

Multiple sclerosis

Investigations:

- MRI with gadolinium enhancement.
- Visual and auditory evoked potentials.
- **Oligoclonal banding** useful for diagnosis.



Oligoclonal banding
Detected by isoelectric focusing of paired CSF (C) and serum (S) samples and immunoblot for IgG.

Symptoms: Episodes of variable neurological defects
e.g. disturbed vision (blurring, loss)
e.g. impaired mobility or co-ordination
e.g. loss of sensation in specific locations

- Symptoms are caused by patches of demyelination (lesions) within the central nervous system i.e. spinal cord or brain.

Oligoclonal banding

- Separate proteins in matched serum and CSF samples by isoelectric focussing, transfer proteins to nitrocellulose membrane, and blot for IgG.
- Compare pattern of bands in matched serum and CSF samples.
 - No bands in either sample = NORMAL.
 - Bands in CSF sample but not serum sample = POSITIVE RESULT (indicates IgG synthesised within CNS) (see lanes 1&2 in figure).
 - Identical bands in serum and CSF = NEGATIVE RESULT (indicates IgG synthesised outside CNS but present in CSF because CSF is an ultrafiltrate of serum produced by choroid plexi in the brain).
- POSITIVE results seen in multiple sclerosis, but also some other neurological conditions
e.g. Guillain Barre syndrome, CNS infection, sarcoidosis.

Meningitis

- Inflammation of the meninges (membranes that surround the brain).
- May be viral or bacterial.

Immunology Investigations:

- Can be associated with immune deficiency
e.g. Viral meningitis – consider T cell deficiency
e.g. Bacterial meningitis due to meningococcus
 - consider complement deficiency (C5-9)
 - consider B cell deficiency or immunoglobulin deficiency
 - consider asplenia/impaired spleen function.
- Investigate with immunoglobulins, CH50, and lymphocyte subsets.

Symptoms:

- Fever
- Rash
- Photophobia
- Headache
- Vomiting
- Stiff neck



Type II (mixed) cryoglobulin

Peripheral neuropathy

- Damage to peripheral nerves can interfere with sensory or motor function.
- Can be associated with antibodies to myelin associated glycoprotein (MAG) – usually IgM antibodies, seen in B cell malignancy. Investigate with specialist assay.
- Can be associated with mixed cryoglobulinaemia, due to immune complex deposition and activation of complement. See Renal poster.

Hyperviscosity syndrome

- Hyperviscosity impairs circulation, and can cause symptoms such as blurred vision, confusion, loss of consciousness.
- Can be associated with high paraprotein concentrations e.g. in Waldenstrom's macroglobulinaemia – see B cell malignancy poster.

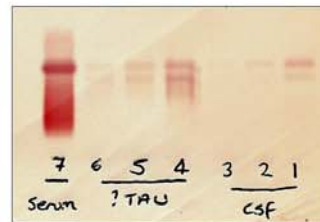
CSF leakage

- CSF is synthesised by choroid plexi in the ventricles of the brain and circulates around the brain and spinal cord before re-entering the serum.
- CSF should be contained within the central nervous system, but can escape when the blood brain barrier is damaged.
- Consider CSF leakage if the patient has:
 - A runny nose without cold symptoms,
 - Fluid in the ear,
 - Fluid at a wound site after neurosurgery.
- Investigate with β 2-transferrin (Tau) (different from Tau protein in Alzheimer's disease).

β 2-transferrin (Tau)

- Separate proteins in fluid sample by protein electrophoresis, transfer to nitrocellulose membrane and immunoblot for transferrin.
- Run between a normal serum and CSF sample e.g. from a patient tested NEGATIVE for oligoclonal banding.
- Transferrin (β 1-transferrin) is a sialylated protein that is synthesised by the liver. Gradually the sialic acid groups are lost, leaving asialotransferrin (β 2-transferrin).
- Serum contains only β 1-transferrin. Asialotransferrin (β 2-transferrin) is rapidly removed by scavenger receptors.
- CSF contains β 1 and β 2-transferrin as the asialotransferrin is not removed until the CSF drains into the blood circulation.
- Therefore, serum has 1 band but CSF has two bands on the transferrin immunoblot.
- If the fluid sample has two bands, this is a POSITIVE result, indicating that the sample is CSF OR that it contains CSF.
- **URGENT TEST** as the patient is at risk of CNS infection. Phone positive results to the clinician.

NEUROIMMUNOLOGY



β 2-transferrin
Detected by protein electrophoresis and immunoblot for transferrin. Upper band = β 1 transferrin, present in serum and CSF. Lower band = β 2-transferrin, present only in CSF.

Paraneoplastic syndromes

- Paraneoplastic syndromes are rare complications of cancer.
- Symptoms occur at a site distant from the tumour, but are not due to metastasis.
- Often affecting the peripheral or central nervous system.
- Patients may present with neurological symptoms before signs of the cancer.
- Can have associated paraneoplastic antibodies.
- Certain cancers are particularly associated with paraneoplastic antibodies.

Paraneoplastic antibodies

- These antibodies are **NOT** clinically sensitive or specific, so of limited diagnostic importance.
- Paraneoplastic antibodies target either cell surface antigens or intracellular antigens.
- Note for some antigens, antibodies may be autoimmune rather than paraneoplastic
e.g. anti-acetylcholine receptor antibodies cause **myasthenia gravis**, and are usually autoimmune, but 10% are paraneoplastic, associated with thymoma.
e.g. anti-voltage gated calcium channel antibodies cause **Lambert Eaton Myasthenic Syndrome (LEMS)** and are usually paraneoplastic (2/3), but can also be autoimmune.

Summary of major paraneoplastic antibodies

Antibody	Antigen	Symptoms	Associated cancer
Intracellular			
Anti-Hu (ANNA-1)	Hu family proteins	Encephalomyelitis	SCLC
Anti-Yo (PCA-1)	Signalling protein	Cerebellar ataxia	Ovarian, breast, adenocarcinoma
Anti-CV2/CRMP5	Signalling protein	Cerebellar ataxia, encephalomyelitis	SCLC, thymoma
Amphiphysin	Synaptic protein	Stiff person syndrome	Breast, SCLC
Cell surface			
VGCC	Calcium channel	Lambert Eaton myasthenic syndrome	SCLC (or autoimmune)
ACR	ACh receptor	Myasthenia gravis	Thymoma (or autoimmune)