitis**

Most systemic autoimmune diseases can cause inflammation of the cerebral vessels. However, cerebral vasculitis can occur in isolation without any peripheral stigmata of systemic vasculitis which can make the diagnosis notoriously difficult. Diagnosis of cerebral vasculitis is of paramount importance because of its reversible nature. The diagnostic stages are the exclusion of alternative possibilities, the confirmation of intracranial vasculitis and pursuit of cause of vasculitis. The most convenient classification is that of the Scott and Watts (58) shown in table 3.

There are two mechanisms of vascular injury, humoral and cellular. Humoral mechanisms involve immune complex mediated vasculitis (hepatitis B, C, cryoglobulinaemia, Henoch-Sconlein purpura), direct antibody attack (Kawasaki disease), cANCA-related (Wegener's granulomatosis) or pANCA-related (Churg-Strauss syndrome, microscopic polyangiitis) process. Cell-mediated mechanisms involves interaction of circulating lymphocytes and adhesion molecules on the endothelial cells. Molecules which are of particular importance in this process are *selectins* which helps movement of lymphocyte along vessel walls, integrin and immunoglobulin gene superfamily adhesion molecules which mediates lymphocyte attachment

to the endothelium. Vascular cellular adhesion molecule-1, intracellular adhesion molecule-1 and lymphocyte function-associated molecule-3 are specifically identified (59,60). Involvement of activated T cells and antigen-presenting MHC Class II cells are clearly showed in microscopic polyarteritis nodosa and Wegener's granulomatosis (61,62). In both primary CNS and peripheral nerve vasculitic lesions, the predominant infiltrate is CD4+ and CD8+ T lymphocytes and monocytes, although eosinophils, B cells, plasma cells and giant cells have also been identified (63,64).

### Behcet's disease

Behcet disease is a systemic vasculitis illness characterized by triad of recurrent oral and/or genital ulcer as well as uveitis. Its higher incidence among Middle and Far East population is well established and is thought to have specific HLA association. Neurological aspects of the disease include cerebral vasculitis, cerebral venous thrombosis, aseptic meningoencephalitis, inflammatory encephalopathy, cranial neuropathies and stroke like episodes. The disease may be mistaken with multiple sclerosis with similar clinical and MRI pattern. However, CSF examination of these patients usually shows lymphocytosis, elevated protein and increased IgA or IgM but not IgG. Typically brain MRI

**Table 4: Paraneoplastic syndromes, underlying malignancies and relevant antibodies**

Syndrome	Tumour	Antibody
Subacute cerebellar degeneration	Breast, ovary	Anti Yo antibody, antipurkinje cell cytoplasmic antibodies (APCA)
Encephalomyelitis, sensory / motor / atonic neuropathies	Small cell lung cancer	Anti-Hu antibodies/ type 1 anti-neuronal nuclear antibodies (ANNA-1)
Opsoclonus/ myoclonus/ ataxia	Breast	Anti -Ri antibodies/ type 2-neuronal nuclear antibodies (ANNA-2)
Cancer-associated retinopathy	Small cell lung cancer	Recoverin antibodies
Cancer associated retinopathy	Melanoma	Anti-bipolar retinal cell antibodies

shows a combination of white and grey matter high signal changes. There are anecdotal evidences that Caucasian patients with Behcet's disease tend to present or develop cerebral thrombosis more often than

Eastern patients. Immunologically the disease is associated with activated T cell, circulating  $\gamma\delta$ -T cells and natural killer cells (65). Recent studies shows that activated lymphocytes in Behcet's disease cross react with heat shock proteins similar to those found in some mycobacteria (66,67). In addition, antiendothelial cell antibodies have also been identified in patients with Behcet's disease (68).

### **Hashimoto's encephalopathy**

Clinicians are often familiar with neurological effect of thyroid disorders however a less well understood disease which is associated with thyroid is Hashimoto's encephalopathy. This is a cause of relapsing encephalopathy which is associated with cognitive impairment, seizure, myoclonus, tremor and stroke like episodes. Brain MRI is often normal, however CSF examination usually shows raised protein with or without lymphocytosis. Thyroid function test may show euthyroid, hypo or hyper thyroidism. Diagnosis is made clinically and supported by presence of anti-thyroid antibodies particularly anti-microsomal antibodies. It seems that the disease causes some degree of giant cell vasculitis.

