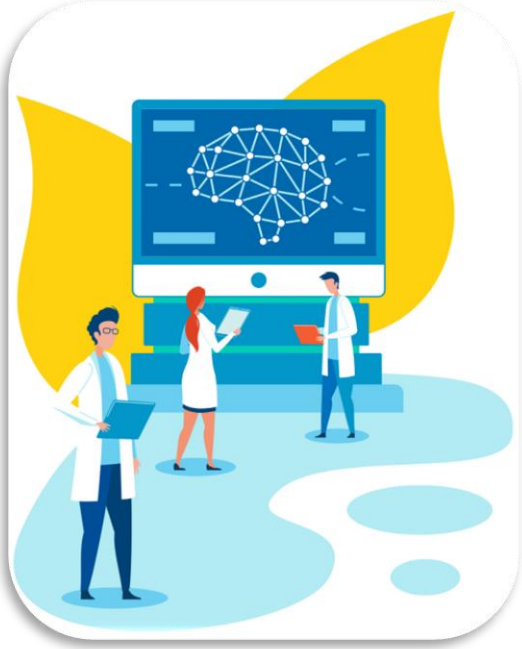
European Reference Network for rare or low prevalence complex diseases
Network Neurological Diseases (ERN-RND)

ean european academy of neurology

European Reference Network for rare or low prevalence complex diseases
Network Neuromuscular Diseases (ERN EURO-NMD)

Joint webinar series



Immune-mediated Choreas

Jan Lewerenz

University Hospital Ulm, Germany

DG ‚Chorea and HD'
21 January 2020

Speaker: Jan Lewerenz

Biography

Current Position	**Since 2011: Senior Attending Neurologist, Dept. Neurology, University Hospital Ulm (Chair Prof A.C. Ludolph)**
• **Since 2018**	**Co-Head of the Huntington's Disease Outpatient Clinic (Head Prof. G.B. Landwehrmeyer)**
• **Since 2015**	**Co-Head of the Cerebrospinal Fluid Laboratory (Head Prof. H. Tumani), special expertise: antineuronal and onconeuronal antibodies**
• **Since 2014**	**Head: Outpatient Clinic for Autoimmune Encephalitides and Paraneoplastic Neurological Disorders**
• 2013	Habilitation in Neurology, Ulm University
• 2011	Board Certification in Neurology
• 2000-2011	Neurology residency, Department of Neurology, University Hospital Hamburg-Eppendorf, (Chair: Prof. Dr. C. Gerloff)
• 2006-2008	Postdoctoral Research Associate, Cellular Neurobiology Laboratory, Salk Institute for Biological Studies, La Jolla, Ca, USA (Chair Prof. Schubert)
• 2003	Doctoral thesis, Dept. of Neurology, University of Hamburg
• 2003	Postgraduate education: Molecular Biology, Center for Molecular Neurobiology Hamburg
• 1992 - 1999	Medical School, Hamburg-Eppendorf, Germany
Other Positions	Extended Executive Board, German Association for Cerebrospinal Fluid Diagnostics
	Scientific Advisory Board, GENERATE (German Network for Research of Autoimmune Encephalitides

General information about the webinars

- RARE neurological, neuromuscular and movement disorders
- 30-35min presentation
- 15min Q&A session at the end (please write your questions in the Q&A)
- Target audience: neurologists, residents, paediatric neurologists, geneticists from RND members, RND affiliated partners, and non-RND HCPs across Europe and worldwide
- Recorded Webinar and presentation to be found at the latest 2 weeks after on: http://www.ern-rnd.eu/education-training/past-webinars/
- Post-webinar survey (2-3min): satisfaction, topic ideas for next webinars

Webinar outline

- **The Classics**
  - Sydenham‘s Chorea
  - Chorea associated with anti-phospholipid syndrome
- **Autoimmune choreas associated with specific antineuronal antibodies**
  - Paraneoplastic neurological syndromes with antibodies against intracellular antigens
  - Autoimmune encephalitides with antibodies against neuronal surface antigens

Learning objectives

By the end of this webinar you will be able to:

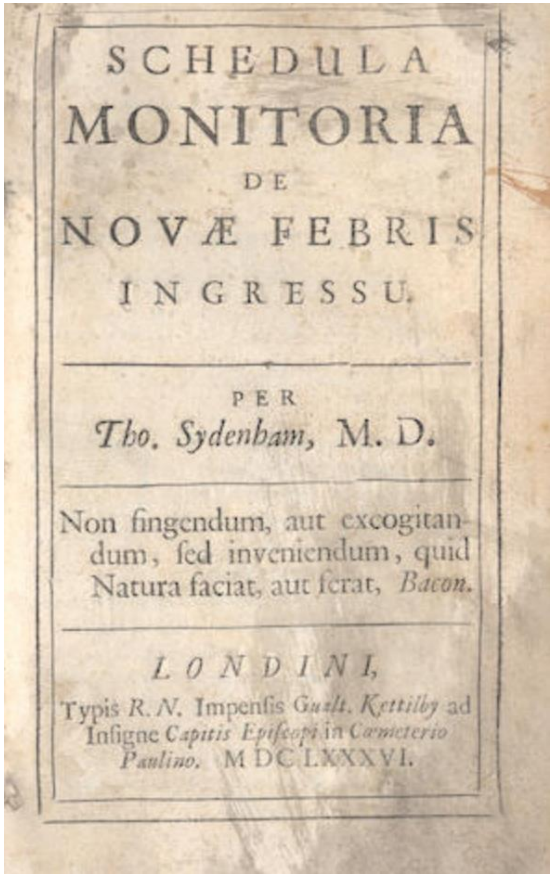
- identify red flags for potentially treatable choreatic movement disorders of autoimmune origin
- choose appropriate diagnostic tests to verify or exclude specific subtypes of autoimmune chorea
- state important therapeutic approaches

The audience

Q1: What is the best description for your profession?

a. Neurologist -> Movement disorders specialist
b. Neurologist -> Immunology specialist
c. Psychiatrist
d. Pediatrician
e. Nurse
f. Neuroscientist
g. other

The classics (part I): Chorea Sydenham



SCHEDULA
MONITORIA
DE
NOVÆ FEBRIS
INGRESSU.

PER
Tho. Sydenham, M. D.

Non fingendum, aut excogitandum, sed inveniendum, quid Natura faciat, aut ferat, *Bacon.*

LONDINI,
Typis *R. N.* Impensis *Guilt. Kettilby* ad Insigne *Capitis Episcopi* in *Cœmeterio Paulino.* M DC LXXXVI.

Erstbeschreibung 1686

*10. 09.1624 (Dorchester); † 29.12.1689 (London)

Pathogenesis of Sydenham‘s Chorea

- Post-infectious
- Group A β-hemolytic Streptococcus
- Immune-mediated dysfunction of striatal pathways as part of rheumatic fever

How to detect a recent Group A β-hemolytic streptococcus infection?

