MAYO CLINIC

Paraneoplastic Neurologic Syndromes: A Contemporary Approach to Diagnosis and Management

Divyanshu Dubey, MD, FAAN, FANA
Professor of Neurology
Professor of Laboratory Medicine & Pathology
Consultant and Co-Director, Neuroimmunology Laboratory
Mayo Clinic, Rochester, MN

DISCLOSURES

- KLHL11 patent licensed as a marker of neurological autoimmunity and testicular germ cell tumor.
- Patent pending for LUZP4, SKOR2 and Cavin-4 as a marker of neurological autoimmunity
- Consulted for UCB, Immunovant, Argenx, Arialys and Astellas. All compensation for consulting activities is paid directly to Mayo Clinic.
- Received funding from UCB, DOD for immunoprofiling/biomarker identification of germ cell tumors (CA210208), inflammatory neuropathies (PR220430) and ALS (AL240239).
- Discuss off label use of immunotherapy for paraneoplastic disorders.

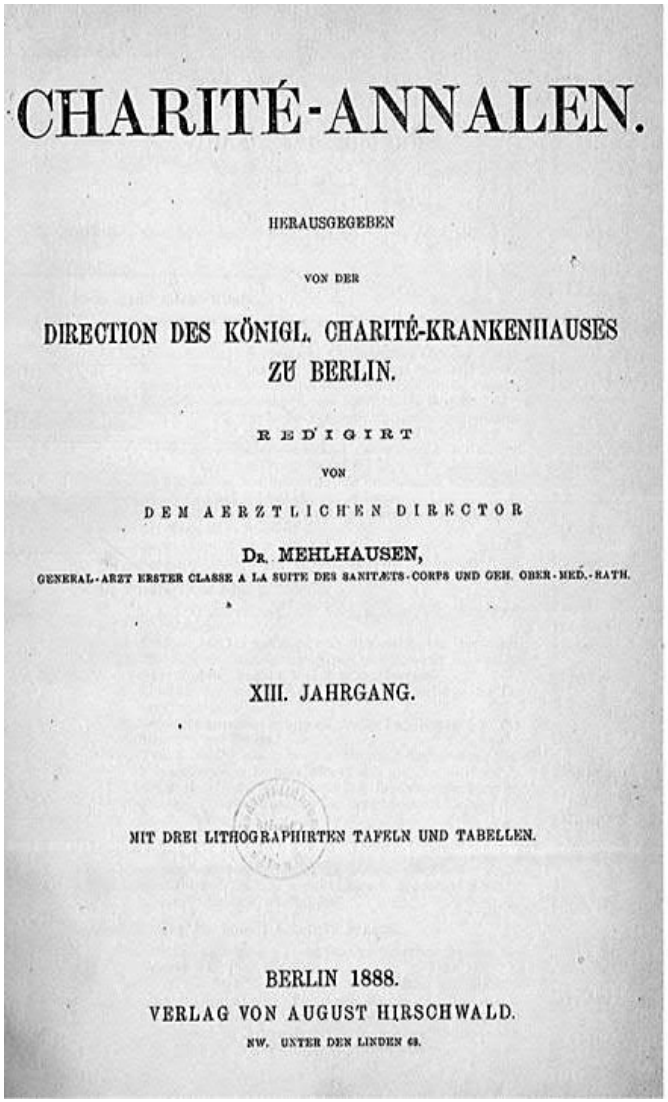
LEARNING OBJECTIVES

Upon conclusion of this activity, participants should be able to:

- Utilize updated paraneoplastic neurological syndrome diagnostic criteria
- Determine the utility of growing repertoire of autoantibody biomarkers in the diagnosis of paraneoplastic neurological syndrome

"On Brain Symptoms Associated With Carcinomatosis Without Detectable Changes in the Brain"

Hermann Oppenheim: Charité Annalen, 1888



CHARITÉ-ANNALEN.

HERAUSGEGEBEN

VON DER

DIRECTION DES KÖNIGL. CHARITÉ-KRANKENHAUSES ZU BERLIN.

REDIGIRT

VON

DEM AERZTLICHEN DIRECTOR

DR. MEHLHAUSEN,

GENERAL-ARZT ERSTER CLASSE A LA SUITE DES SANITÄTS-CORPS UND GEH. OBER-MED.-RATH.

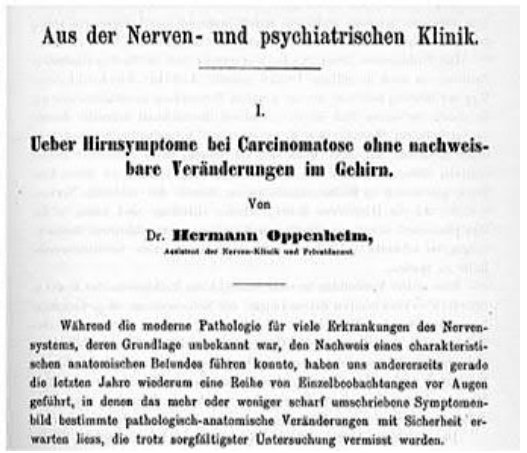
XIII. JAHRGANG.

MIT DREI LITHOGRAPHIRTEN TAFELN UND TABELLEN.

BERLIN 1888.

VERLAG VON AUGUST HIRSCHWALD.

NW. UNTER DEN LINDEN 68.



Aus der Nerven- und psychiatrischen Klinik.

I.

Ueber Hirnsymptome bei Carcinomatose ohne nachweisbare Veränderungen im Gehirn.

Von

Dr. **Hermann Oppenheim,**

Assistent der Nerven-Klinik und Privatdocent.

Während die moderne Pathologie für viele Erkrankungen des Nervensystems, deren Grundlage unbekannt war, den Nachweis eines charakteristischen anatomischen Befundes führen konnte, haben uns andererseits gerade die letzten Jahre wiederum eine Reihe von Einzelbeobachtungen vor Augen geführt, in denen das mehr oder weniger scharf umschriebene Symptomenbild bestimmte pathologisch-anatomische Veränderungen mit Sicherheit erwarten liess, die trotz sorgfältigster Untersuchung vermisst wurden.

