PARANEOPLASTIC NEUROLOGICAL SYNDROME

Maham Malik
University of Manchester; MS3

Definition

- Neurological consequences of cancer that are not directly caused by tumour invasion or treatment
- Thought to be due to an autoimmune response launched by the body in response to cancer, which consequently targets the nervous system
- Often these syndromes can precede cancer (60%)[1]

Autoantibodies

- Expression of neuronal antigens by the cancer cells (known as onconeural antigens)
- However:

30-40% of PNSs are not associated with any kind of onconeural antibody[2]

AND

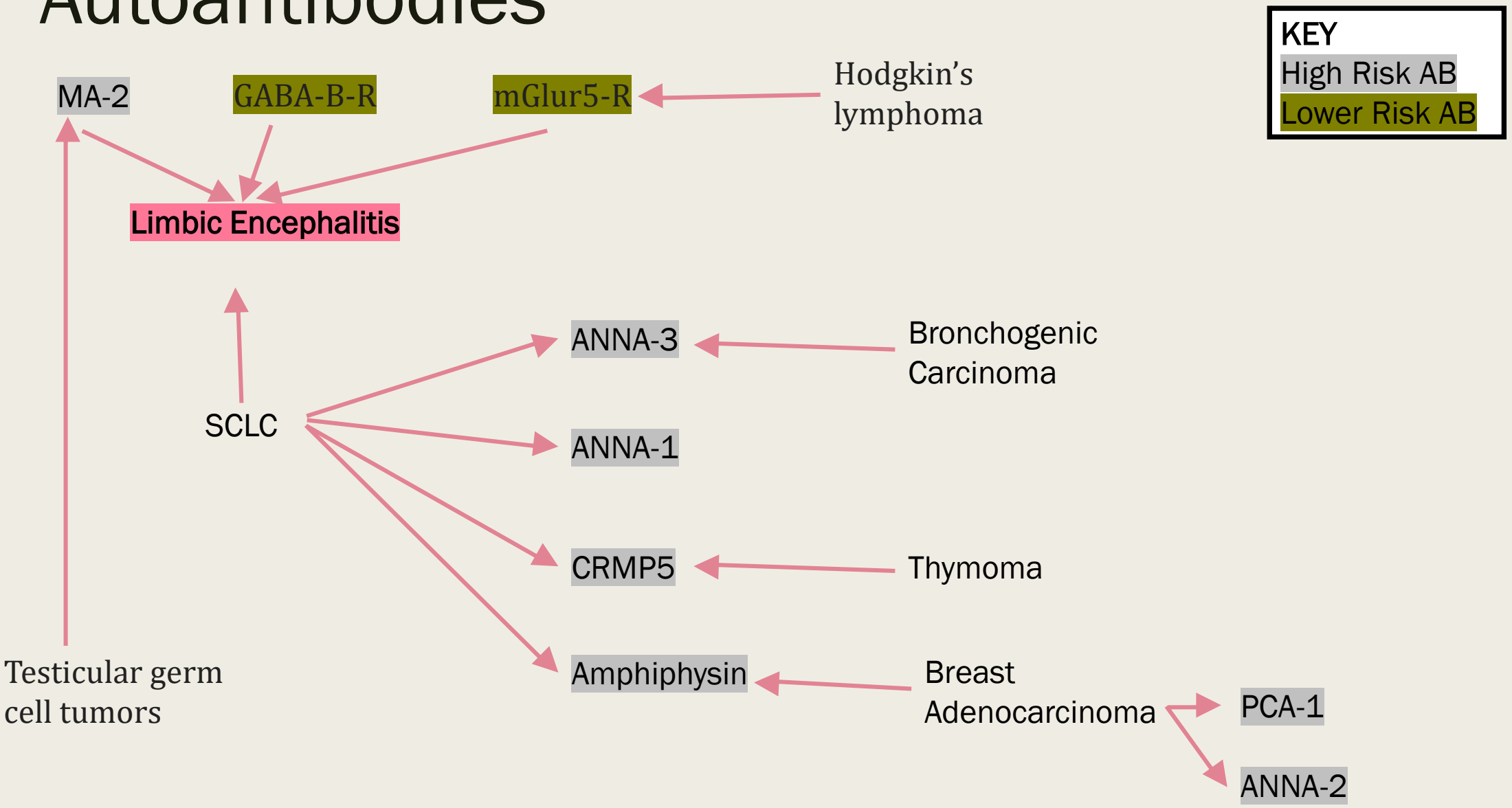
Onconeural antibodies have been seen in cases of cancer without PNS