1. Increased or rising anti-streptolysin O titer oder other streptococcal antibodies (anti-DNASE B, rise is better than a single titer)
2. A positive throat culture for group A β-hemolytic streptococci
3. A positive rapid group A streptococcal carbohydrate antigen test in child with a high clinical pretest probability of a streptococcal pharyngitis

Gewitz et al.. Circulation 2015;131:1806-1818

Sydenham‘s chorea is one symptome complex of rheumatic fever!

The 2015 revised Jones criteria for acute rheumatic fever

A. Evidence of preceding group A streptococcal infection +

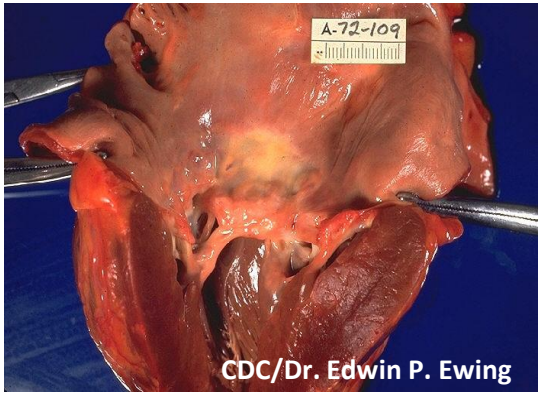
B. Major criteria

- Carditis (clinical and/or subclinical)
- Arthritis (polyarthritis only)
- Chorea
- Erythema marginatum
- Subcutaneous nodules

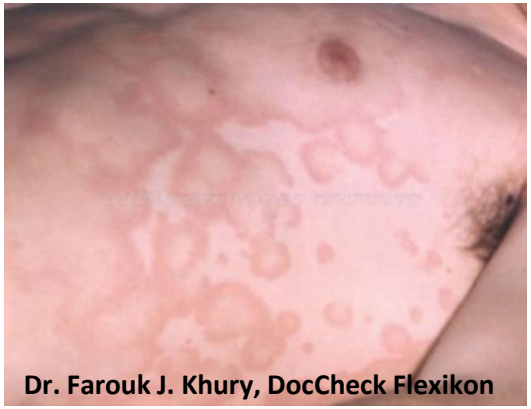
C. Minor criteria

- Polyarthralgia
- Fever (≥38.5°C)
- ESR ≥ 60 mm/h and/or CRP ≥3.0 mg/dl
- Prolonged PR interval (unless carditis is present)

Required for the diagnosis of acute rheumatic fever: 2 major or 1 major+2 mi



CDC/Dr. Edwin P. Ewing


Dr. Farouk J. Khury, DocCheck Flexikon

Gewitz et al. Circulation. 2015;131:1806-1818

How often do patients with rheumatic fever have Sydenham‘s chorea?

- Annual incidence of ARF 3.2-9.6 per 100.000 5-14 years old children in Northern Italy (Licciardi et al., J Pediatr 2018 Jul;198:25-28.e1.)
- Relative frequency of the major criteria (Gewitz et al. Circulation. 2015;131:1806-1818)
  - carditis (50%–70%)
  - arthritis (35%–66%)
  - chorea (10%–30%,female predominance)
  - subcutaneous nodules (0%–10%)
  - erythema marginatum(<6%)

Clinical findings patients with rheumatic fever with and without in Sydenham‘s chorea

TABLE 2. *Findings on neurologic examination*[a]

	Total	Chorea	No chorea
Number of patients	50	13	37
Dysarthria	2 (4)	2 (15.4)	0
Hypotonia	10 (20)	9 (69.2)	1 (2.7)
Motor impersistence	5 (10)	4 (30.8)	1 (2.7)
Hang-up reflexes	4 (8)	4 (30.8)	0
Hypometric saccades	10 (20)	5 (38.5)	5 (13.5)
Oculogyric crisis	1 (2)	1 (7.7)	0

[a] Percentages are within parentheses.

Cardoso et al., Movement Disorders 1997; 12(5): 701-703

Neuropsychiatric findings in Sydenham‘s chorea

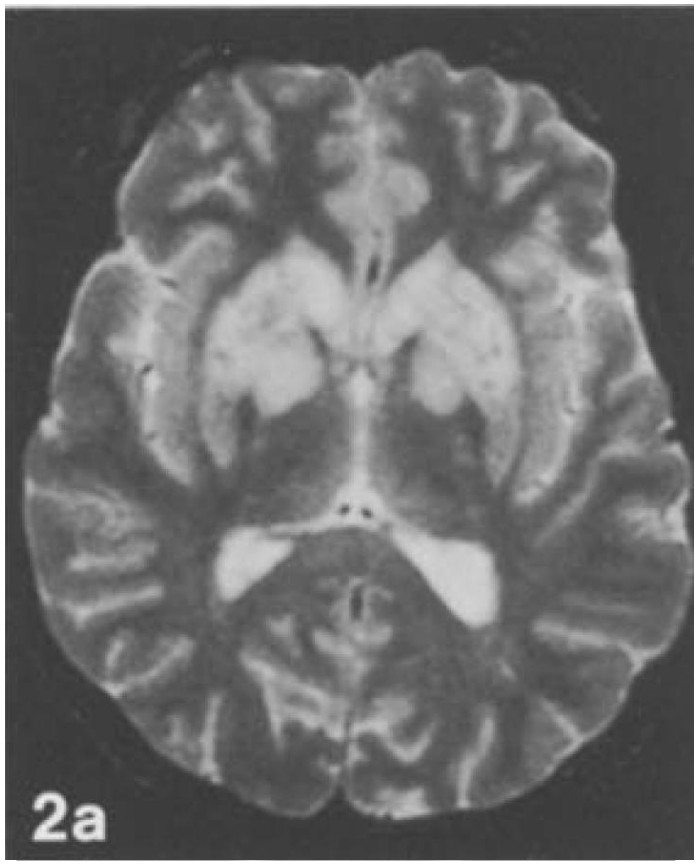
Children with Syndenham‘s chorea were found to be more likely to experience

– major depressive disorder
– tic disorders
– attention deficit hyperactivity disorder (ADHD)