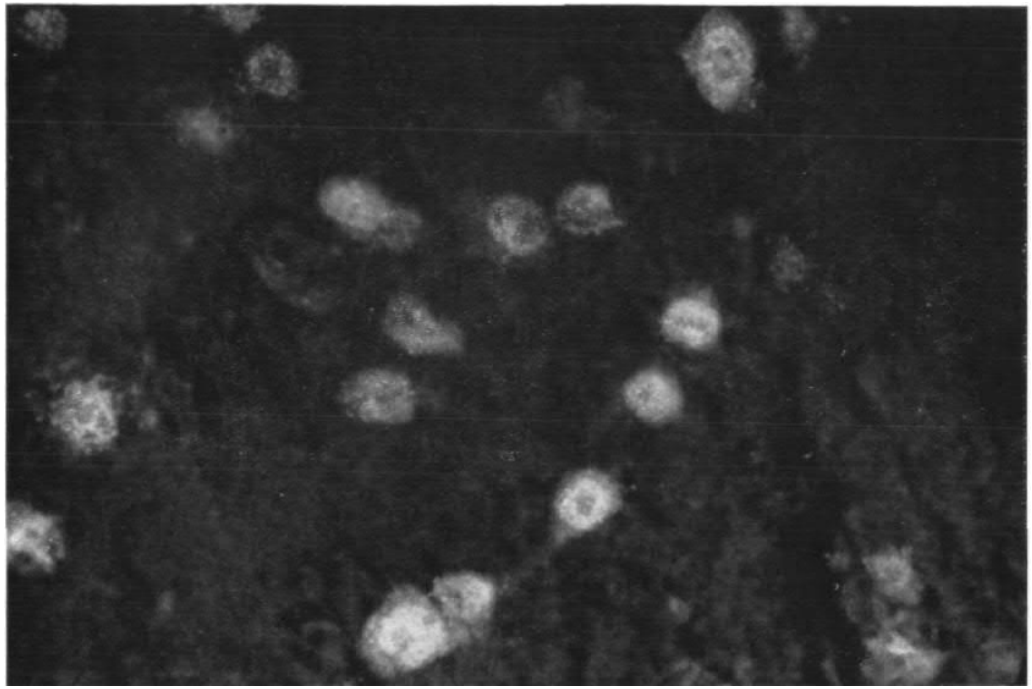
ANTIBODY BIOMARKERS

IMMUNOFLUORESCENT DETECTION OF ANTIBODIES AGAINST NEURONES IN SENSORY CARCINOMATOUS NEUROPATHY

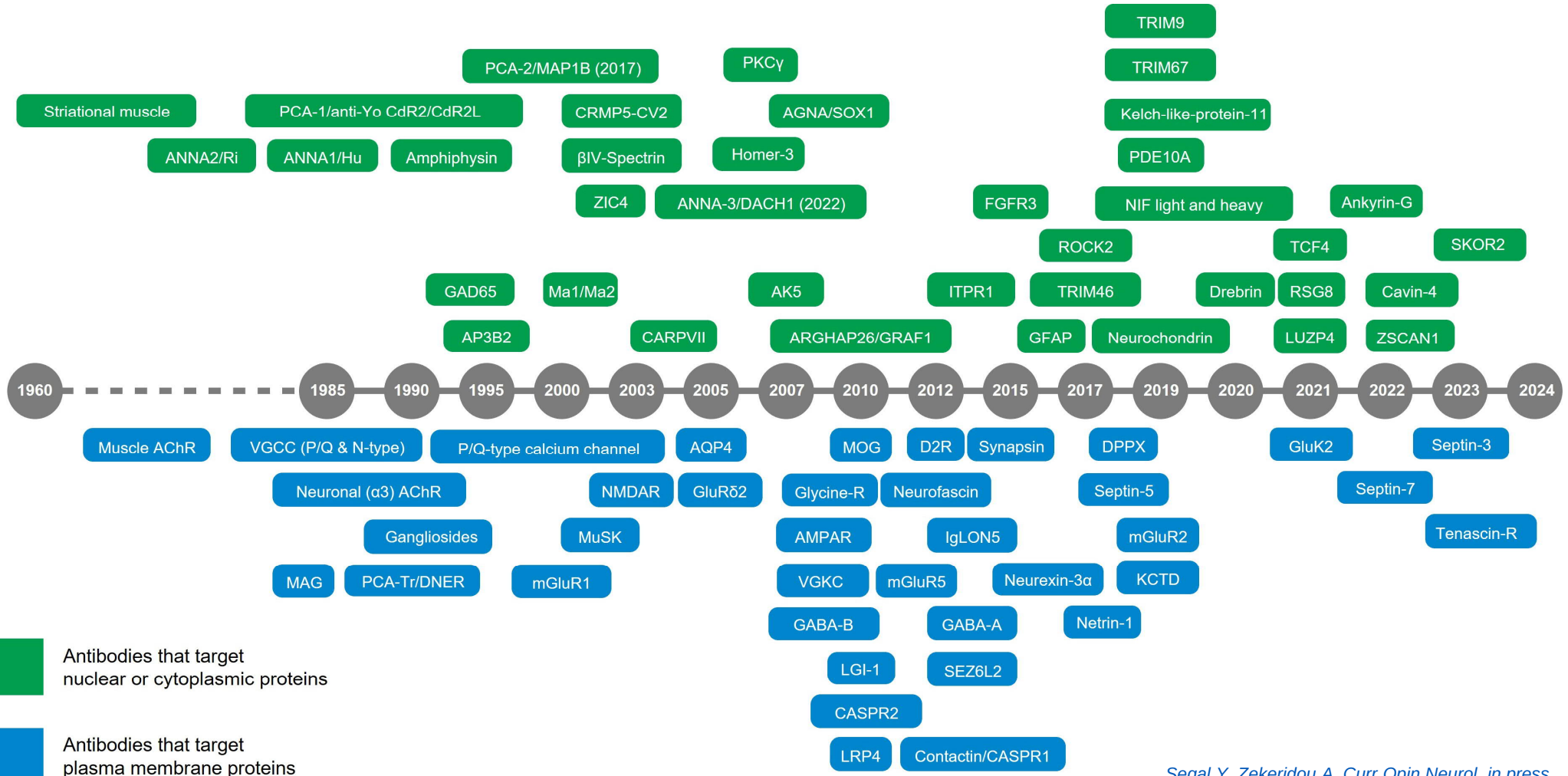
BY

P. C. WILKINSON[1] AND J. ZEROMSKI[1]

University Department of Bacteriology, Western Infirmary, Glasgow



Neural autoantibody discovery over the years

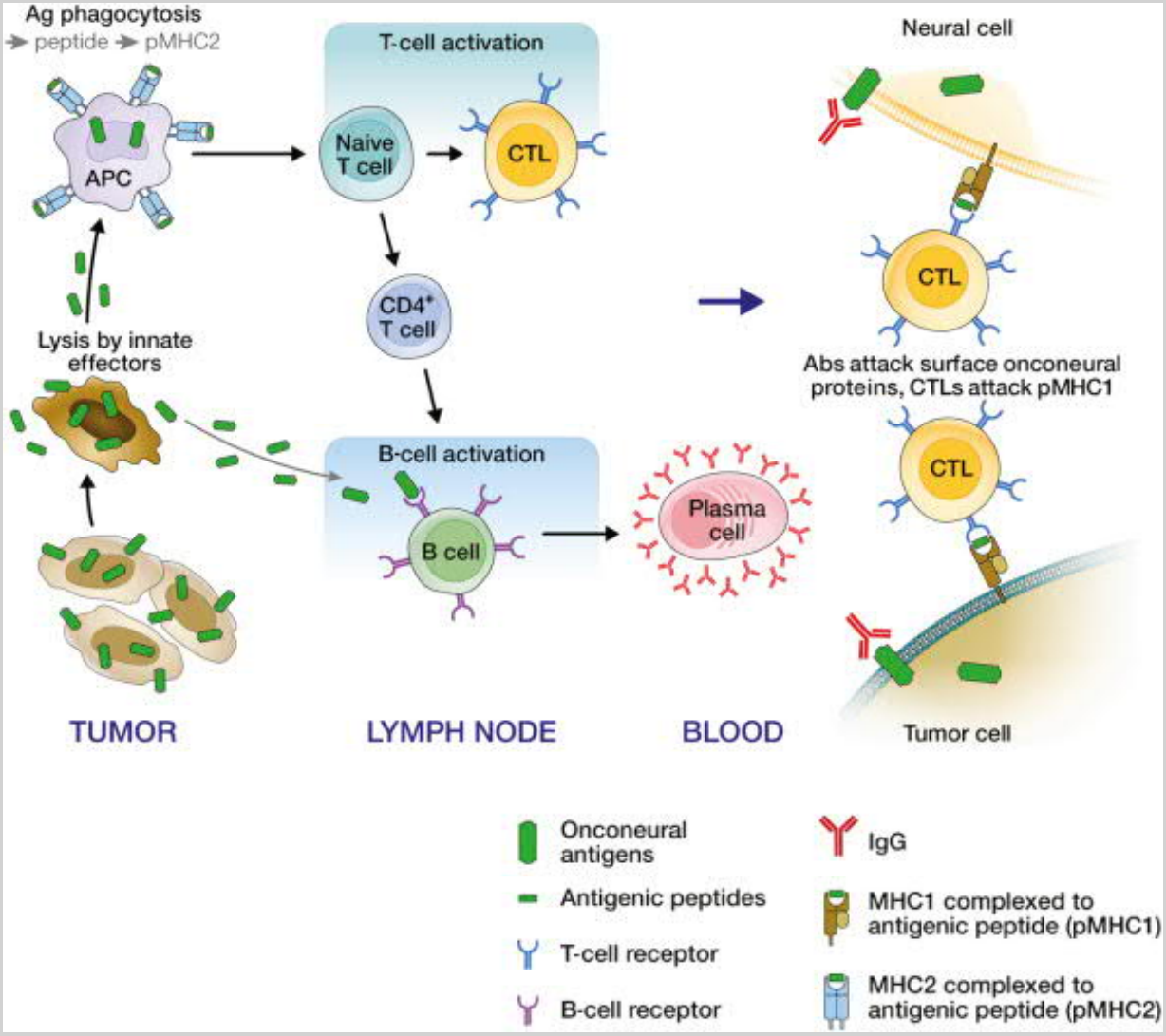


Antibodies that target nuclear or cytoplasmic proteins

Antibodies that target plasma membrane proteins

Segal Y, Zekeridou A, Curr Opin Neurol, in press

Pathophysiology

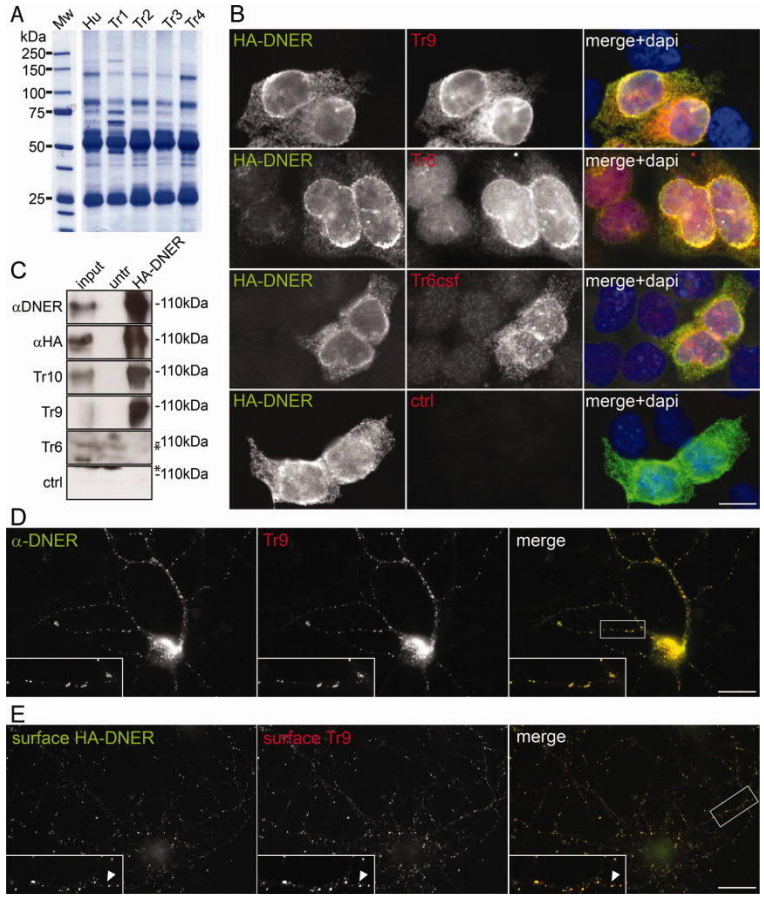


Identification of Delta/Notch-like Epidermal Growth Factor-Related Receptor as the Tr Antigen in Paraneoplastic Cerebellar Degeneration

Esther de Graaff, PhD,[1,2,3] Peter Maat, MD,[2] Esther Hulsenboom, BSc,[2] Robert van den Berg, MSc,[1,3] Martin van den Bent, MD, PhD,[2] Jeroen Demmers, PhD,[4] Pieternella J. Lugtenburg, MD, PhD,[5] Casper C. Hoogenraad, PhD,[1,3] and Peter Sillevis Smitt, MD, PhD[2]

Objective: Anti-Tr is among the better described autoantibodies in paraneoplastic cerebellar degeneration (PCD) combined with Hodgkin lymphoma (HL); however, the Tr antigen remains unidentified.
Methods: We used immunoprecipitation of total rat brain extract followed by mass spectrometry to identify the antigen recognized by anti-Tr–positive sera. By Western blotting and cell-based assays, we tested a total of 12 anti-Tr–positive and 246 control sera and determined the region of the epitope recognized by the anti-Tr antibodies. Deletion and mutant constructs were generated to further map the antigenic region.
Results: Mass spectrometry analysis of immunopurified rat brain extract using 4 different anti-Tr–positive sera led to the identification of Delta/Notch-like epidermal growth factor-related receptor (DNER) as the Tr antigen. All but 1 of 246 control samples were negative in the HeLa cell-based screening assay, whereas 12 of the 12 anti-Tr–positive sera stained hemagglutinin-tagged DNER-expressing cells. Only 1 control subject with HL but no ataxia was found to be both DNER and Tr positive. Using deletion constructs, we pinpointed the main epitope to the extracellular domain. Knockdown of endogenous DNER in hippocampal and N-glycosylation mutations abolished the anti-Tr staining, indicating that glycosylation of DNER is required for it to be recognized by anti-Tr antibodies.
Interpretation: DNER is the antigen detected by anti-Tr–positive sera. Presence of anti-Tr antibodies in patients with PCD and HL or HL only can now be screened quickly and reliably by using a cell-based screening assay.

ANN NEUROL 2012;71:815–824



Paraneoplastic stiff-person syndrome: passive transfer to rats by means of IgG antibodies to amphiphysin

Lancet 2005; 365: 1406–11

See Comment

Claudia Sommer, Andreas Weishaupt, Jörg Brinkhoff, Lydia Biko, Carsten Wessig, Ralf Gold, Klaus V Toyka

Department of Neurology, University of Würzburg, Würzburg, Germany (C Sommer MD, A Weishaupt PhD, J Brinkhoff MD, L Biko MS, C Wessig MD, R Gold MD, K V Toyka MD); **and Institut für MS-Forschung, Bereich Humanmedizin der Universität Göttingen und Gemeinnützige Hertie-Stiftung, Göttingen, Germany** (R Gold)

Correspondence to: Dr Claudia Sommer, Neurologische Universitätsklinik, Josef-Schneider-Strasse 11, D-97080 Würzburg, Germany **sommer@mail.uni-wuerzburg.de**

Summary

Background Stiff-person syndrome (SPS) with antibodies to amphiphysin is a paraneoplastic disorder of the central nervous system with a putative autoimmune pathogenesis. Proof of a causal role of the antibodies is still lacking for this and all other antibody-associated paraneoplastic syndromes of the central nervous system.

Methods We obtained the plasma filtrate of a patient with breast cancer and SPS that responded to therapeutic plasmapheresis. The purified IgG fraction included high-titre antibodies to the synaptic protein amphiphysin. In a cotransfer design, this IgG fraction was injected intraperitoneally into female Lewis rats that had received encephalitogenic T-helper (Th) lymphocytes specific for myelin basic protein, to induce an immune-mediated leaky blood–brain barrier. The rats were followed up with behavioural tests, video photography, and electromyography.

Findings The injection of the IgG fraction including antibodies to amphiphysin resulted in a dose-dependent stiffness with spasms resembling human SPS. Control IgG injected into rats that had received the same encephalitogenic Th cells had no effect. IgG binding was demonstrated in the central nervous system of rats that showed signs of the disorder.

Interpretation These experiments support the hypothesis of a pathogenetic role of antibodies to amphiphysin, thus adding paraneoplastic SPS to the group of antibody-mediated autoimmune disorders.

Rat 1 and 3 received high titre anti-amphiphysin antibodies whereas rat 8 received antibodies from the control patient.

Type IIa ('anti-Hu') antineuronal antibodies produce destruction of rat cerebellar granule neurons in vitro

John E. Greenlee, MD; Thomas N. Parks, PhD; and Kurt A. Jaeckle, MD

NEUROLOGY 1993;43:2049-2054

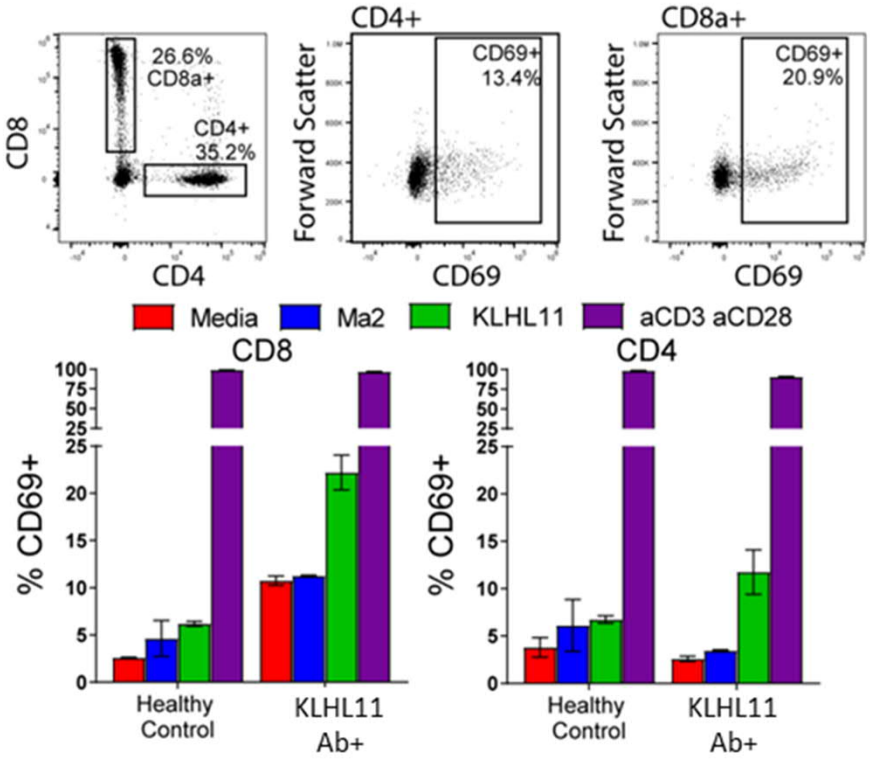
Immunization with the paraneoplastic encephalomyelitis antigen HuD does not cause neurologic disease in mice

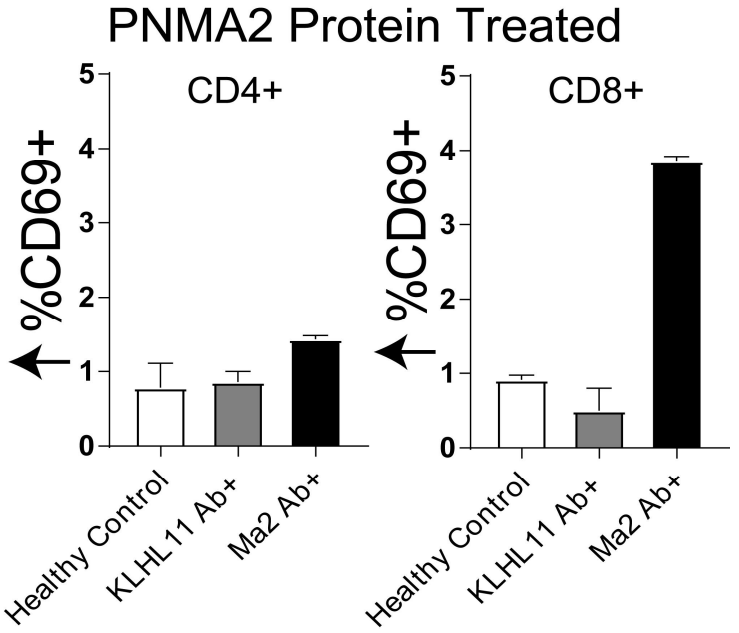
P.A.E. Sillevis Smitt, MD; G.T. Manley, PhD; and J.B. Posner, MD

Article abstract—Paraneoplastic encephalomyelitis/paraneoplastic sensory neuronopathy (PEM/PSN) associated with small cell lung cancer is characterized by high serum and CSF titers of anti-neuronal (anti-Hu) antibodies and by intrathecal synthesis of anti-Hu IgG. A pathologic role for the anti-Hu antibodies in PEM/PSN is further suggested by reported intraneuronal accumulation of the antibodies in the nervous system of PEM/PSN patients at autopsy. We immunized SJL/J mice, Lewis rats, and Hartley guinea pigs with purified recombinant HuD fusion protein. In spite of high-titer anti-HuD antibodies, neurologic and pathologic examination of the animals was normal. Apparent uptake of purified IgG by neurons in the brain proved to be artifactual.