Early diagnosis and treatment of peripheral or cerebral vasculitis is essential. Treatment may prevent or even reverse neurological deficit. The first line of treatment would be intravenous high dose steroid, methyl prednisolone 1gram daily for three days followed by a reducing dose of oral prednisolone. If no response was obtained then intravenous immunoglobulines or cyclophosphamide should be tried. Long term immuno-suppressant and close follow up is often required.

### **Immunology of paraneoplastic syndromes**

Paraneoplastic syndromes are a rare group of disorders caused by remote or indirect effect of a malignancy. Table 4 summarises clinical syndrome, relevant antibodies and underlying malignancy. Recognised clinical syndromes are subacute cerebellar degeneration (69), encephalomyelitis e.g. limbic, brain stem or spinal cord (70), subacute sensory neuropathy (71), motor neuropathy and neuronopathy (69), opsoclonus/myoclonus (72) and retinopathy. There are similarities in histopathology of all paraneoplastic syndromes. They are all characterised by pronounced

neuronal loss, with pyknotic changes and neuronophagia. In addition, inflammatory process including perivascular lymphocytic cuffing with parenchymal infiltration by lymphocytes and macrophages as well as the formation of microglial nodules, presence of ubiquitous and non-specific astrogliosis.

### **Paraneoplastic antibodies**

APCA (anti-Yo) is polyclonal IgG antibodies, found in higher concentration in CSF than in serum (73). They are specific to PCD-AA, CDR62, CDR3, CDR34 and all DNA-binding proteins which direct gene transcription of the leucine zipper family (74) or zinc finger binding activity (75) which are found in cerebellar cortex as well as in ovarian and breast carcinoma (76).

ANNA-1 (anti-Hu) is also polyclonal IgG antibodies which like APCA is synthesized locally in the CNS (77). Ubiquitous staining of neuronal nuclei by ANNA-1 is found in the brain, spinal cord, dorsal horn and autonomic ganglia (78). Antigens (HuC, HuD, Hel-N1, Hel-N2) of these antibodies are all RNA binding proteins and involved in post-transcriptional gene processing (79,80). These antigens are invariably found in small cell lung cancer cells (81). About 50% of patients with paraneoplastic limbic encephalitis would have ANNA-1 positive (82). ANNA-2 (anti-Ri) is very similar to ANNA-1 except that it is not found in dorsal horns and enteric nervous system. Its antigen has been identified as Nova protein which is restricted to the nucleus of neurones in the CNS (83). It reacts with breast tumour cells in patients who develop opsoclonus (84), therefore it is highly specific marker in this context.

A number of antibodies are found in retinopathy-associated malignancies. These are against recoverin, bipolar retinal neurones, optic nerve, and enolase (85,86). Recoverin is located in photoreceptor cells in the retina and is important in light/dark adaptation. These antigens are also expressed in small cell lung cancers (87). Antibodies to oligodendrocytes have been found in CNS paraneoplastic syndromes with cerebellar or limbic involvement (88). Anti-GAD antibody in stiff person syndrome with progressive encephalomyelitis with rigidity (PEWR) has been reported in patients with breast cancer and small cell lung cancer (89,90).

Several therapeutic interventions have been tried for the treatment of

paraneoplastic syndromes. There are reports supporting use of steroids, intravenous immunoglobulins and plasma-exchange with variable outcome, however the most sensible approach would be treatment of the underlying cancer. The outcome of such treatment varies between full recovery of neurological symptoms to static status of progression. Nevertheless, it is essential that the underlying malignancy is found.

### **Stiffman Syndrome**

This is a type of movement disorder characterised by stiffness of one or more limbs or the entire body. The antibody against glutamic acid decarboxylase (GAD) interferes with GABAergic interneurons of the spinal cord and causes lack of inhibition of motor neurones to the muscles, hence stiffness (91,92). In these patients, continuous firing of motor units in agonist and antagonist muscle groups can be recorded by EMG. The antibody is found in 60% of cases with stiff person syndrome. Fifty-five percent of cases show antibody to islet cells of pancreas. Interestingly, diabetes mellitus is associated with stiff person syndrome. Successful treatment with plasma exchange, steroid has been reported in some but not all cases (93,94).

### **CONCLUSION**

Brain is no longer assumed to be exempted from the immune system. Neuroimmunological disorders are common and to some extent treatable. Their diagnosis is therefore important. For this reason development of immunological test is essential for early diagnosis and treatment.

### **NOTE ADDED IN PROOF**

A new variant of multiple sclerosis which exclusively or predominantly affects cerebral cortex was reported recently by the author.

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