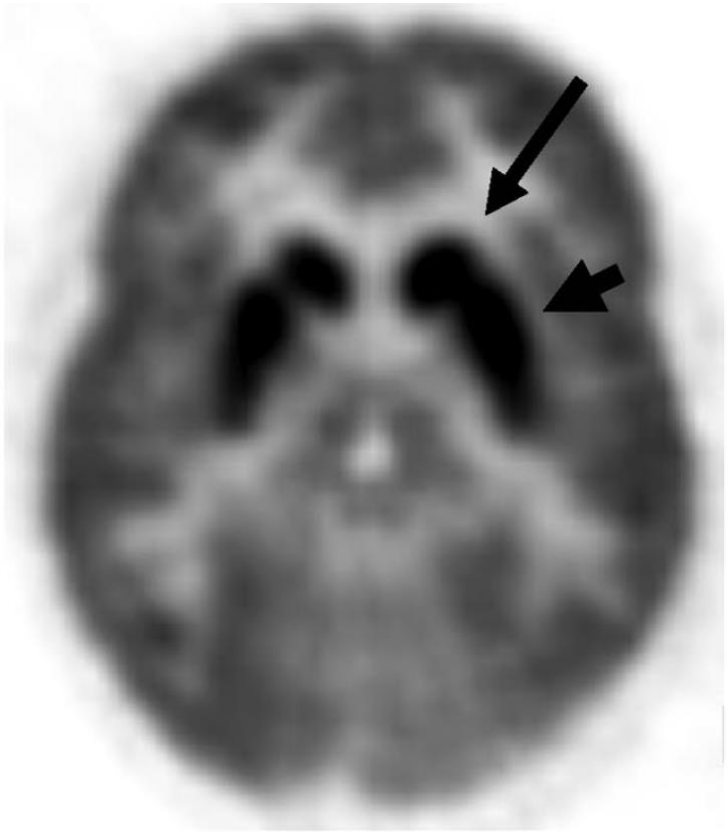
than both healthy childen and those with acute rheumatic fever without chorea

Am J Psychiatry. 2000 Dec;157(12):2036-8.Mercadante

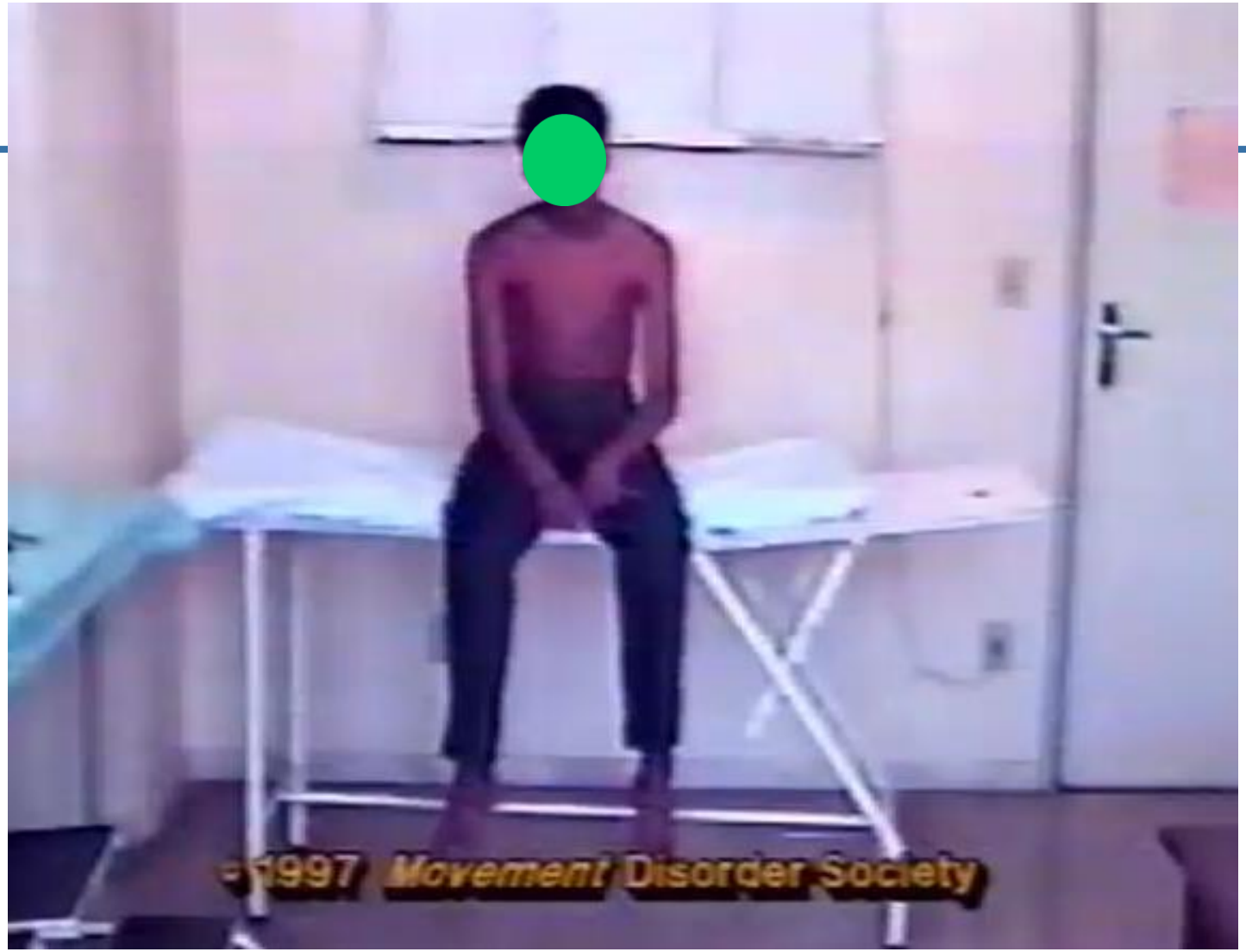
Imaging studies in Sydenham‘s chorea



Heye et aJ. Neurol (1993) 240 : 121-12



Ho Clin Nucl Med. 2009 Feb;34(2):114-6.



Cardoso et al., Movement Disorders 1997; 12(5): 701-703

Treatment and outcome

- Eradication of streptococci (penicillin, in some cases tonsillectomy)
- Cardiac work-up
- Long-term penicillin treatment to prevent relapses (until the age of 21)
- Steroids, NSARs
- Chorea: valproid acid, carbamazepine, neuroleptics

Outcome: Remission without residual neurological impairment in 90%

Immunosuppressive treatment

Placebo-controlled trial, 37 patients , 4 weeks 2mg/kg body weight prednisone

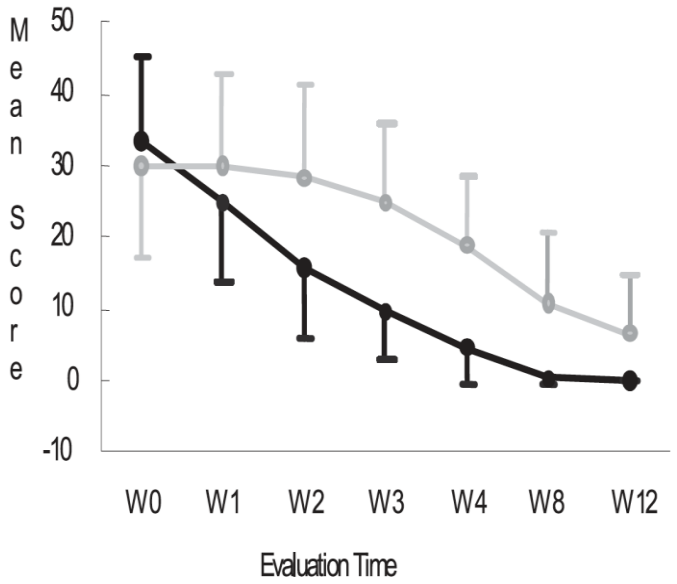


Table 3. Weekly rate improvement of chorea intensity score, for prednisone and placebo groups

Week	Total	Prednisone	Placebo	*P*
1	−16.3	−25.5	−1.1	<0.001
2	−34.8	−53	−4.8	<0.001
3	−51.5	−71.8	−18.2	<0.001
4	−65.5	−85	−33.4	<0.001
8	−86.3	−98.6	−65.9	<0.001
12	−79.8	−100	−79.8	<0.001

Paz et al. Pediatr Neurol 2006;34:264-269.