Autoantibodies

- Antibodies are not specific
- Antibodies are classed into high, medium, and lower-risk categories

Class	% Associated With Cancer
High Risk	>70
Medium Risk	30-70
Lower Risk	<30

Autoantibodies



Symptoms: Central

- **Cerebellar Degeneration**
  Ataxia, nystagmus, dysarthria, dysphagia
  Associated with SCLC, breast, ovarian [3]

- **Limbic encephalitis**
  Short term memory loss, seizures, personality change
  Associated with SCLC, testicular germ cell, breast [4]

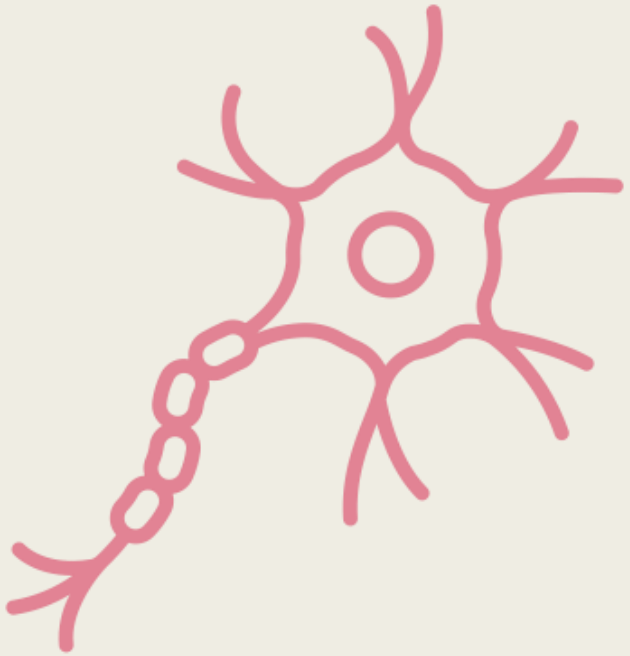
- **Opsoclonus-myoclonus**

Symptoms: Peripheral

- **Sensory neuropathy**
  Asymmetric limb paraesthesia, proprioceptive loss
  Associated with SCLC, colon, lymphoma

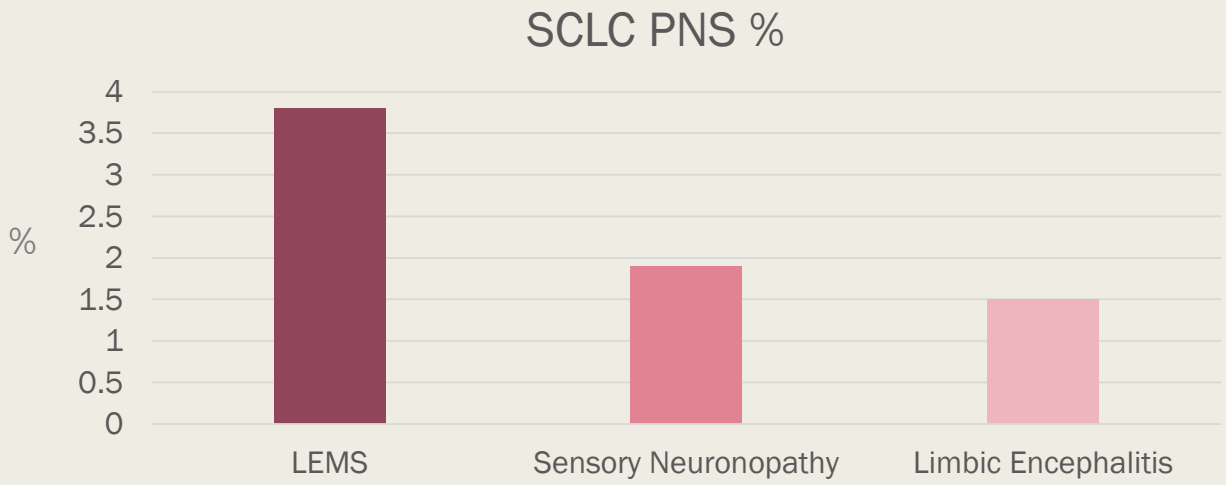
- **Gastrointestinal pseudo-obstruction**
  Associated with SCLC, NSCLC