NEUROLOGY 1995;45:1873-1878

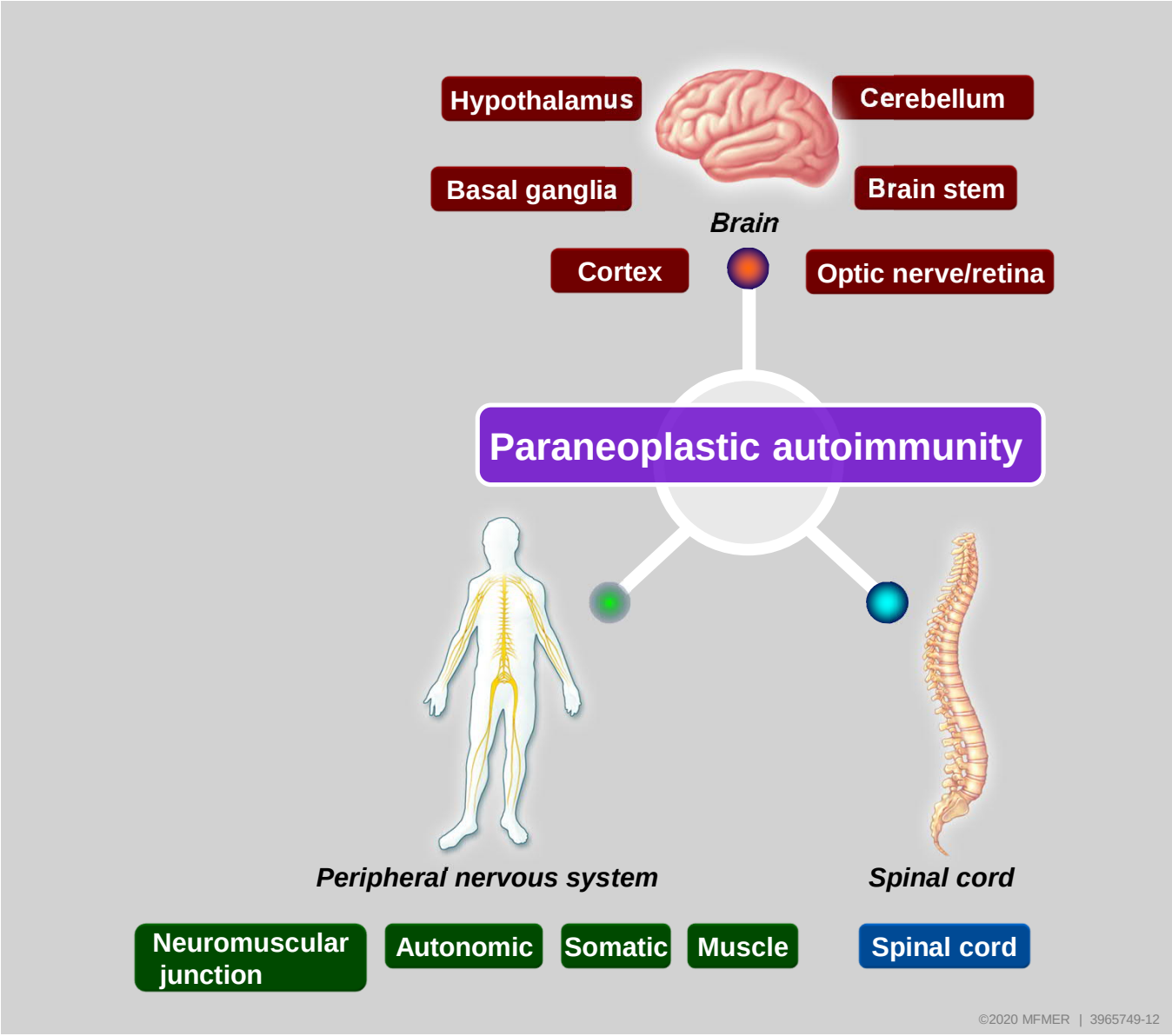
KLHL11 specific T-cell response





Dubey et al. JAMA Neurol. 2020

DIAGNOSTIC CRITERIA & SYNDROMES



Recommended diagnostic criteria for paraneoplastic neurological syndromes

F Graus, J Y Delattre, J C Antoine, J Dalmau, B Giometto, W Grisold, J Honnorat, P Sillevis Smitt, Ch Vedeler, J J G M Verschuuren, A Vincent, R Voltz, for the Paraneoplastic Neurological Syndrome Euronetwork

See Editorial Commentary, p 1090

J Neurol Neurosurg Psychiatry 2004;**75**:1135–1140. doi: 10.1136/jnnp.2003.034447

Updated Diagnostic Criteria for Paraneoplastic Neurologic Syndromes

Francesc Graus, MD, PhD,* Alberto Vogrig, MD,* Sergio Muñiz-Castrillo, MD,* Jean-Christophe G. Antoine, MD, PhD, Virginie Desestret, MD, PhD, Divyanshu Dubey, MD, Bruno Giometto, MD, Sarosh R. Irani, MD, PhD, Bastien Joubert, MD, PhD, Frank Leypoldt, MD, PhD, Andrew McKeon, MD, Harald Prüss, MD, Dimitri Psimaras, MD, Laure Thomas, MD, Maarten J. Titulaer, MD, PhD, Christian A. Vedeler, MD, PhD, Jan J. Verschuuren, MD, PhD, Josep Dalmau, MD, PhD, and Jerome Honnorat, MD, PhD

Neurol Neuroimmunol Neuroinflamm 2021;8:e1014. doi:10.1212/NXI.0000000000001014

Updated PNS criteria

- Substitute “classical syndromes” with the term “high-risk phenotypes” for cancer
- Introduce the concept of “intermediate-risk phenotypes”
- “Onconeural antibody” was replaced by
  - “high risk” (>70% associated with cancer) antibodies
  - “intermediate risk” (30%–70% associated with cancer) antibodies
- Three levels of evidence for PNS by using the PNS-Care Score: definite, probable, and possible.
- Factors: clinical phenotype, antibody type, presence or absence of cancer, and time of follow-up.

PNS Care score

	Points
Clinical level	
High-risk phenotypes	3
Intermediate-risk phenotypes	2
Defined phenotype epidemiologically not associated with cancer	0
Laboratory level[a]	
High-risk antibody (>70% cancer association)	3
Intermediate risk antibody (30%–70%)	2
Lower risk antibody (<30%) or negative	0
Cancer	
Found, consistent with phenotype and (if present) antibody, or not consistent but antigen expression demonstrated	4
Not found (or not consistent) but follow-up <2 y	1
Not found and follow-up ≥2 y	0

Diagnostic level
Definite ≥8
Probable 6–7
Possible 4–5
Non-PNS ≤3

Abbreviation: PNS = paraneoplastic neurologic syndrome.
[a] See text for recommended diagnostic methods.

Antibody positivity needed for Definite PNS, except for OMS

Graus et al, N2 2021

ARTICLE OPEN ACCESS

Population-Based Epidemiology Study of Paraneoplastic Neurologic Syndromes

Shailee Shah, MD, Eoin P. Flanagan, MBBCh, Pritikanta Paul, MD, Carin Y. Smith, BS, Sandra C. Bryant, MS, Michelle F. Devine, MD, Vanda A. Lennon, MD, PhD, Andrew McKeon, MD, Sean J. Pittock, MD, and Divyanshu Dubey, MD

Neurol Neuroimmunol Neuroinflamm 2022;9:e1124. doi:10.1212/NXI.0000000000001124

Abstract

Objectives

Population-based epidemiologic data for paraneoplastic neurologic syndromes (PNSs) in the United States are lacking. Our objective was to evaluate the incidence, prevalence, and associated morbidity of PNS.

Methods

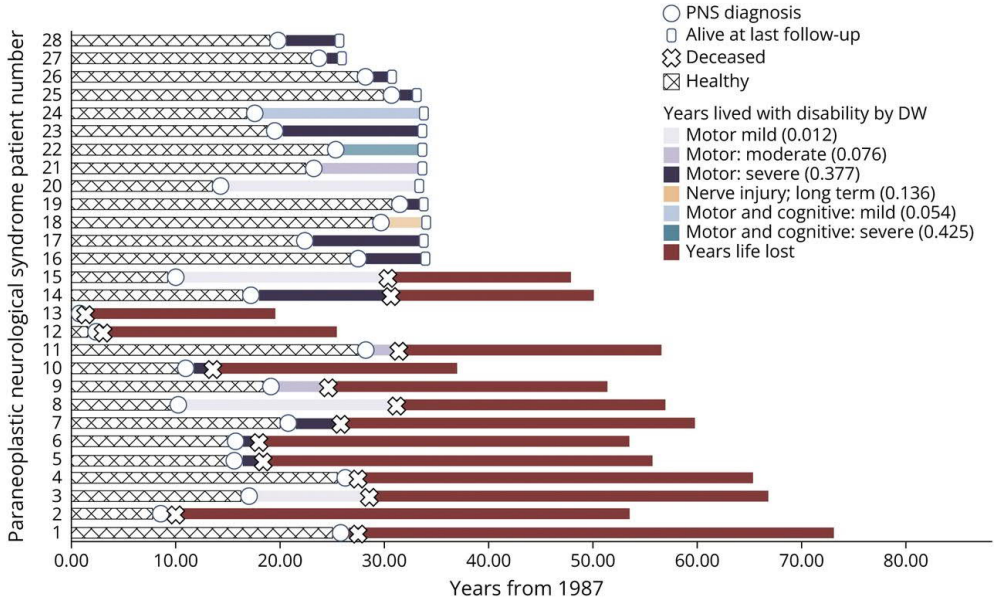
We performed a population-based epidemiology study in Olmsted County, Minnesota, with patients identified between January 1, 1987, and December 31, 2018, using the medical records linkage system of the Rochester Epidemiology Project (REP) who met the definite/probable 2021 PNS criteria and 2004 PNS criteria. Patients with dermatomyositis and myasthenia gravis with underlying tumors were included. Age- and sex-specific population counts were obtained from REP resources for January 1, 2014 (prevalence denominator) and annually for 1987–2018 (incidence denominator). Morbidity was estimated using disability-adjusted life years (DALYs; years lived with disability [YLD] plus years of life lost [YLL]).

Results

There were 28 patients with PNS identified (50% female) residing in Olmsted County, Minnesota, with median age at diagnosis of 54.5 (IQR 46.5–69.0) years. All patients had a cancer diagnosis, and 18 (64%) patients were neural autoantibody positive including antineuronal nuclear autoantibody type 1 (ANNA-1/anti-Hu; n = 1), ANNA-2/anti-Ri (n = 1), muscle-type acetylcholine receptor (AChR; n = 6), Purkinje cell cytoplasmic antibody type 1 (PCA-1/anti-Yo; n = 1), kelch-like protein 11 (KLH11; n = 3), collapsin response mediator protein 5 (CRMP-5/anti-CV2; n = 2), a-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (n = 1), neurofilament light chain (n = 1), leucine zipper 4 (LUZP4; n = 1), and unclassified neural antibodies (n = 1). PNS incidence was 0.6/100,000 person-years and increased over time from 0.4/100,000 person-years (1987–2002) to 0.8/100,000 person-years (2003–2018) ($p = 0.06$). Prevalence was 5.4/100,000 people. The median follow-up period after PNS diagnosis was 3.1 years (IQR, 1.1–9.9 years). Total disability-adjusted life years (DALYs) for 28 patients with PNS were 472.7 years, based on total years of life lost (YLL) for patients dying between 1987 and 2018 (n = 15) of 445.3 years plus years lived with disability (YLD) 27.4 years.

Discussion

PNSs are rare neurologic disorders but are associated with severe morbidity and mortality. The estimated number of prevalent PNS cases in the United States is 17,099, and predicted DALY for all US PNS cases is 292,393 years. Their apparent increasing rate of detection is attributable to increasing physician awareness and availability of serologic testing.

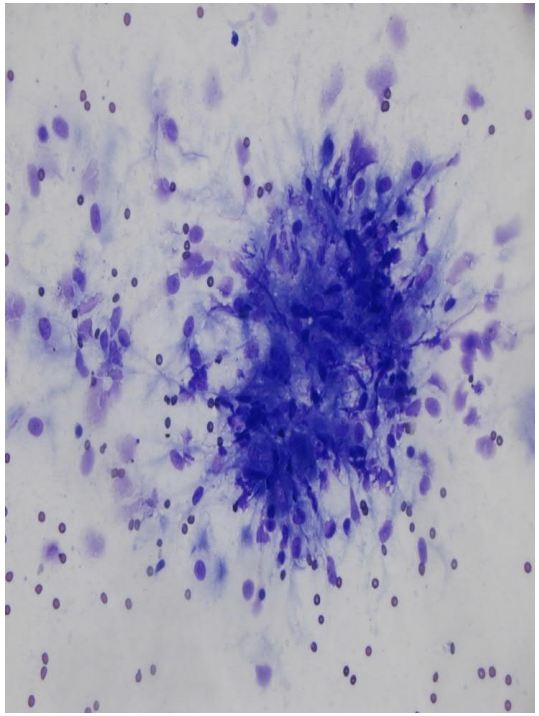


High risk antibodies (>70% cancer association)	Intermediate risk antibodies (30%-70% cancer association)	Low risk antibodies (<30% cancer association)
ANNA1(Anti-Hu)	AMPAR	mGluR1
CRMP5(CV2)	GABABR	GABAAR
SOX1	mGluR5	CASPR2
PCA2 (MAP1B)	P/Q VGCC	GFAP
Amphiphysin	NMDAR	GAD65
ANNA2(Anti-Ri)	CASPR2 (Morvan Syndrome)	LGI1
PCA1(Anti-Yo)		DPPX
Ma2 and/or Ma		GlyR
DNER(PCA-Tr)		AQP4
KLHL11		MOG
LUZP4*		
TRIM46*		
PDE10A*		
KCTD16*		
ANNA3*		

High risk phenotypes

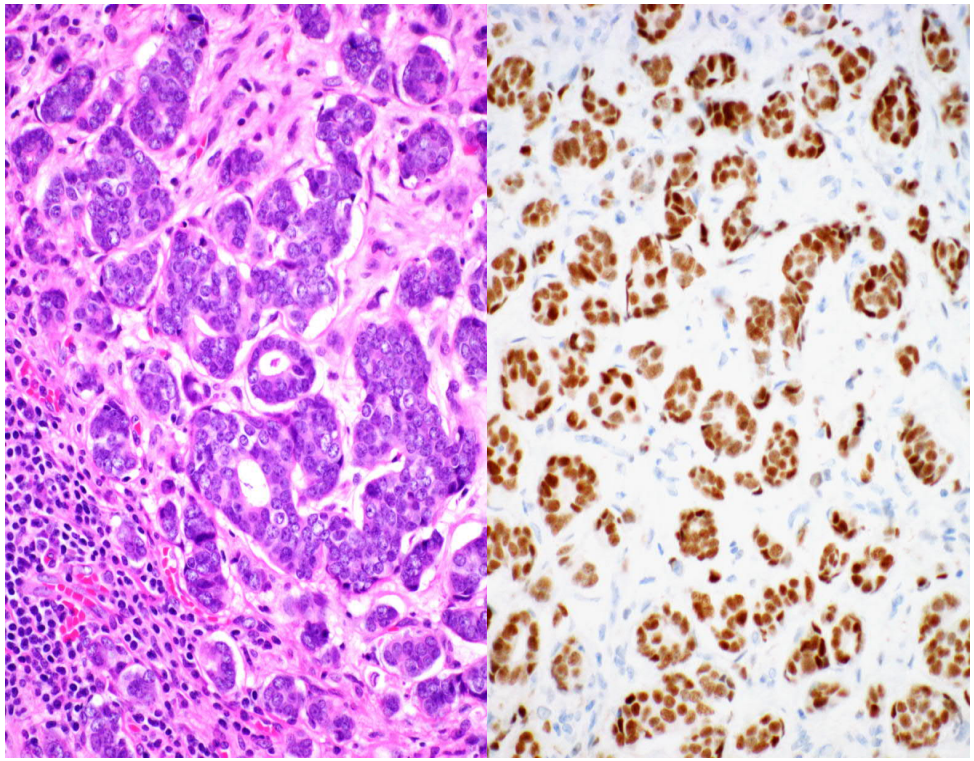
Phenotype	Associated antibodies	Associated neoplasms
Encephalomyelitis	ANNA1(Anti-Hu), CRMP5(CV2), amphiphysin	SCLC
Limbic encephalitis	ANNA1(Anti-Hu), Ma2, amphiphysin, ANNA3, AMPAR, GABABR, LGI1, CASPR2	SCLC
Rapidly progressive cerebellar syndrome	PCA1(Anti-Yo), DNER(PCA-Tr), MAP1B, CRMP5(CV2), KLHL11, Ma2, LUZP4, ANNA3; TRIM46	SCLC, Hodgkin's lymphoma, ovarian cancer, breast adenocarcinoma, uterine/fallopian tube cancer, testicular germ cell tumors
Opsoclonus-myoclonus	ANNA2(Anti-Ri), ANNA1(Anti-Hu) (rarely)	Neuroblastoma (children), SCLC or breast cancer (adults)
Sensory neuronopathy	ANNA1(Anti-Hu), CRMP5(CV2), PCA2(MAP1B), amphiphysin	SCLC
Gastrointestinal pseudo-obstruction (enteric neuropathy)	ANNA1(Anti-Hu), CRMP5(CV2)	SCLC
Lambert-Eaton myasthenic syndrome	P/Q VGCC	SCLC