Pathophysiology: cross-reacting antibodies?

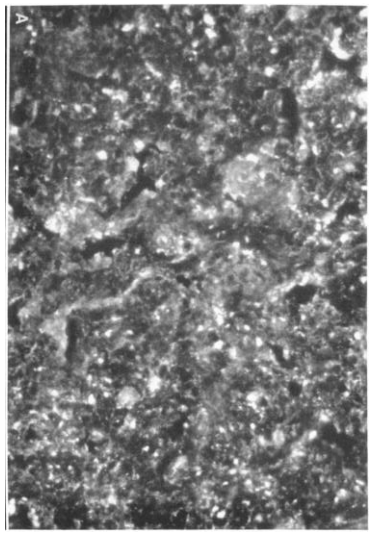
0022-1767/93/1515-2820$02.00/0
The Journal of Immunology

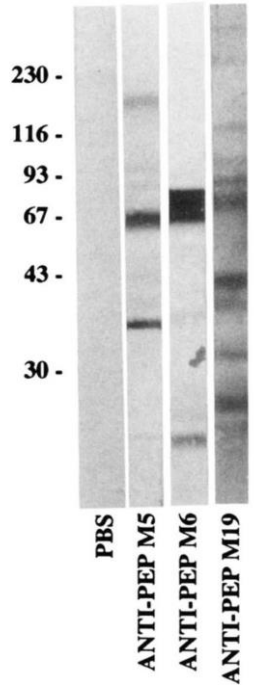
Vol 151, 2820–2828, No. 5, September 1, 1993
Printed in U.S.A.

Epitopes of Streptococcal M Proteins that Evoke Antibodies that Cross-React with Human Brain[1]

Michael S. Bronze and James B. Dale[2]

Department of Veterans Affairs Medical Center and the Department of Medicine, University of Tennessee, Memphis, TN 38104





DG ‚Chorea and HD‘
21 January 2020

Nester et al. Microbiology 2-28602-01 Figure 23.7

What are the target antigens?

nature medicine

Gangliosides?

Mimicry and autoantibody-mediated neuronal cell signaling in Sydenham chorea

Christine A Kirvan[1], Susan E Swedo[2], Janet S Heuser[1] & Madeleine W Cunningham[1]

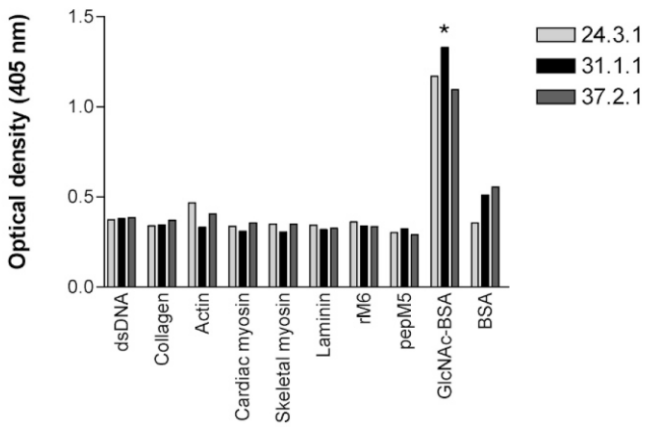


Table 2 Lysoganglioside GM1 inhibition of acute chorea sera binding to GlcNAc-BSA

Acute serum	Lysoganglioside GM1 (μg/ml)[a]
60	7.3
61	6.9
101	79.4
118	11.4
123	108.3
A1	20.3

Kirvan et al., Nat Med. 2003 Jul;9(7):914-20.

What are the target antigens?

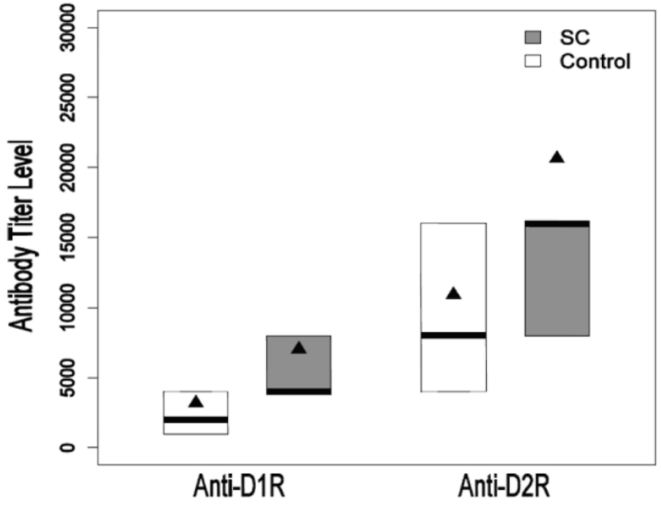
OPEN ACCESS Freely available online

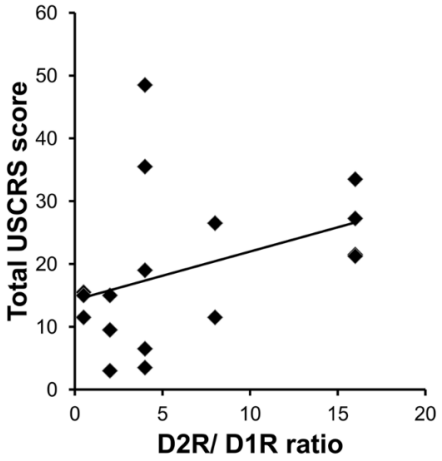
Dopamin receptors?

PLOS ONE

Dopamine Receptor Autoantibodies Correlate with Symptoms in Sydenham's Chorea

Hilla Ben-Pazi[1]*, Julie A. Stoner[2], Madeleine W. Cunningham[3]





Ben-Pazi et al., PLoS One 2013 Sep 20;8(9):e73516

Institutional Logo,
‚Speakers' picture or disease related picture

Basal ganglia antibodies in Sydenham's chorea: A road to nowhere?