- **Lambert-Eaton Myasthenic Syndrome (LEMS)**
  Proximal muscle weakness, loss of reflexes, autonomic dysfunction
  Associated with SCLC, thymoma, prostate cancer



Common Cancers: SCLC

- Small Cell Lung Cancer is the malignancy that is most associated with PNSs
- RF: smoking, radon, asbestos
- PNS frequency of 9.4% in a study of 264 SCLC patients [5]



Common Cancers: Ovarian

Ovarian tumors account for about 10 % of malignancies associated with PNS [6]

RF = hormone therapy, obesity, HNPCC

Most associated with

- **Subacute Cerebellar degeneration**
  In one study, 18/19 patients with PCD were diagnosed with ovarian cancer [7]
- **Dermatomyositis**
  In one study, 9% of DM cases were diagnosed with ovarian cancer [8]

Common Cancers: Lymphatic

Hodgkin's lymphoma = LE, PCD, dermato/polymyositis [9]

Non-Hodgkin's = dermato/polymyositis

PNS develops later in disease as opposed to other cancers

Onconeural antibodies are absent in most of these PNSs with few exceptions

Antigens for onconeural antibodies are not expressed by tumour cells…

Diagnostic Criteria – 2004

Used for clinical and research purposes

Criteria for 2 Classes [10]:

- **Definite** PNS
- **Possible** PNS

- Definite PNS could be diagnosed solely based on the presence of onconeural antibodies
- Immense advances in antibody discovery since, especially in the case of limbic encephalitis
- High tumour burden in elderly: tumour + antibody ≠ PNS

Diagnostic Criteria – 2019

PNS CARE SCORE [11]

Clinical	
High Risk Phenotype	3
Intermediate Risk Phenotype	2
Not associated w Cancer	0
Labs	
High risk AB	3
Intermediate risk AB	2
Lower risk AB	0
Cancer	
Found, consistent with syndrome and antibody, or inconsistent but antigen found	4
Not found but follow-up <2y	1
Not found and follow-up >2y	0

Diagnostic Criteria – 2019

PNS CARE SCORE

Score	Probability of PNS
≥ 8	Definite
6-7	Probable
4-5	Possible
≤ 3	Not PNS

The Special Case of Opsoclonus-Myoclonus

- Rapid repeated eye movements (opsoclonus) + brief muscle jerks in limbs (myoclonus)
- May also include ataxia, tremors, dysarthria

- In children, 50% of OMS = neuroblastoma
- In adults, OMS associated with Breast cancer or SCLC

The Special Case of Opsoclonus-Myoclonus

- **Update:**

  "With the exception of opsoclonus-myoclonus, the diagnosis of definite PNS requires the presence of high- or intermediate-risk antibodies."

Why?

- No specific antibody association
- OMS Scores 7

Therefore…

- Should still be considered **definite** when associated with specific cancers

Suspecting PNS?