49-year-old woman with progressive numbness and gait instability



Non-caseating granuloma

Amphiphysin IgG (serum and CSF)

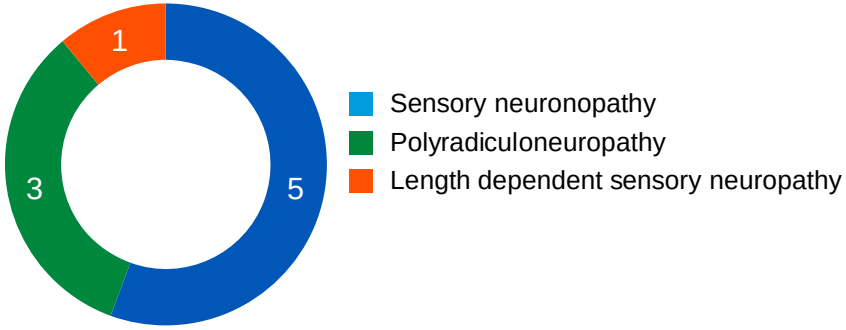


Breast Cancer

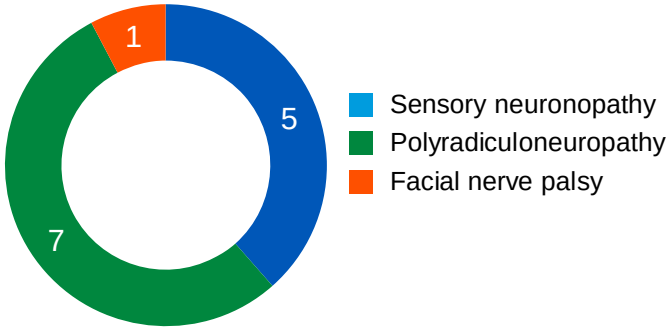
Zahid et al. Neurology. 2021

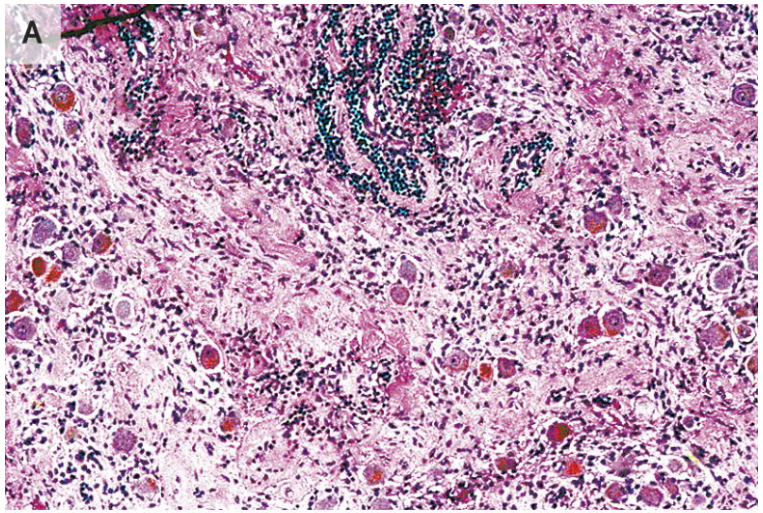
AMPHIPHYSIN-IgG ALONE (n=21)

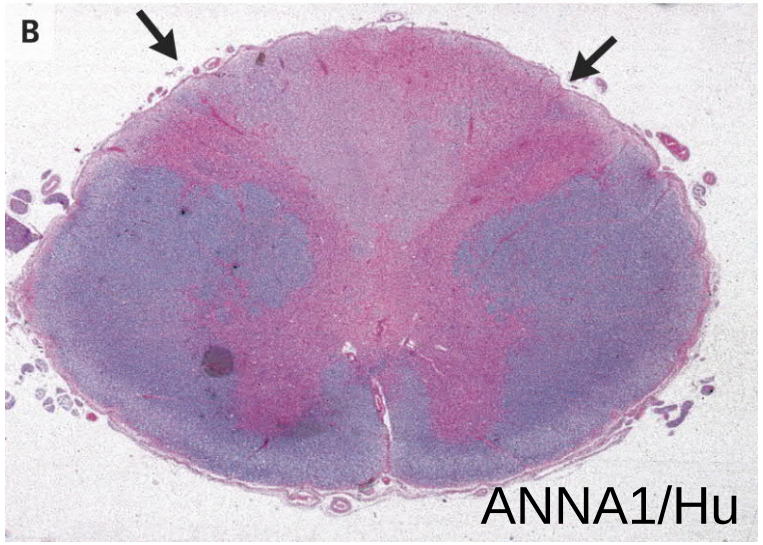
SMALL CELL LUNG CANCER



BREAST ADENOCARCINOMA

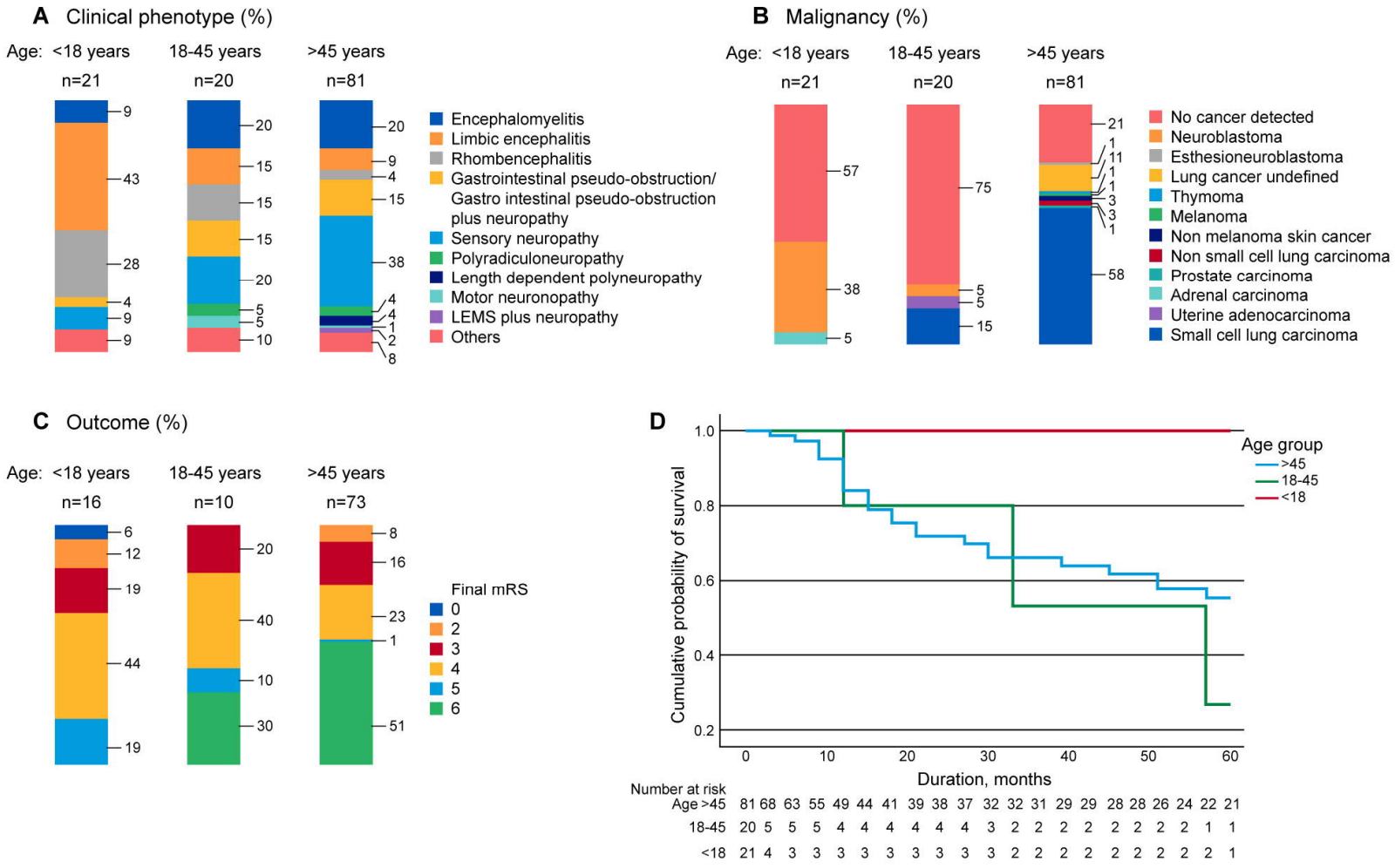




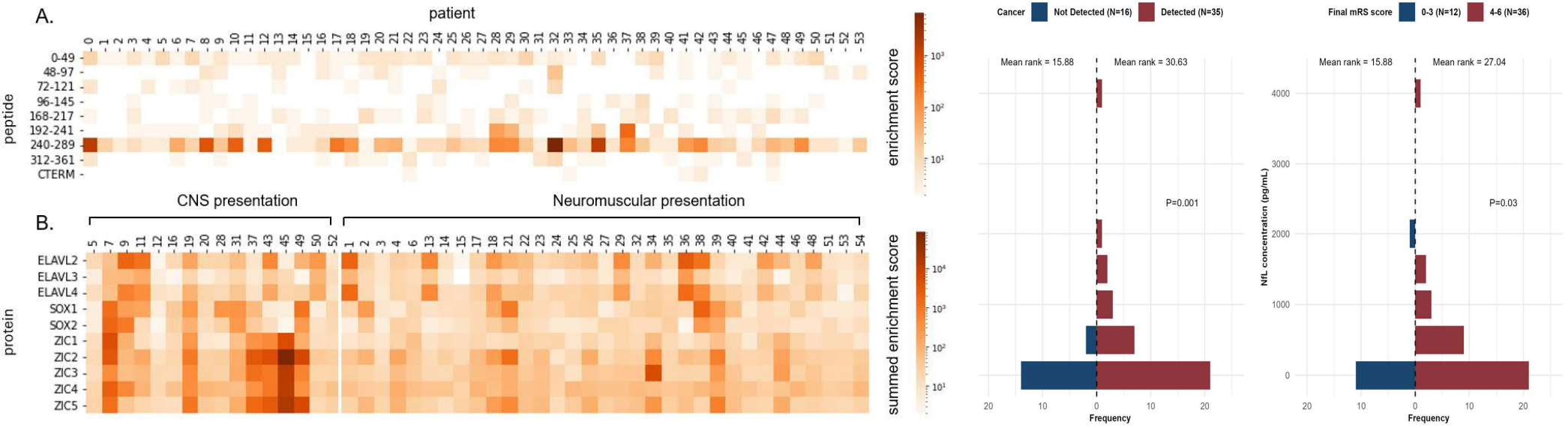


Amato & Ropper. NEJM. 2020

ANNA1 or Ant-Hu IgG



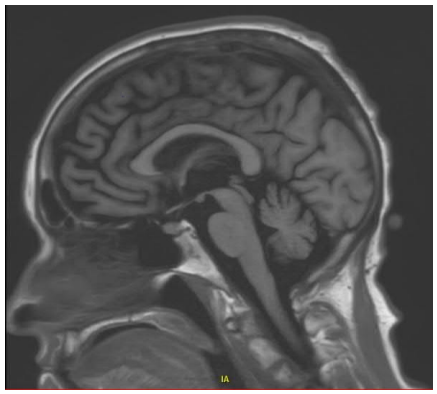
ANNA1 Immunoprofiling (PhIP-Seq) and potential role of serum neurofilament light chain



Paramasivan…Dubey. Ann Clin Transl Neurol. 2024

F/69: progressive imbalance

- Progressive loss of balance over 6 months → wheelchair/bed-bound
- Unintentional loss of weight
- Clinical exam: tetrappendicular, ocular and truncal cerebellar ataxia and dysarthria
- Inflammatory CSF; PCA1 (anti-Yo) + in serum and CSF
- Ovarian & uterine adenocarcinoma
- Treatment: cancer resection, chemo, IVMP, IVIg, PLEX and cyclophosphamide
- →Progressive decline, death



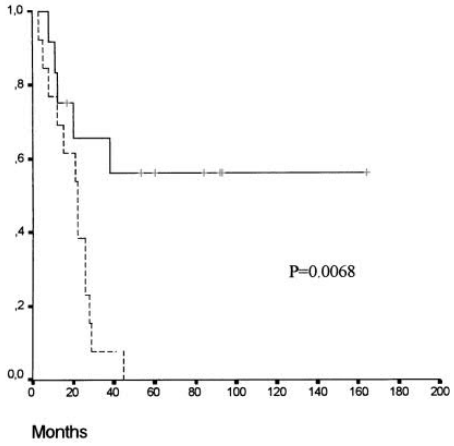
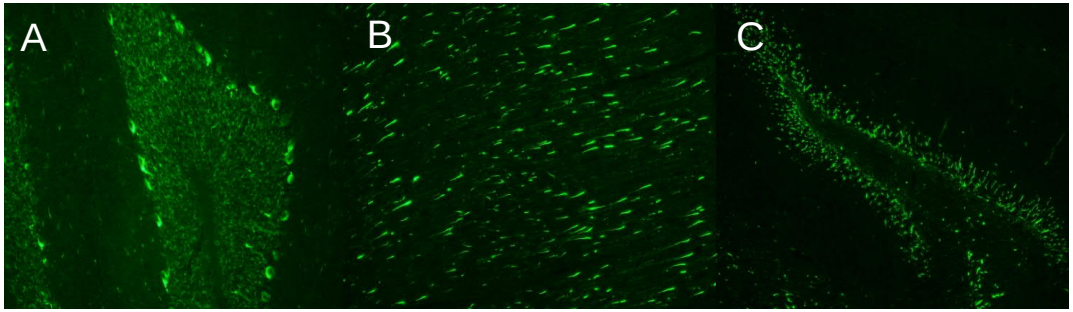
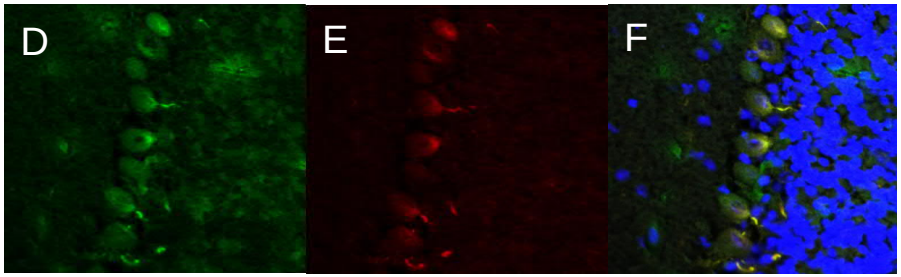


Figure. Kaplan-Meier survival curves for 25 patients with paraneoplastic cerebellar degeneration who received anti-neoplastic treatment. Solid line indicates breast cancer; dotted line, gynecologic cancer.