Chorea in Lupus erythematodes and anti-phospholipid syndrome

- Initial description in 1987 by Asherson et al. in SLE + antiphospholipid antibodies[1]
- Later described also in primary APS[2]
- <4% of SLE patients develop chorea[2]
- 70% SLE or “Lupus-like“ disease, 30% primary APS[2]
- Female/male ratio >20:1[2]
- Median age 23 ±12 years[2]

[1]Asherson et al., Semin Arthritis Rheum 1987 May;16(4):253-9.
[2]Cervera et al. Medicine (Baltimore). 1997 May;76(3):203-12.

Accompanying clinical manifestations

Several other manifestations of APS in most patients:

- Ischemic stroke (~25%)
- Deep vein thrombosis (~25%)
- Miscarriages (~20%)
- Peripheral artery occlusion (~5%)
- Myocardial infarction (~5%)

Manifestations of SLE in many patients:

- Polyarthritis/-arthralgia (~30%)
- Nephritis (~30%)
- Serositis, pericarditis/pleuritis (~10%)
- Valve lesions (~10%)

Other

- Migraine (~10%)
- Psychosis (~5%)

Cervera et al. Medicine (Baltimore). 1997 May;76(3):203-12.

Laboratory findings and imaging

Laboratory findings[1]

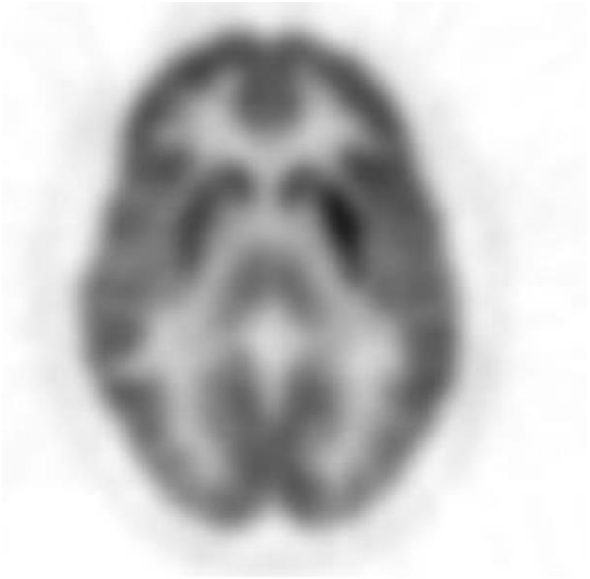
- Lupus anticoagulans (~90%)
- Anti-Cardiolipin-Abs (~90%) + b_2-Glykoprotein Abs
- Anti-nuclear Abs (~80%)
- Ds-DNA Abs (~80%)
- Thrombocytopenia (~50%)
- Hemolytic anemia (~5%)

Cerebral MRI[1]

- Normal (~40%)
- Subcortical and basal ganglia postischemic lesions (~60%)

PET[2]

- Contralateral glucoce hypermetabolism



[1]Cervera et al. Medicine (Baltimore). 1997 May;76(3):203-12,
[2]Wu et al., Movement Disorders, Vol. 22, No. 12, 2007

Clinical course

- Mostly first presentation of APS
- Episodic (mostly 1, 30% >1)
- Sometimes exacerbate by oral co
- 50% bilateral chorea / 50% hemichorea
- Other neurologic disturbance due to ischemic leasion in ~25%
- Responsive to steroid /neuroleptics

Mechanism: unknown

Cervera et al. Medicine (Baltimore). 1997 May;76(3):203-12.

Q2- Which answer is correct?

Brain-specific antibodies found in Sydenham‘s chorea

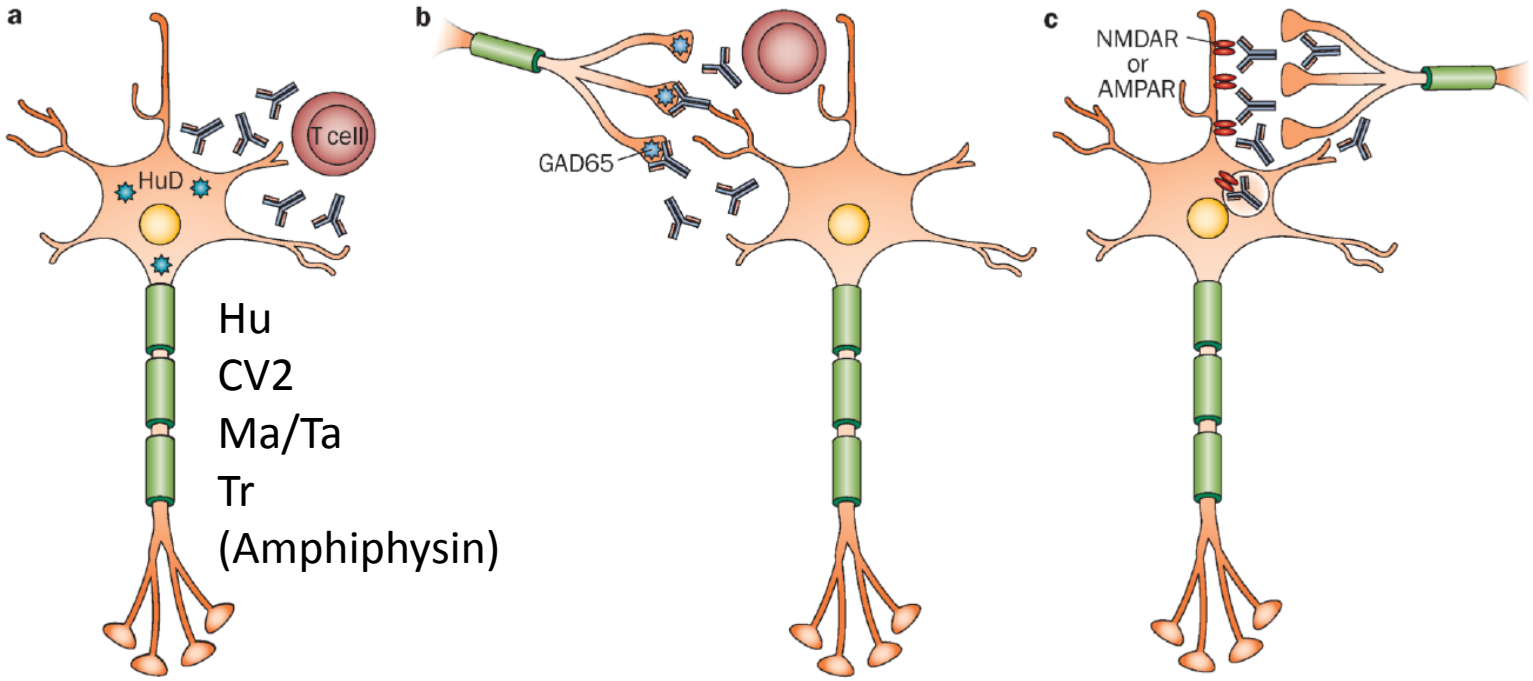
a. are essential for the diagnosis of both diseases

b. have been reproducibly shown to target gangliosides

c. have been published to bind to diverse brain-specific targets, however not resulting in a specific routine diagnostic test

d. lead to irreversible basal ganglia damage

Part II: Autoimmune choreas associated with specific antineuronal antibodies



Hu
CV2
Ma/Ta
Tr
(Amphiphysin)

Lancaster & Dalmau, Nat Rev Neurol. 2012 Jun 19;8(7):380-90.