Start immunotherapy immediately

If high/intermediate risk AB

- Cancer screening guided by phenotype
- If initial screen is negative
- Repeat every 4-6 mos for 2 years

If lower risk AB

- Cancer screening at presentation is enough

If Cancer found: Treat

Investigation

Deficits caused by PNS can be irreversible, so it’s important to initiate therapy as soon as possible after diagnosis

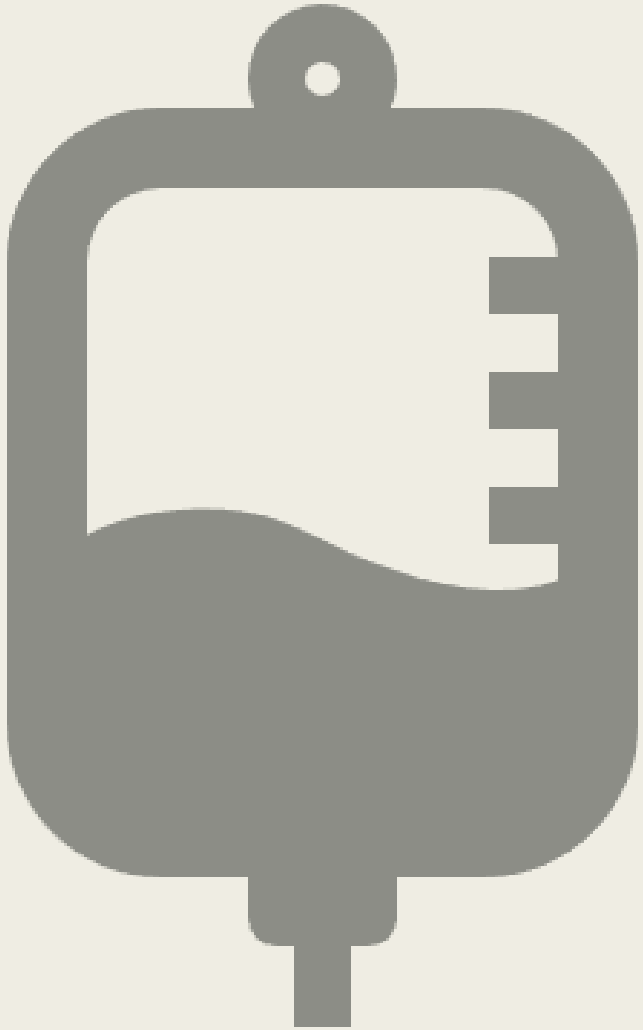
Cancer Screen
→ CT Thorax, Abdomen, Pelvis
→ Scrotal/ Breast Cancer Screen
→ Pelvic Imaging (Gynecological cancers)
→ Skin Exam

→ FDG PET if initial assessment is negative

Treatment

- Treat underlying cancer
- Immunotherapy [12]
  → IV Methylprednisolone (long-term?)
  → IVIG
  → PLEX

  → Cytotoxic T cell = Cyclophosphamide, mycophenolate, azathioprine
  → Antibody-mediated = rituximab



Prognosis

- PNSs occur in 1 in 300 patients with cancer [13]
- Timely diagnosis of PNS is important as it has the potential to provide early warning of malignancy.

- Dampening immune response adversely affects cancer prognosis
  Has been observed in cutaneous SCC and Merkel cell cancer
- May also increase chemotherapy toxicity

Immune-checkpoint inhibitors (ICIs)

- ICIs work by blocking proteins (e.g. CTLA4, PDL1) on cells that otherwise act to inhibit the immune response.

→ Enhanced immune response → PNS [14]

- ICI-specific
- Same Tx as idiopathic PNS
- Varying response dependent on antigen

THANK YOU FOR LISTENING

Sources

1. Dalmau J, Rosenfeild MR. Paraneoplastic Neurologic syndromes. In: Fauci, Braunwald, Kasper, et al., editors. *Harrison's Principles of Internal Medicine.* 17th ed. Vol. 1. New York: McGraw Hill Medical; 2008. pp. 623–7.