Rojas et al. Neurol.2000

TRIM46 (25 patients)





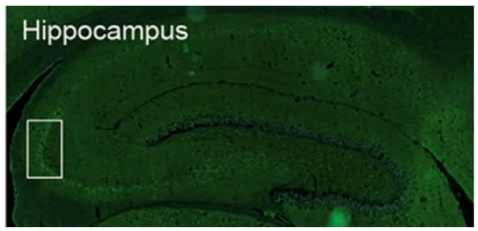
Patients
- Females (70%)
- Median age 67 years (range 25-87)

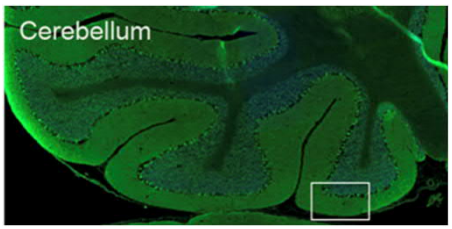
Clinical findings
- Subacute cerebellar syndrome (15, 68%)
- Limbic encephalitis (3)
- Myelopathy (2)
- Encephalopathy with/without seizures (2)

Oncological associations
- Cancer diagnosed in 18 patients (82%)
- Neuroendocrine carcinomas, common
- 3 developed neurological symptoms after immune checkpoint inhibitor (ICI) therapy

Sanchez…Dubey. JNNP. 2021; van Beuningen et al. Neuron. 2015

Trim9&67-IgG (3 patients)

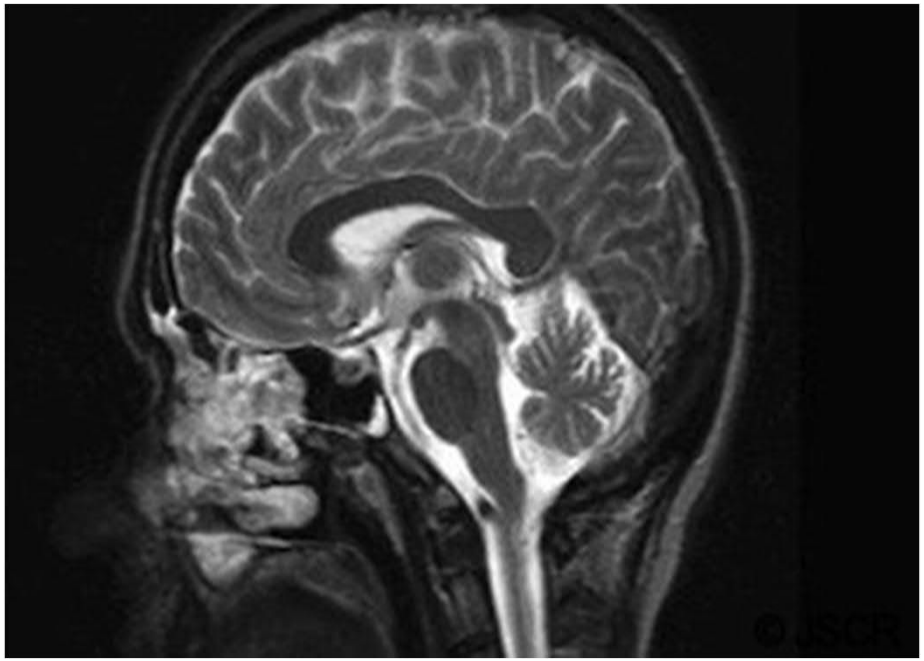




- **Clinical presentation:** cerebellar ataxia (F78, M65, F59)
- **MRI:** normal
- **Cancer association:** Pulmonary adenocarcinoma, melanoma

Le Luy et al, Cerebellum 2019; Larman et al. Nature Biotechnology. 2011

Paraneoplastic cerebellar degeneration



PCA1 or anti-Yo PCD

- **Clinical features:**
  - Ataxia (usually subacute onset)
  - Dysarthria
  - Diplopia
  - Dysphagia

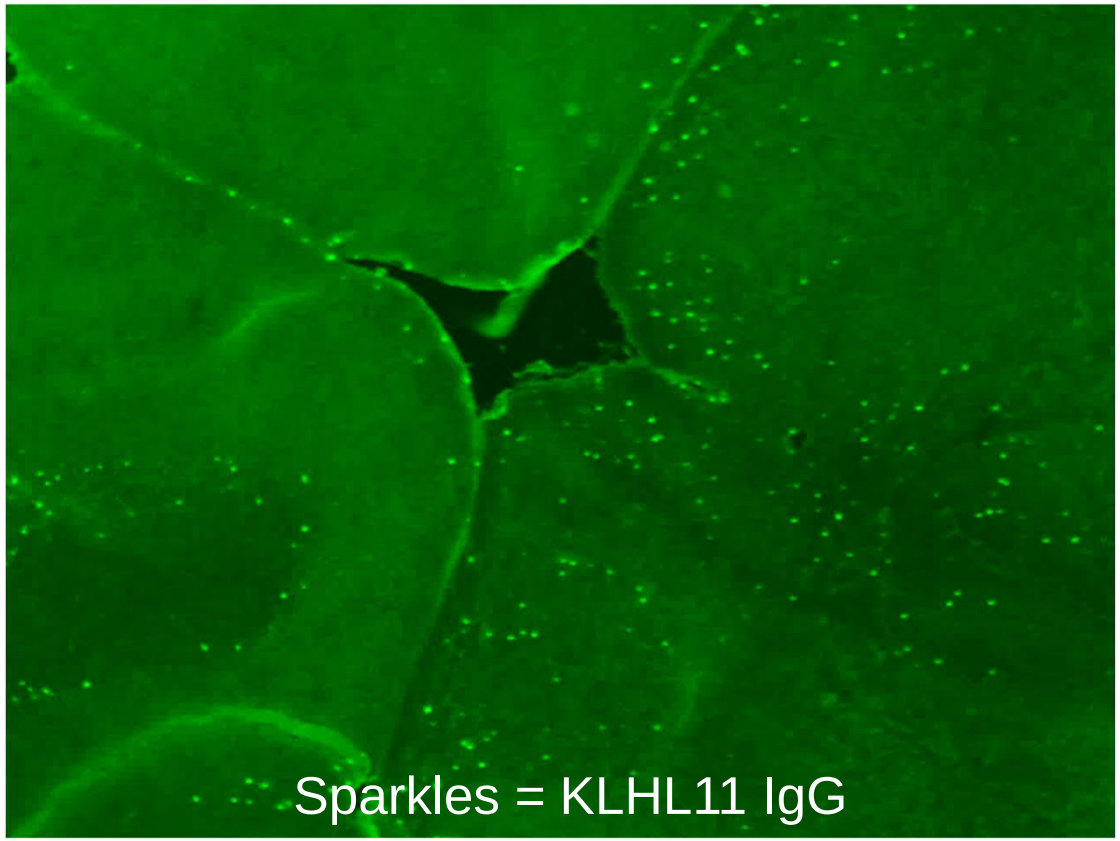
- **Associated antibodies:**
  - PCA1 or anti-Yo
  - PCA2 or MAP1B
  - Ma2
  - CRMP5
  - Amphiphysin
  - mGluR1
  - ANNA2 or anti-Ri
  - TRIM46
  - TRIM9/67
  - KLHL11
  - Neurofilament light chain

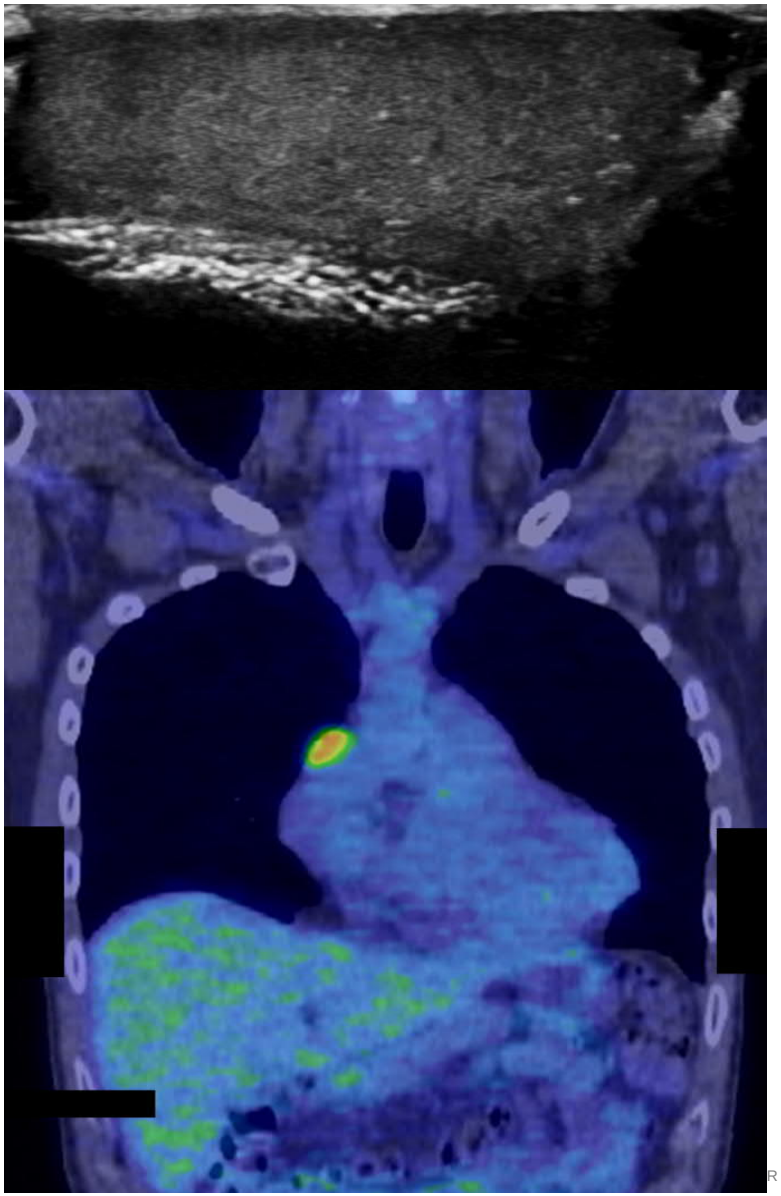
Intermediate risk phenotypes		
Brainstem encephalitis	KLHL11, Ma2, LUZP4, ANNA2(Anti-Ri), TRIM46	testicular germ cell tumors or non-SCLC, SCLC
anti-NMDAR encephalitis	NMDA-R	ovarian or extraovarian teratomas
Morvan syndrome	CASPR2, LGI1	Thymoma, thymic carcinoma
Isolated myelopathy	CRMP5(CV2), amphiphysin, PCA2(MAP1B)	SCLC, breast adenocarcinoma
Stiff-person syndrome	Amphiphysin, DPPX	Breast adenocarcinoma, SCLC, non-Hodgkin's lymphoma
Polyradiculoneuropathies	CRMP5(CV2), PCA2(MAP1B), amphiphysin, ANNA1(Anti-Hu)	SCLC, breast adenocarcinoma, thymoma

41-year-old man

- **Initial presentation**:
  - New right sided tinnitus and sensorineural hearing loss
  - Mild intermittent dizziness
  - MRI brain - normal
  - **Diagnosis:** presumed viral labrynthitis
  - Treated with prednisone and acyclovir
  - Vestibular rehab
  - Tinnitus and hearing loss improved partially
- **Five months later:** developed diplopia, nystagmus and ataxia

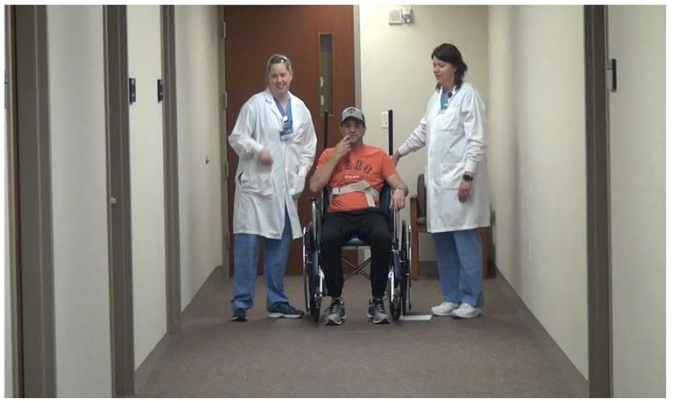
TESTING





Madel-Brehm & Dubey et al. NEJM, 2019; Dubey et al. JAMA Neurol 2020

KLHL11 IgG



Prevalence (males) : 2.8/100,000 population

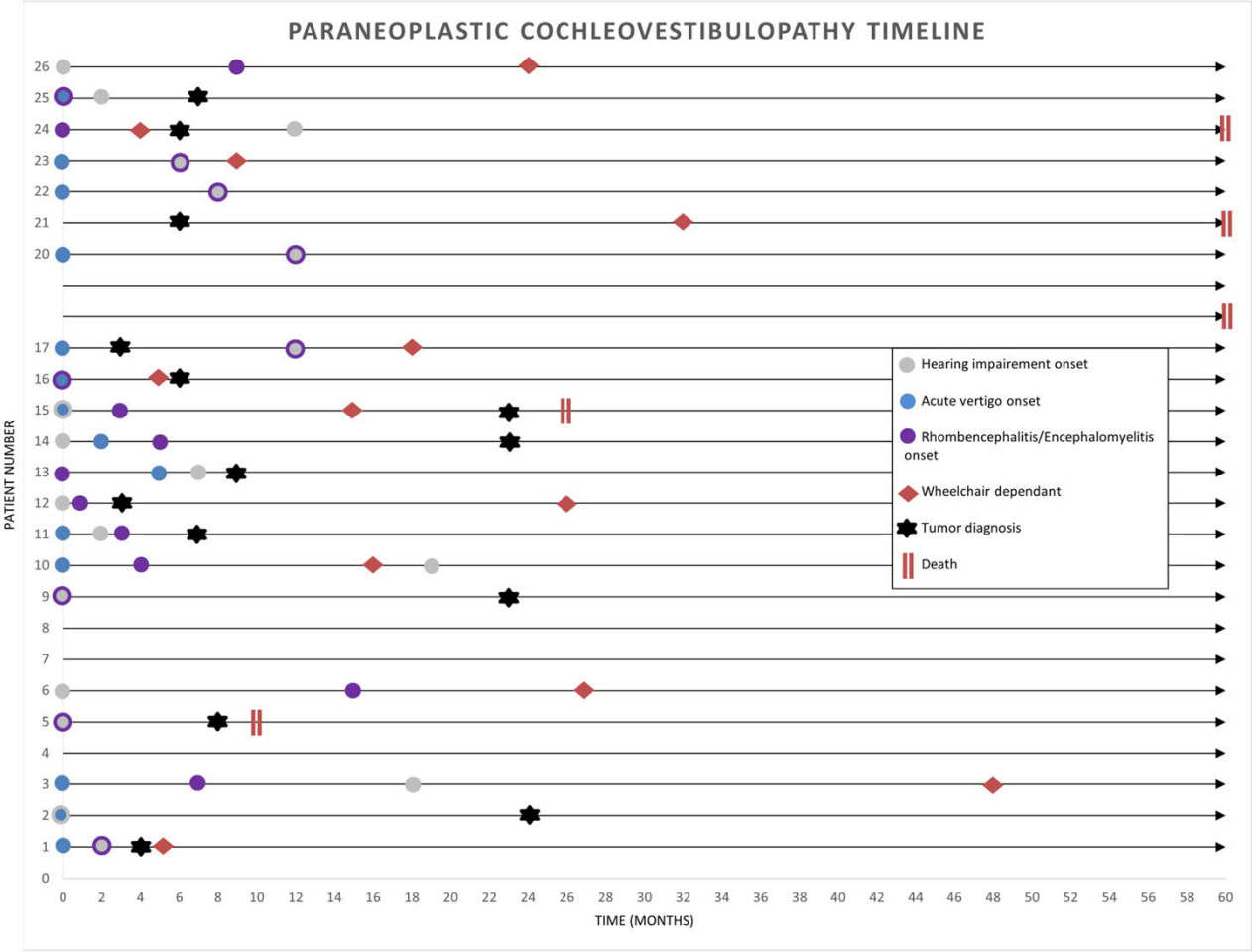
Clinical presentation:

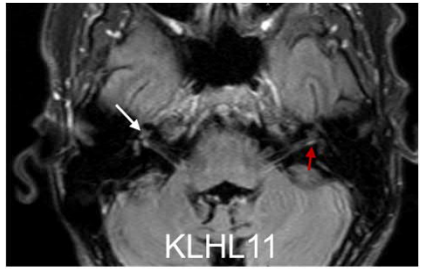
- Rhomboencephalitis (70%)
- Limbic encephalitis (15%)
- Both (15%)

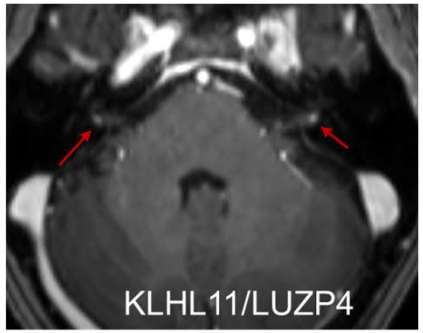
Hearing loss and tinnitus may precede other neurological presentations (40%)

Testicular cancer: >70% (commonly seminoma)

Madel-Brehm & Dubey et al. *NEJM,* 2019; Dubey et al. *JAMA Neurol* 2020, Devine & Dubey. JAMA Neurology. 2021



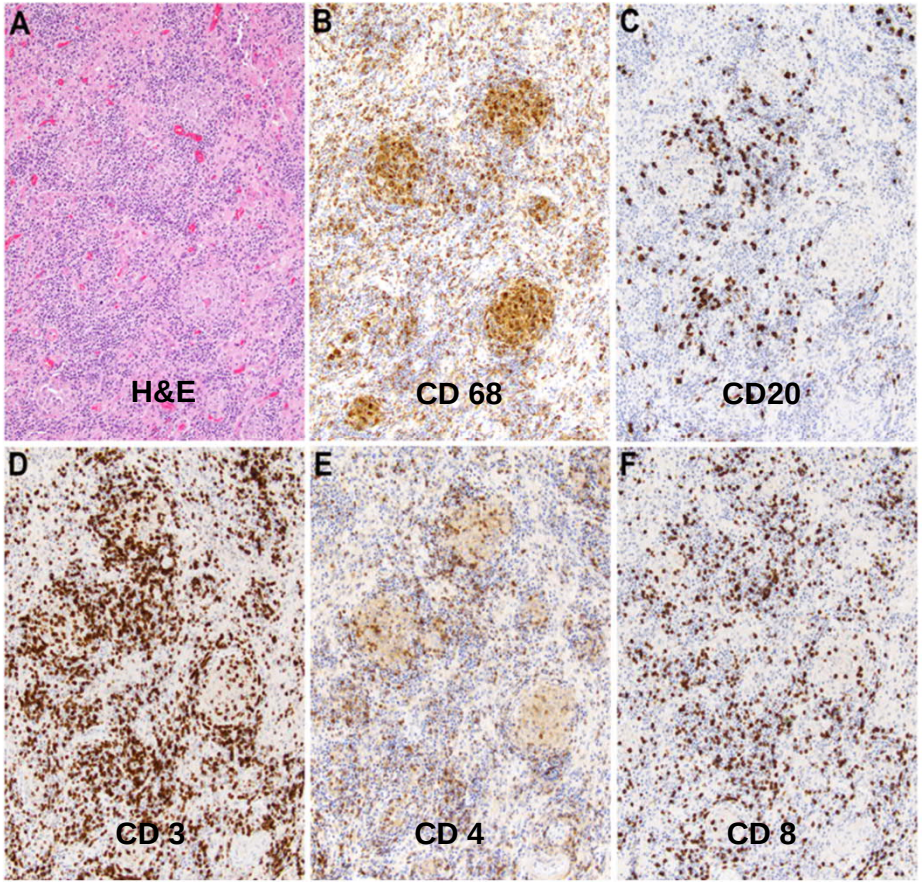




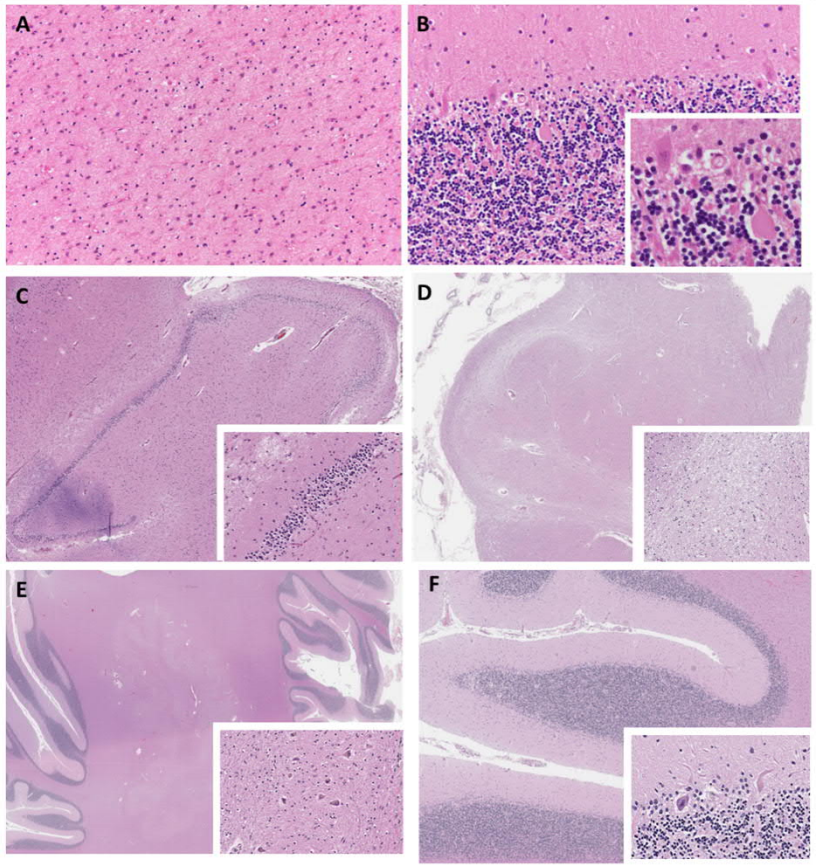
Median duration from onset of hearing loss and/or vertigo until CNS manifestation was 5.5 months (range 1–16)

Hammami, Eggers…Dubey. JNNP. 2021

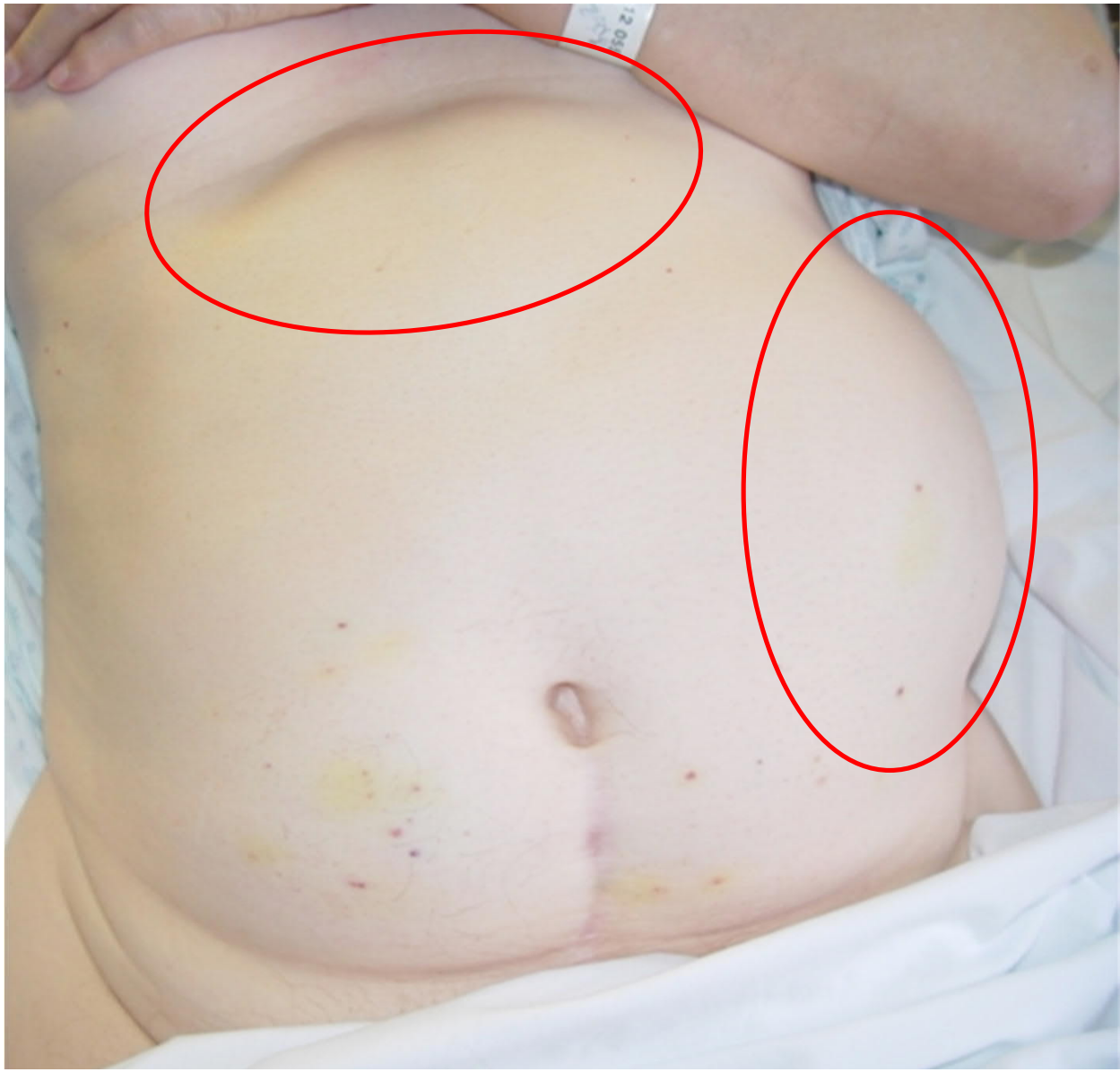
Active disease



Autopsy/late-stage biopsy: brain pathology

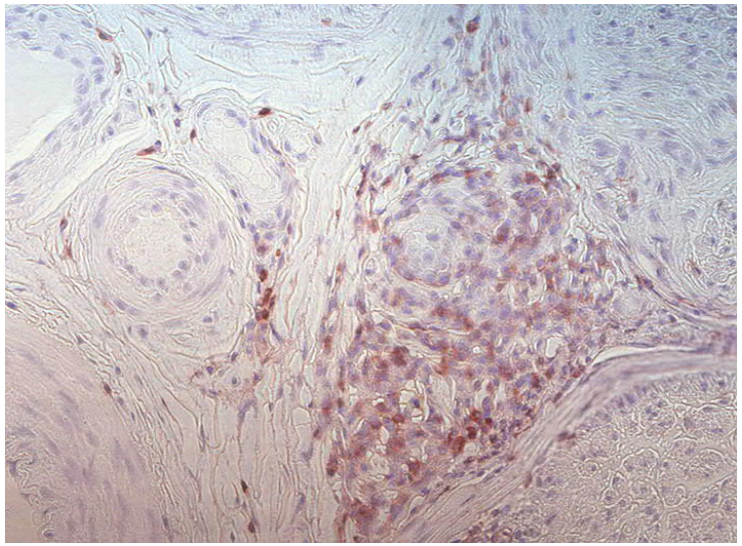


69-year-old man,
>120 pack/year history
of smoking presented with pain
and asymmetric lower
extremity weakness and
numbness



Axonal polyradiculoneuropathy

Epineurial Perivascular Lymphocytic Cuffing



Patient Information Edit Patient Info

Date Of Birth:

Race: • Unknown

Smoker: Current

Pack Years: 153

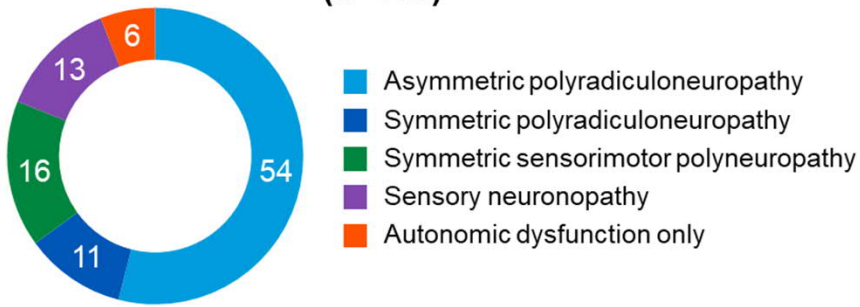
Final Results:

Alpha-3 0.05 **CCPQ** 0 **CRMP-5** 122880

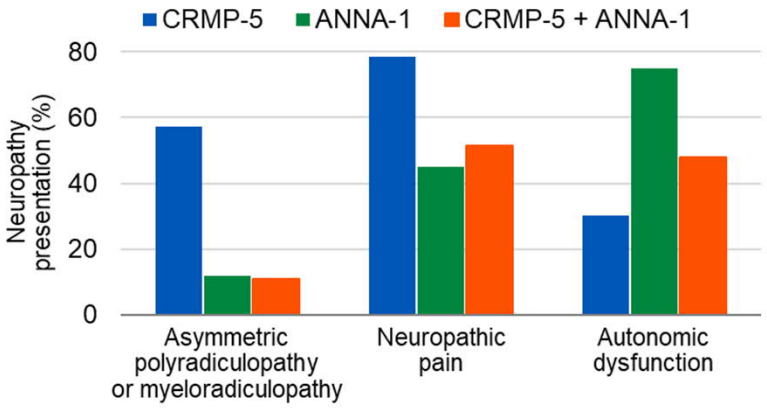
CCN 0 **GAD65** 0.56 **PCA-Tr** Negative

CRMP5 vs ANNA1 NEUROPATHY

A CRMP-5 IgG Neuropathy Patterns (%), (n=105)