Patients with paraneoplastic chorea in the PNS EuroNetwork registry

11 of 913 patients had chorea (1.2%)

Table 1 Data of PNS EuroNetwork patients

Case	Sex, age (years)	Type of chorea	Associated syndrome	Tumor and delay[d]	Antibody	CSF	MRI	Response to cancer therapy	Outcome
Definite paraneoplastic chorea									
1	M, 63	Classical chorea	Previous PN	SCLC 1 month after	CV2/CRMP5		Diffuse leukoencephalopathy. Gadolinium enhancement. After few months lenticular hypointensity	No response	Alive after 5 years
2	M, 54	Classical chorea	Myoclonus	SCLC 16 months after	CV2/CRMP5	[a]Cells 5 Prot:58	Normal	Mild response	Death from tumor after 23 months
3[b]	F, 49	Classical chorea	PN Opsoclonus	SCLC 1 month after	Hu/ANNA1	[b]Cells:0 Prot: 5 OB:+: 9	Diffuse leuko-encephalopathy	Mild response	Death from tumor after 19 months
4	M, 78	Classical chorea	–	NSCLC 1 month after	CV2/CRMP5	–	Normal	No response	Death from tumor after 15 months
5	M, 77	Cl		SCLC 3 months after	Hu/ANNA1 CV2/CRMP5	–	Mild frontal atrophy	No response	Death from tumor after 14 months
6[c]	M, 81	O		SCLC 1 month before	CV2/CRMP5	–	Diffuse leuko-encephalopathy	Mild response	Dead after 3 months
7	M, 77	Cl		SCLC 7 months after	CV2/CRMP5		Normal	No response	Alive after 24 months
8	F, 76	Classical chorea	–	Kidney cancer 4 months after	CV2/CRMP5	Cells: 3 Prot: n.n.	Diffuse leuko-encephalopathy; bilateral hyperintensity of BG (after 4 months)	No therapy	Alive after 18 months
9	M, 65	Oral dyskinesia, slow speech, vocal tics and gnashing of teeth	LE PN	SCLC 4 months after	Hu/ANNA1 CV2/CRMP5	[a]Cells:55 Prot: 1 OB: +	Normal	Good response	Death from PNS after 9 months
10	M, 75	Unilateral chorea	Cognitive disorders	Colon cancer 4 months after	Hu/ANNA1	–	Temporobasal and temporomesial bilateral hyperintensity	No therapy	Death from PNS after 6 months
Possible paraneoplastic chorea									
11	F, 73	Classical chorea		SCLC 17 months before	No Ab	Cells: 1 Prot:40	Normal	No response	
12[b]	F, 59	Cervical dystonia and choreic jerks at left shoulder	Anxiety	Colon cancer 7 months after	No Ab	[a]Cells:1 Prot:60 ↑ IgG index	Normal	No response	Death from tumor after 15 months
13	M, 82	Classical chorea	LE	Colon cancer 6 months after	No Ab	Cells: 3 Prot:49 OB: neg	MRI:NA CT: Normal	No therapy	Death from tumor after 1 month

PN polyneuropathy, *CT* computed tomography, *MRI* magnetic resonance imaging, *OCD* obsessive–compulsive disorder, *LE* limbic encephalitis, *SCLC* small cell lung cancer, *NSCLC* non small cell lung cancer, *CSF* cerebrospinal fluid, *Cell* X cell/mm^3, *Prot* proteins mg/dl, *OB* oligoclonal bands, *IgG* intravenous immunoglobulins, *BG* basal ganglia, *PNS* paraneoplastic neurological syndrome, *NA* not available

[a] Pathologic CSF

Mostly 60 yrs +
9/13 male

Vigliani et al., Neurol 2011; 258:2058–2068

Patients with paraneoplastic chorea in the PNS EuroNetwork registry

11 of 913 patients had chorea (1.2%)

Table 1 Data of PNS EuroNetwork patients

Case	Sex, age (years)	Type of chorea	Associated syndrome	Tumor and delay[d]	Antibody	CSF	MRI	Response to cancer therapy	Outcome
Definite paraneoplastic chorea									
1	M, 63	Classical chorea	Previous PN	SCLC 1 month after	CV2/CRMP5		Diffuse leukoencephalopathy. Gadolinium enhancement. After few months lenticular hypointensity	No response	Alive after 5 years
2	M, 54	Classical chorea	Myoclonus	SCLC 16 months after	CV2/CRMP5	[a]Cells 5 Prot:58	Normal	Mild response	Death from tumor after 23 months
3[b]	F, 49	Classical chorea	PN Opsoclonus	SCLC 1 month after	Hu/ANNA1	[b]Cells:0 Prot: 5 OB:+: 9	Diffuse leuko-encephalopathy	Mild response	Death from tumor after 19 months
4	M, 78	Classical chorea	–	NSCLC 1 month after	CV2/CRMP5	–	Normal	No response	Death from tumor after 15 months
5	M, 77	Classical chorea	–	SCLC 3 months after	Hu/ANNA1 CV	–	Mild frontal atrophy	No response	Death from tumor after 14 months
6[c]	M, 81	Oral dyskinesia cervical dystonia	OCD PN	SCLC 1 month before	CV2/		Diffuse leuko-encephalopathy	Mild response	Dead after 3 months
7	M, 77	Classical chorea	–	SCLC 7 months after	CV2/CRMP5		Normal	No response	Alive after 24 months
8	F, 76	Classical chorea	–	Kidney cancer 4 months after	CV2/CRMP5	Cells: 3 Prot: n.n.	Diffuse leuko-encephalopathy; bilateral hyperintensity of BG (after 4 months)	No therapy	Alive after 18 months
9	M, 65	Oral dyskinesia, slow speech, vocal tics and gnashing of teeth	LE PN	SCLC 4 months after	Hu/ANNA1 CV2/CRMP5	[a]Cells:55 Prot: 1 OB: +	Normal	Good response	Death from PNS after 9 months
10	M, 75	Unilateral chorea	Cognitive disorders	Colon cancer 4 months after	Hu/ANNA1	–	Temporobasal and temporomesial bilateral hyperintensity	No therapy	Death from PNS after 6 months
Possible paraneoplastic chorea									
11	F, 73	Classical chorea		SCLC 17 months before	No Ab	Cells: 1 Prot:40	Normal	No response	
12[b]	F, 59	Cervical dystonia and choreic jerks at left shoulder	Anxiety	Colon cancer 7 months after	No Ab	[a]Cells:1 Prot:60 ↑ IgG index	Normal	No response	Death from tumor after 15 months
13	M, 82	Classical chorea	LE	Colon cancer 6 months after	No Ab	Cells: 3 Prot:49 OB: neg	MRI:NA CT: Normal	No therapy	Death from tumor after 1 month