2. Kannoth S. Paraneoplastic neurologic syndrome: A practical approach. Ann Indian Acad Neurol. 2012 Jan;15(1):6-12. doi: 10.4103/0972-2327.93267. PMID: 22412264; PMCID: PMC3299076.

3. Aly R, Emmady PD. Paraneoplastic Cerebellar Degeneration. [Updated 2022 Jul 4]. In: StatPearls . Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560638/

4. S. Humayun Gultekin and others, Paraneoplastic limbic encephalitis: neurological symptoms, immunological findings and tumour association in 50 patients, *Brain*, Volume 123, Issue 7, July 2000, Pages 1481–1494, https://doi.org/10.1093/brain/123.7.1481

5. Gozzard P, Woodhall M, Chapman et al Paraneoplastic neurologic disorders in small cell lung carcinoma: A prospective study. Neurology. 2015 Jul 21;85(3):235-9. doi: 10.1212/WNL.0000000000001721. Epub 2015 Jun 24. PMID: 26109714; PMCID: PMC4516293.

6. Giometto B, Grisold W, Vitaliani R, Graus F, Honnorat J, Bertolini G; PNS Euronetwork. Paraneoplastic neurologic syndrome in the PNS Euronetwork database: a European study from 20 centers. Arch Neurol. 2010 Mar;67(3):330-5. doi: 10.1001/archneurol.2009.341. PMID: 20212230.

7. Zaborowski MP, Spaczynski M, Nowak-Markwitz E, Michalak S. Paraneoplastic neurological syndromes associated with ovarian tumors. J Cancer Res Clin Oncol. 2015 Jan;141(1):99-108. doi: 10.1007/s00432-014-1745-9. Epub 2014 Jun 26. PMID: 24965744; PMCID: PMC4282879.

8. Zahr, Z.A., Baer, A.N. Malignancy in Myositis. *Curr Rheumatol Rep* 13, 208–215 (2011). https://doi.org/10.1007/s11926-011-0169-7

9. Graus F, Ariño H, Dalmau J. Paraneoplastic neurological syndromes in Hodgkin and non-Hodgkin lymphomas. Blood. 2014 May 22;123(21):3230-8. doi: 10.1182/blood-2014-03-537506. Epub 2014 Apr 4. PMID: 24705493; PMCID: PMC4046430.

10. Graus F, Delattre JY, Antoine JC, et al Recommended diagnostic criteria for paraneoplastic neurological syndromes Journal of Neurology, Neurosurgery & Psychiatry 2004;75:1135-1140.

11. Graus F, Vogrig A, Muñiz-Castrillo S et al Updated Diagnostic Criteria for Paraneoplastic Neurologic Syndromes. Neurol Neuroimmunol Neuroinflamm. 2021 May 18;8(4):e1014. doi: 10.1212/NXI.0000000000001014. PMID: 34006622; PMCID: PMC8237398.

12. Devine MF, Kothapalli N, Elkhooly M, Dubey D. Paraneoplastic neurological syndromes: clinical presentations and management. Ther Adv Neurol Disord. 2021 Feb 1;14:1756286420985323. doi: 10.1177/1756286420985323. PMID: 33796141; PMCID: PMC7970694.

13. Vogrig A, Gigli GL, Segatti S, Corazza E, Marini A, Bernardini A, Valent F, Fabris M, Curcio F, Brigo F, Iacono D, Passadore P, Rana M, Honnorat J, Valente M. Epidemiology of paraneoplastic neurological syndromes: a population-based study. J Neurol. 2020 Jan;267(1):26-35. doi: 10.1007/s00415-019-09544-1. Epub 2019 Sep 24. PMID: 31552550.

14. Graus, F., Dalmau, J. Paraneoplastic neurological syndromes in the era of immune-checkpoint inhibitors. *Nat Rev Clin Oncol* **16**, 535–548 (2019). https://doi.org/10.1038/s41571-019-0194-4