C CRMP5 vs ANNA1

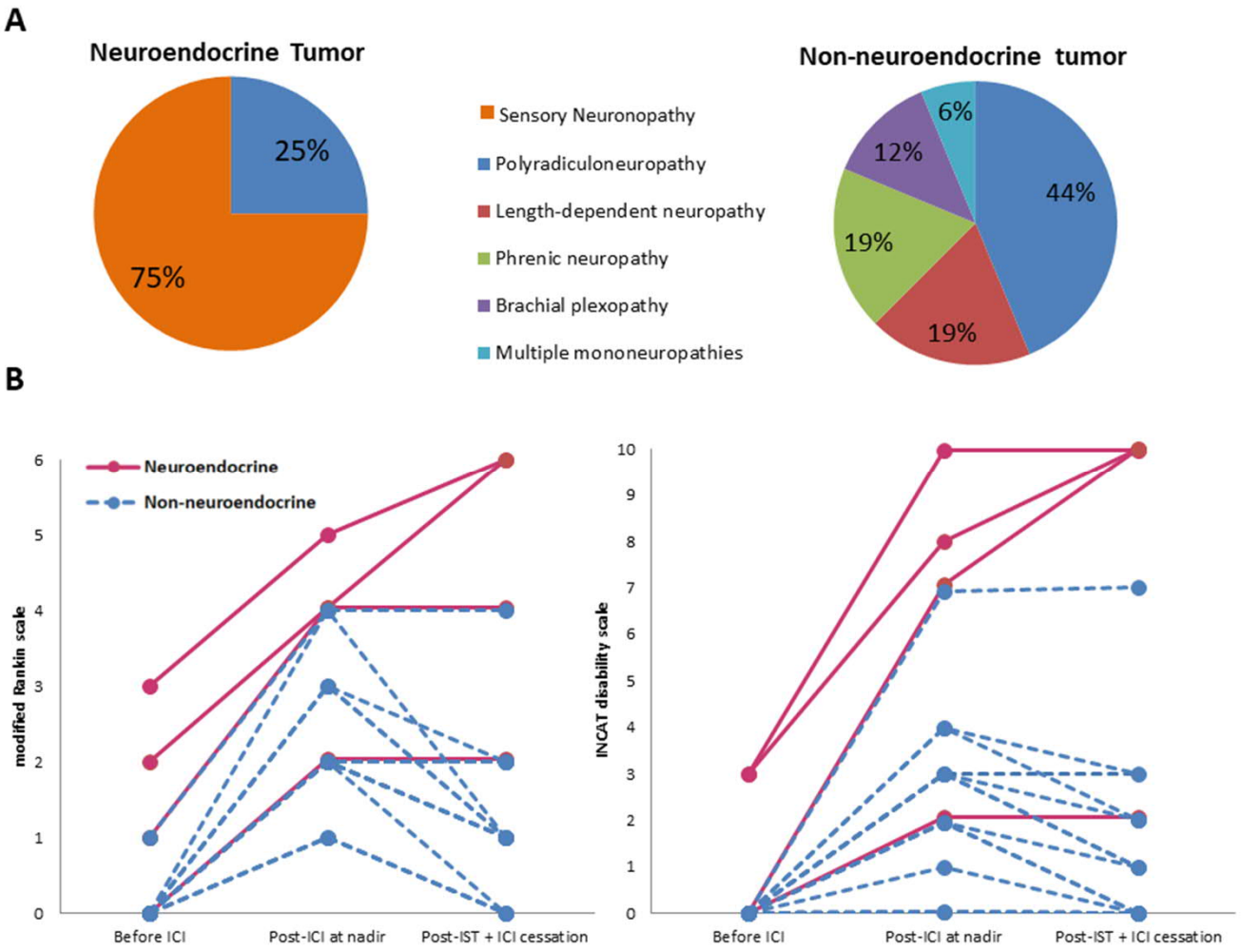


Dubey et al: Neurology, 2018

Polyradiculoneuropathy

62-year-old women with paresthesia

- February 2020: started noticing numbness and paresthesias involving her upper and lower extremities
- March 2020: she had bilateral lower extremity weakness, and sensory ataxia. During work up diagnosed of small cell cancer (outside facility)
- April 2020, she received immune check point inhibitor therapy (atezolizumab), soon after which her neurological symptoms worsened significantly.
- May 2020: severe neuropathic pain, progressive weakness, wheel chair bound. EMG/NCS consistent with polyradiculoneuropathy.
- June 2020: Paraneoplastic evaluation was positive for ANNA1 or anti-Hu
- Solu-Medrol and PLEX without any improvement. Refused cyclophosphamide.
- July 2020: Patient died.

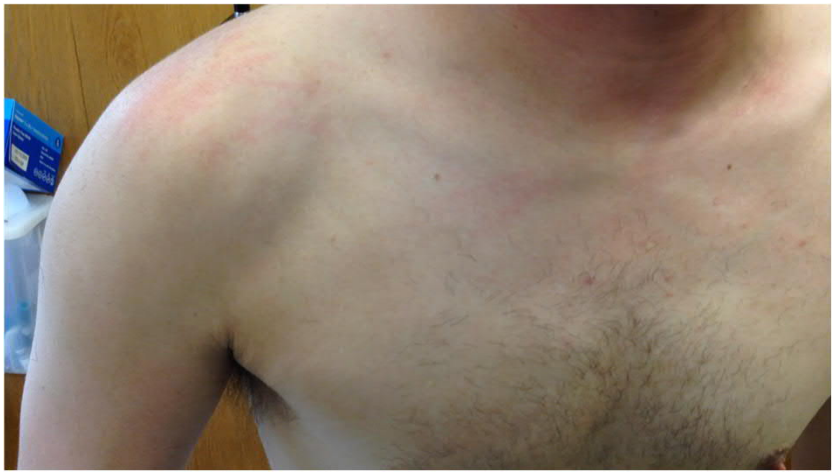


All irNeuropathies associated with neuroendocrine tumor were onconeural antibody seropositive

Chompoopong… Dubey. JNNP. 2021
Sechi...Zekeridou et al, Neurology. 2020

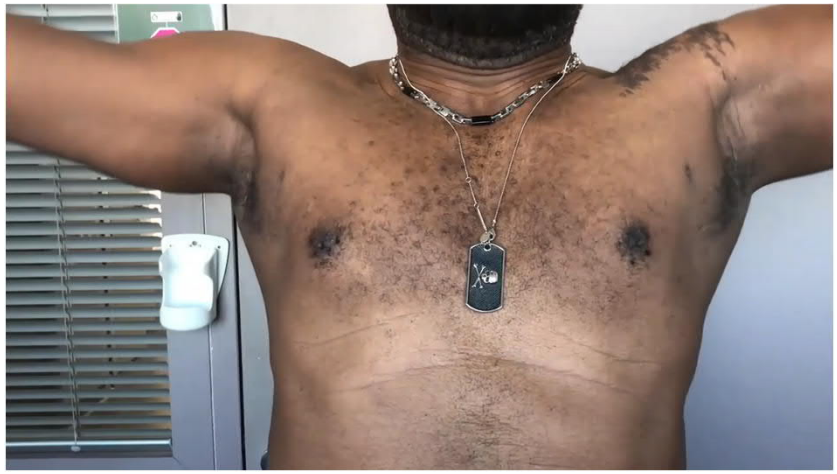
Peripheral hyperexcitability

Nerve



CASPR2 IgG

Muscle



Cavin-4 IgG

Dubey et al. JAMA Neurol. 2022
Svahn et al. Neurol Neuroimmunol Neuroinflamm Jan 2023

62-year-old man with weakness and imbalance

- **Presentation:** Lower extremity weakness, dry eyes, dry mouth, gait instability (cerebellar ataxia), EMG (postexercise facilitation)
- Clinical level: 3 (LEMS+ Cerebellar ataxia)
- **Antibody panel:** P/Q VGCC IgG
- Antibody level: 2 (50% cancer association with LEMS, cancer association higher with ataxia)
- **CT chest/cancer search:** Small mediastinal nodule, history of prostrate cancer (patient lost to follow up)
- Cancer level: 1 (follow up for <2 years)
- **Total: 6 (Probable PNS)**

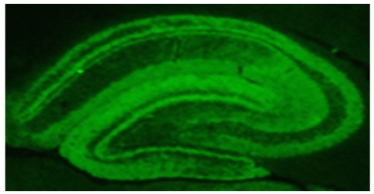
N=479, suspected to have PNS	2021 criteria, probable/definite
Sensitivity	88%
Specificity	99%
Area under the curve	0.99

Swart et al. N2. 2024

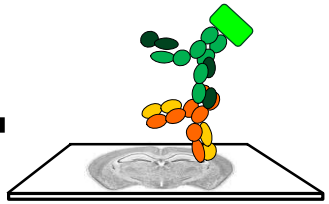
	Points
Clinical level	
High-risk phenotypes	3
Intermediate-risk phenotypes	2
Defined phenotype epidemiologically not associated with cancer	0
Laboratory level[a]	
High-risk antibody (>70% cancer association)	3
Intermediate risk antibody (30%–70%)	2
Lower risk antibody (<30%) or negative	0
Cancer	
Found, consistent with phenotype and (if present) antibody, or not consistent but antigen expression demonstrated	4
Not found (or not consistent) but follow-up <2 y	1
Not found and follow-up ≥2 y	0
Diagnostic level	
Definite ≥8	
Probable 6–7	
Possible 4–5	
Non-PNS ≤3	

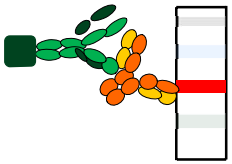
Abbreviation: PNS = paraneoplastic neurologic syndrome.
[a] See text for recommended diagnostic methods.