8/13 SCLC

PN polyneuropathy, *CT* computed tomography, *MRI* magnetic resonance imaging, *OCD* obsessive–compulsive disorder, *LE* limbic encephalitis, *SCLC* small cell lung cancer, *NSCLC* non small cell lung cancer, *CSF* cerebrospinal fluid, *Cell* X cell/mm^3, *Prot* proteins mg/dl, *OB* oligoclonal bands, *IgG* intravenous immunoglobulins, *BG* basal ganglia, *PNS* paraneoplastic neurological syndrome, *NA* not available

[a] Pathologic CSF

Vigliani et al., Neurol 2011; 258:2058–2068

Patients with paraneoplastic chorea in the PNS EuroNetwork registry

11 of 913 patients had chorea (1.2%)

Table 1 Data of PNS EuroNetwork patients

Case	Sex, age (years)	Type of chorea	Associated syndrome	Tumor and delay[d]	Antibody	CSF	MRI	Response to cancer therapy	Outcome
Definite paraneoplastic chorea									
1	M, 63	Classical chorea	Previous PN	SCLC 1 month after	CV2/CRMP5		Diffuse leukoencephalopathy. Gadolinium enhancement. After few months lenticular hypointensity	No response	Alive after 5 years
2	M, 54	Classical chorea	Myoclonus	SCLC 16 months after	CV2/CRMP5	[a]Cells 5 Prot:58	Normal	Mild response	Death from tumor after 23 months
3[b]	F, 49	Classical chorea	PN Opsoclonus	SCLC 1 month after	Hu/ANNA1	[b]Cells:0 Prot: 5 OB:+: 9	Diffuse leuko-encephalopathy	Mild response	Death from tumor after 19 months
4	M, 78	Classical chorea	–	NSCLC 1 month after	CV2/CRMP5	–	Normal	No response	Death from tumor after 15 months
5	M, 77	Classical chorea	–	SCLC 3 months after	Hu/ANNA1 CV2/CRMP5	–	Mild frontal atrophy	No response	Death from tumor after 14 months
6[c]	M, 81	Oral dyskinesia cervical dystonia	OCD PN	SCLC 1 month before	CV2/CRMP5	–	Diffuse leuko-encephalopathy	Mild response	Dead after 3 months
7	M, 77	Classical chorea	–	SCLC 7 months after	CV2/CRMP5		Normal	No response	Alive after 24 months
8	F, 76	Classical chorea	–	Kidney cancer 4 months after	CV2/CRMP5	Cells: 3 Prot: n.n.	Diffuse leuko-encephalopathy; bilateral hyperintensity of BG (after 4 months)	No therapy	Alive after 18 months
9	M, 65	Oral dyskinesia, slow speech, vocal tics and gnashing of teeth	LE PN	SCLC 4 months after	Hu/ANNA1 CV2/CRMP5	[a]Cells:55 Prot: 1 OB: +	Normal	Good response	Death from PNS after 9 months
10	M, 75	Unilateral chorea	Cognitive disorders	Colon cancer 4 months after	Hu/ANNA1	–	Temporobasal and temporomesial bilateral hyperintensity	No therapy	Death from PNS after 6 months
Possible paraneoplastic chorea									
11	F, 73	Classical chorea		SCLC 17 months before	No Ab	Cells: 1 Prot:40	Normal	No response	
12[b]	F, 59	Cervical dystonia and choreic jerks at left shoulder	Anxiety	Colon cancer 7 months after	No Ab	[a]Cells:1 Prot:60 ↑ IgG index	Normal	No response	Death from tumor after 15 months
13	M, 82	Classical chorea	LE	Colon cancer 6 months after	No Ab	Cells: 3 Prot:49 OB: neg	MRI:NA CT: Normal	No therapy	Death from tumor after 1 month

PN polyneuropathy, *CT* computed tomography, *MRI* magnetic resonance imaging, *OCD* obsessive–compulsive disorder, *LE* limbic encephalitis, *SCLC* small cell lung cancer, *NSCLC* non small cell lung cancer, *CSF* cerebrospinal fluid, *Cell* X cell/mm^3, *Prot* proteins mg/dl, *OB* oligoclonal bands, *IgG* intravenous immunoglobulins, *BG* basal ganglia, *PNS* paraneoplastic neurological syndrome, *NA* not available

[a] Pathologic CSF

Vigliani et al., Neurol 2011; 258:2058–2068

Patients with paraneoplastic chorea in the PNS EuroNetwork registry

11 of 913 patients had chorea (1.2%)