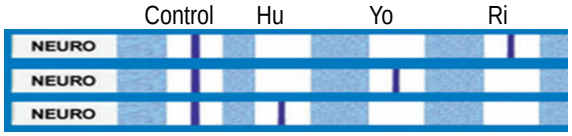
SIX TECHNIQUES FREQUENTLY USED TO DETECT ANTIBODIES IN AUTOIMMUNE NEUROLOGY



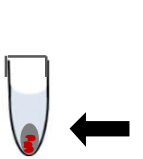
(A) Indirect immunohistochemistry

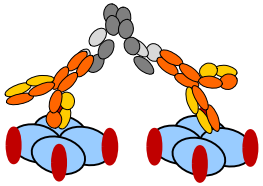




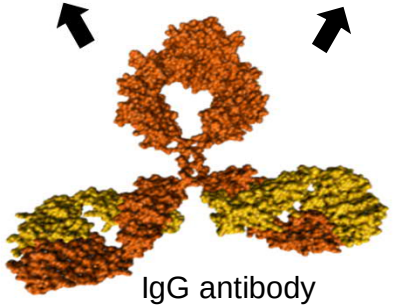


(B) Western or line blot

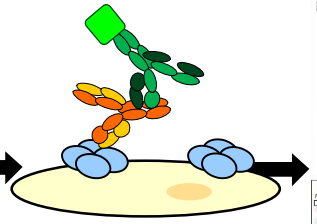


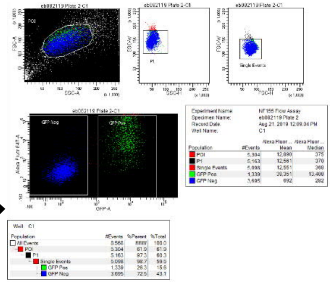


(C) Immunoprecipitation

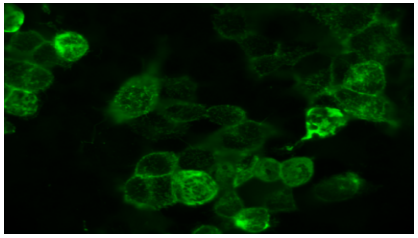


IgG antibody

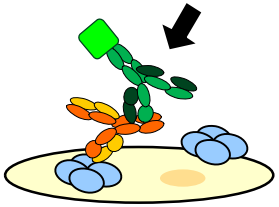


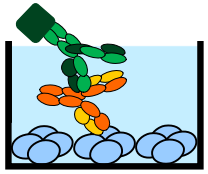


(D) Flowcytometry

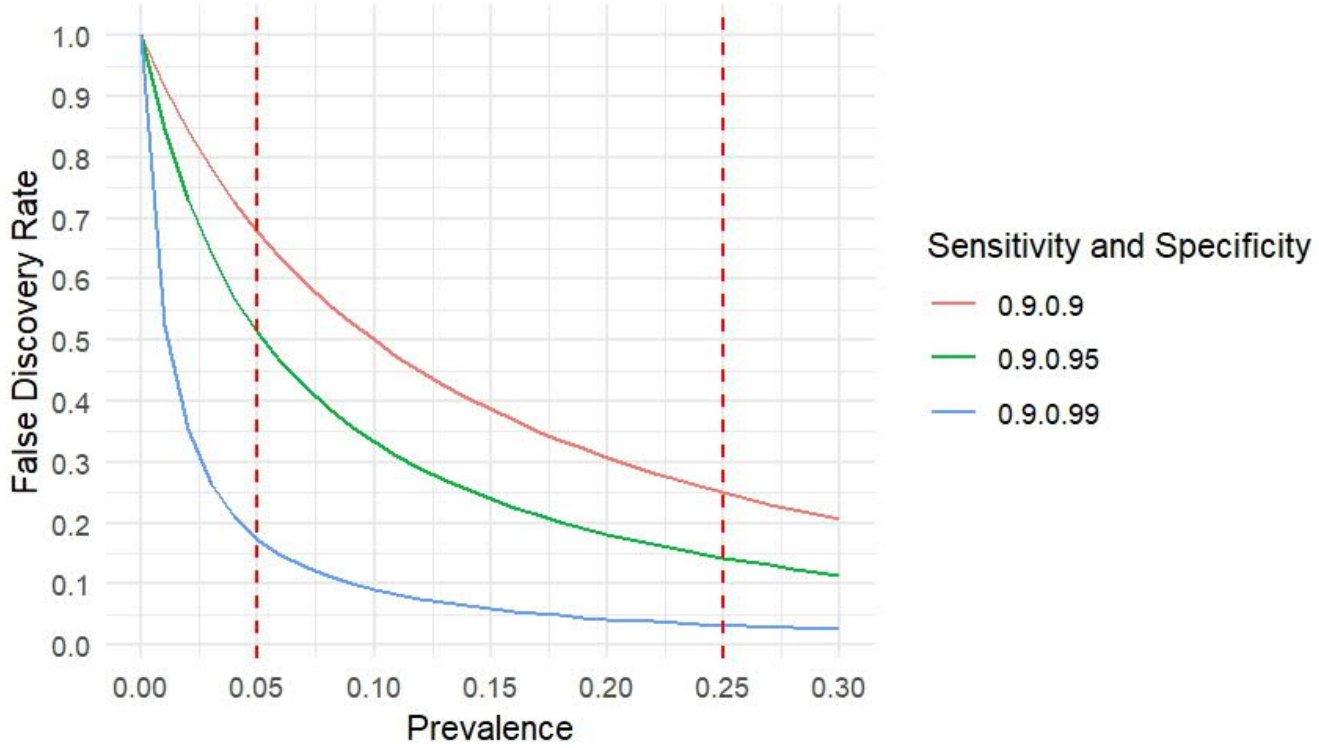


(E) Cell based assay/Flow cytometry





(F) ELISA



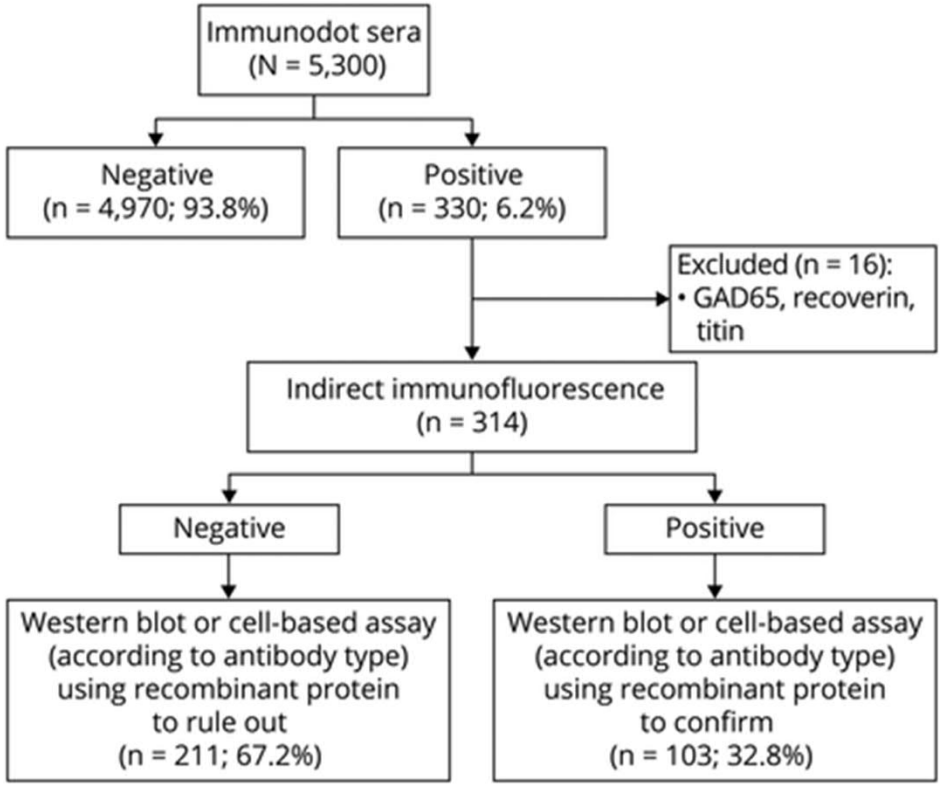
False discovery rate x disease prevalence

- Illustration of the relationship between false discovery rate (i.e., proportion of false positive tests) and disease prevalence:
  - blue: sensitivity 90%, specificity 99%;
  - green: sensitivity 90%, specificity 95%;
  - red: sensitivity 90%, specificity 90%.
- Notice the relatively *high false discovery rates with lower disease prevalences*, despite high assay specificities, in comparison to higher disease prevalence.
- Notice the *higher impact small changes in specificity have on false discovery rate in low prevalence* settings.

Jones FS & Dubey D. Neurology. 2025

SENSITIVITY/ SPECIFICITY/PPV VARIES

Assay utilized



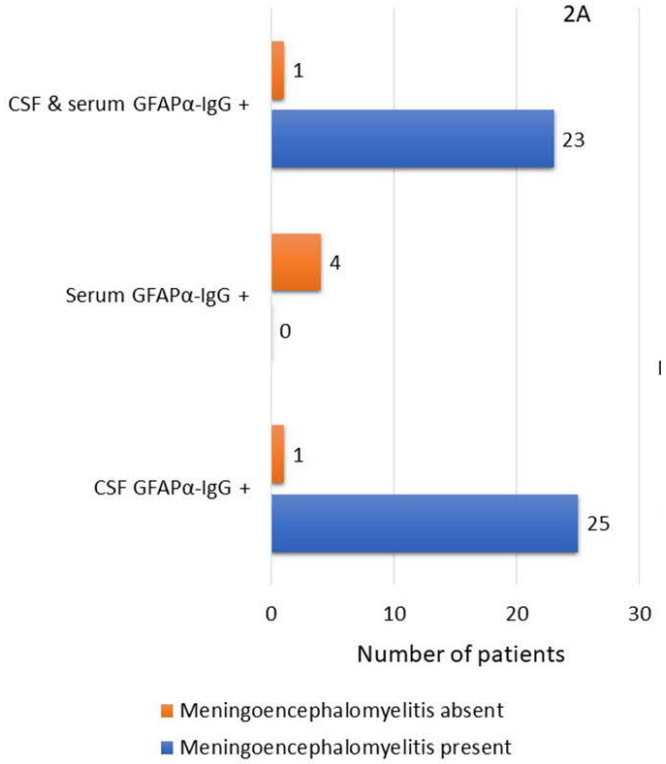
- Clinical data collected for:
  - 58 IFA positive immunodot + cases
  - 90 IFA negative immunodot + cases
- All patients with IFA confirmed presented clinical symptoms classically described with the identified antibody.
- *The clinical presentation of most **(84%)** of the IFA negative cases was incompatible with the antibody identified by immunodots.*

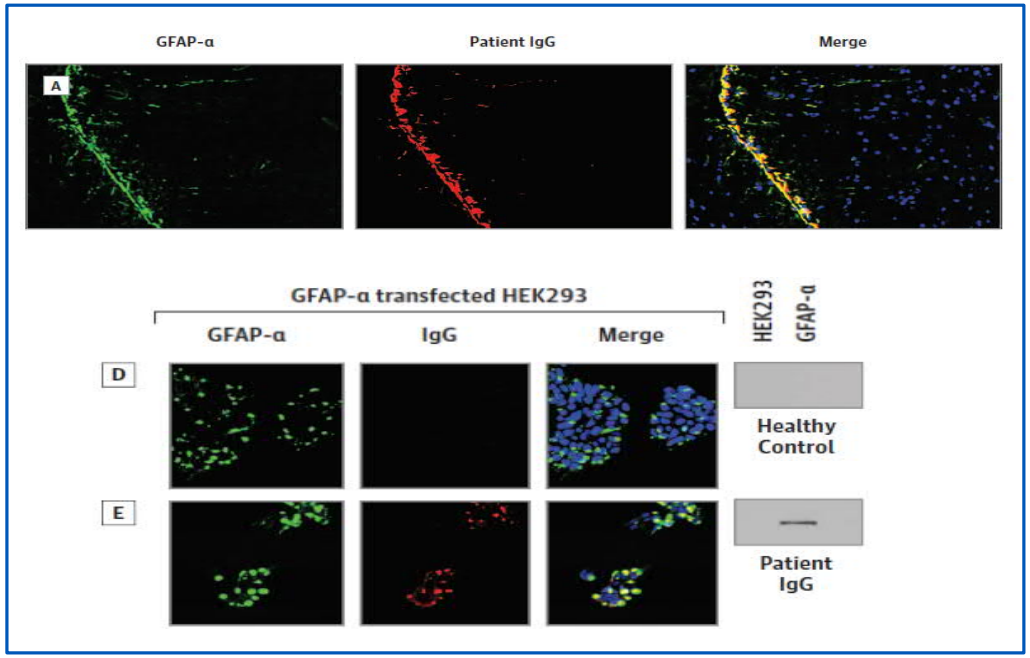
Déchelotte B, Et al. Neurol Neuroimmunol Neuroinflamm. 2020

SENSITIVITY/ SPECIFICITY/PPV VARIES

Antibody testing method and sample type

GFAP-IgG testing - CSF and + on 2 methods provides optimal testing methodology: >99% meningoencephalomyelitis





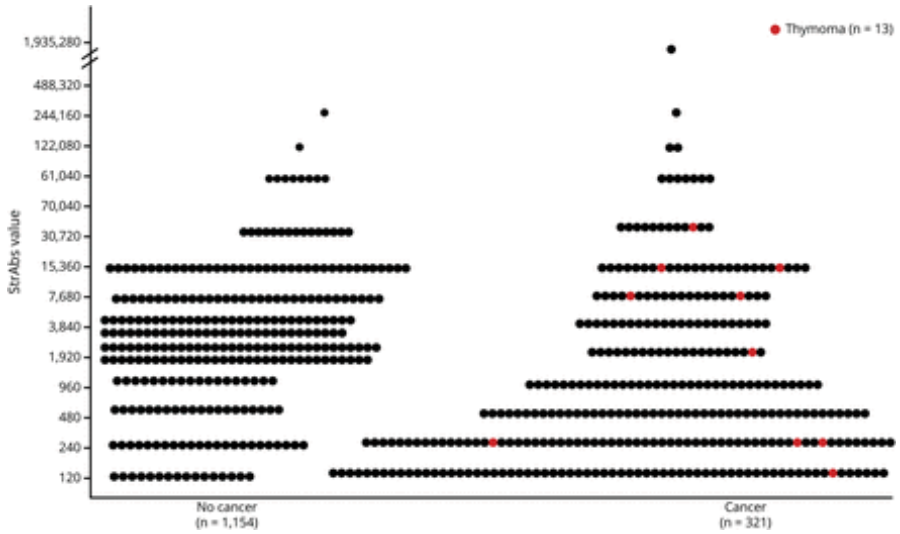
Dubey et al. JNI. 2018
Fang & Mckeon et al. JAMA Neurol. 2016

SENSITIVITY/ SPECIFICITY/PPV VARIES

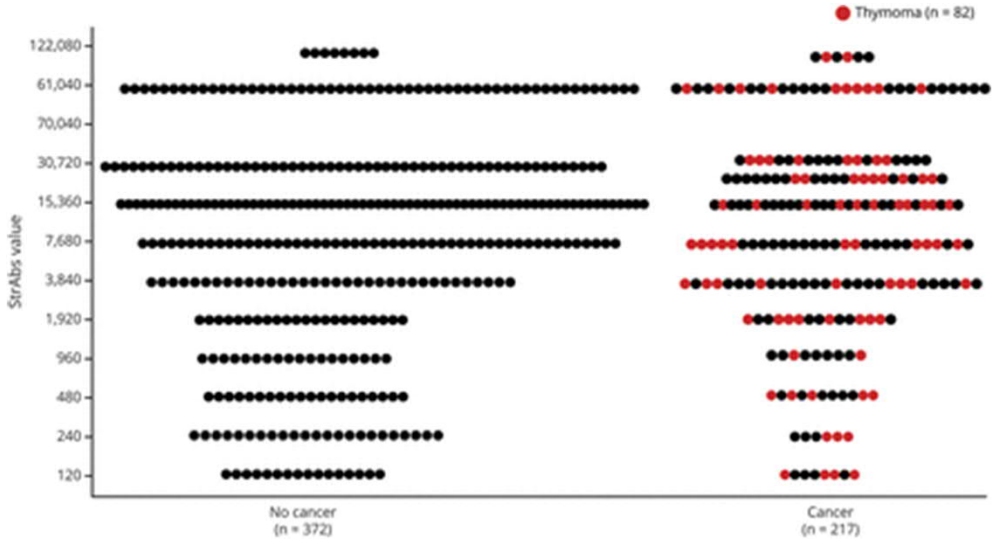
Antibodies with limited utility

Striational testing ***removed*** from evaluations

Striational antibody



Paraneoplastic evaluation



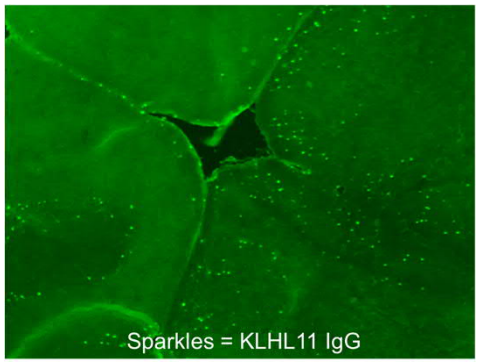
MG evaluation

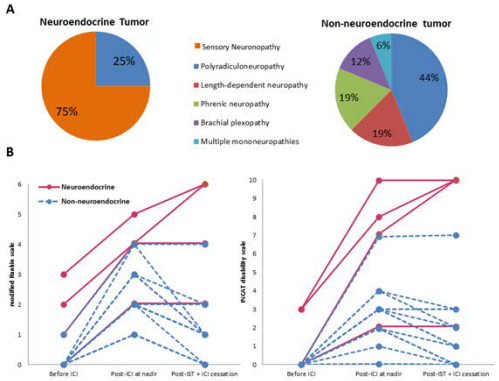
Shelly et al. Neurology. 2021

Take home points

	Points
Clinical level	
High-risk phenotypes	3
Intermediate-risk phenotypes	2
Defined phenotype epidemiologically not associated with cancer	0
Laboratory level[a]	
High-risk antibody (>70% cancer association)	3
Intermediate risk antibody (30%–70%)	2
Lower risk antibody (<30%) or negative	0
Cancer	
Found, consistent with phenotype and (if present) antibody, or not consistent but antigen expression demonstrated	4
Not found (or not consistent) but follow-up <2 y	1
Not found and follow-up ≥2 y	0

PNS CARE





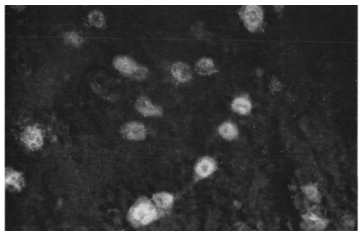
ICI Neurologic AE

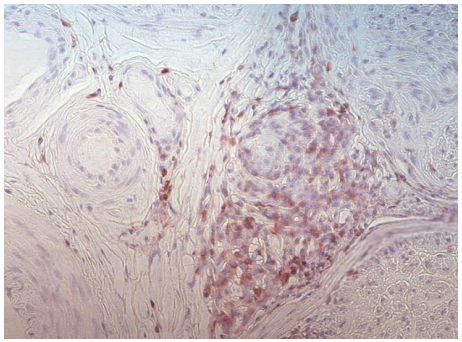
IMMUNOFLUORESCENT DETECTION OF ANTIBODIES AGAINST NEURONES IN SENSORY CARCINOMATOUS NEUROPATHY

BY

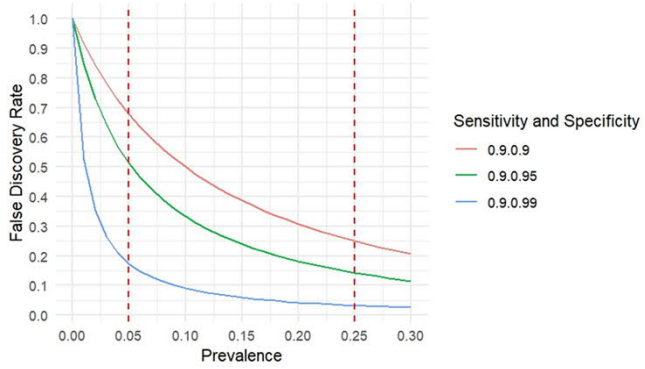
P. C. WILKINSON[1] AND J. ZEROMSKI[1]

University Department of Bacteriology, Western Infirmary, Glasgow





CRMP5 Polyradiculoneuropathy



THANK YOU!

QUESTIONS