Table 1 Data of PNS EuroNetwork patients

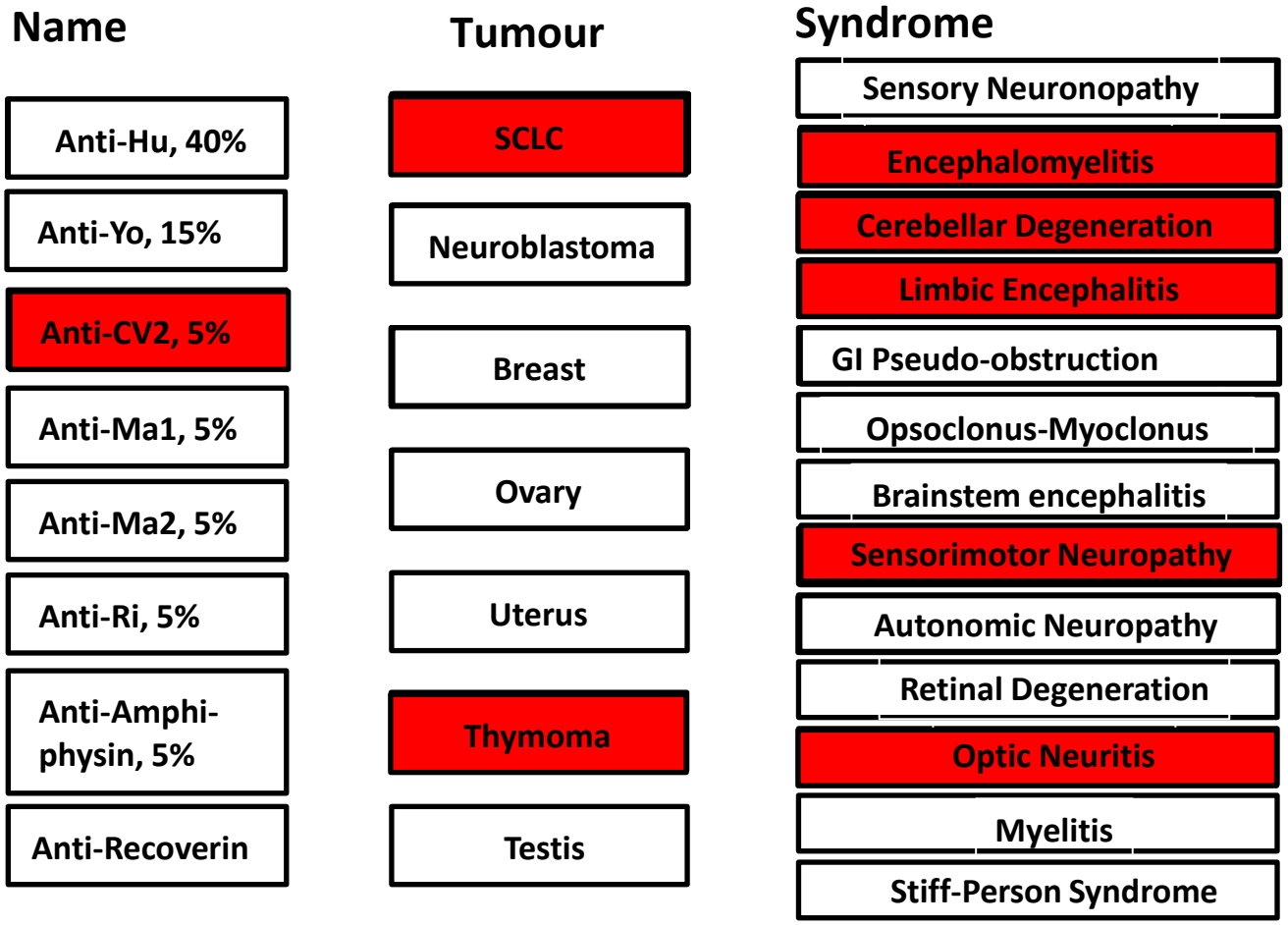
Case	Sex, age (years)	Type of chorea	Associated syndrome	Tumor and delay[d]	Antibody	CSF	MRI	Response to cancer therapy	Outcome
Definite paraneoplastic chorea									
1	M, 63	Classical chorea	Previous PN	SCLC 1 month after	CV2/CRMP5		Diffuse leukoencephalopathy. Gadolinium enhancement. After few months lenticular hypointensity	No response	Alive after 5 years
2	M, 54	Classical chorea	Myoclonus	SCLC 16 months after	CV2/CRMP5	[a]Cells 5 Prot:58	Normal	Mild response	Death from tumor after 23 months
3[b]	F, 49	Classical chorea	PN Opsoclonus	SCLC 1 month after	Hu/ANNA1	[b]Cells:0 Prot: 5 OB:+: 9	Diffuse leuko-encephalopathy	Mild response	Death from tumor after 19 months
4	M, 78	Classical chorea	–	NSCLC 1 month after	CV2/CRMP5	–	Normal	No response	Death from tumor after 15 months
5	M, 77	Classical chorea	–	SCLC 3 months after	Hu/ANNA1 CV2/CRMP5	–	Mild frontal atrophy	No response	Death from tumor after 14 months
6[c]	M, 81	Oral dyskinesia cervical dystonia	OCD PN	SCLC 1 month before	CV2/CRMP5	–	Diffuse leuko-encephalopathy	Mild response	Dead after 3 months
7	M, 77	Classical chorea	–	SCLC 7 months after	CV2/CRMP5		Normal	No response	Alive after 24 months
8	F, 76	Classical chorea	–	Kidney cancer 4 months after	CV2/CRMP5	Cells: 3 Prot: n.n.	Diffuse leuko-encephalopathy; bilateral hyperintensity of BG (after 4 months)	No therapy	Alive after 18 months
9	M, 65	Oral dyskinesia, slow speech, vocal tics and gnashing of teeth	LE PN	SCLC 4 months after	Hu/ANNA1 CV2/CRMP5	[a]Cells:55 Prot: 1 OB: +	Normal	Good response	Death from PNS after 9 months
10	M, 75	Unilateral chorea	Cognitive disorders	Colon cancer 4 months after	Hu/ANNA1	–	Temporobasal and temporomesial bilateral hyperintensity	No therapy	Death from PNS after 6 months
Possible paraneoplastic chorea									
11	F, 73	Classical chorea		SCLC 17 months before	No Ab	Cells: 1 Prot:40	Normal	No response	
12[b]	F, 59	Cervical dystonia and choreic jerks at left shoulder	Anxiety	Colon cancer 7 months after	No Ab	[a]Cells:1 Prot:60 ↑ IgG index	Normal	No response	Death from tumor after 15 months
13	M, 82	Classical chorea	LE	Colon cancer 6 months after	No Ab	Cells: 3 Prot:49 OB: neg	MRI:NA CT: Normal	No therapy	Death from tumor after 1 month

PN polyneuropathy, *CT* computed tomography, *MRI* magnetic resonance imaging, *OCD* obsessive–compulsive disorder, *LE* limbic encephalitis, *SCLC* small cell lung cancer, *NSCLC* non small cell lung cancer, *CSF* cerebrospinal fluid, *Cell* X cell/mm^3, *Prot* proteins mg/dl, *OB* oligoclonal bands, *IgG* intravenous immunoglobulins, *BG* basal ganglia, *PNS* paraneoplastic neurological syndrome, *NA* not available

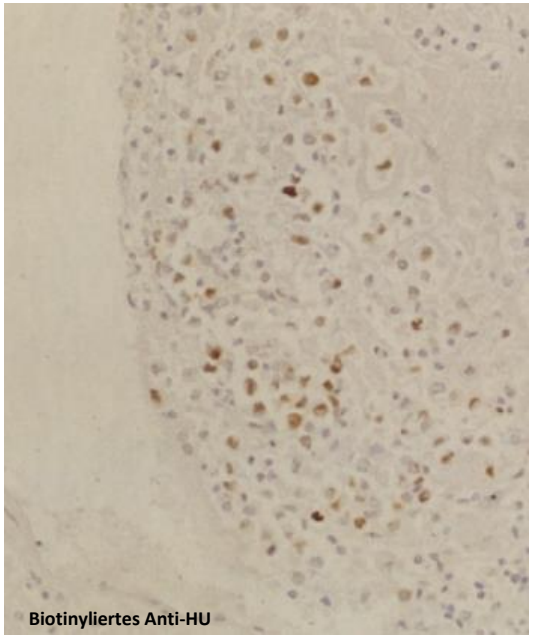
[a] Pathologic CSF

Vigliani et al., Neurol 2011; 258:2058–2068

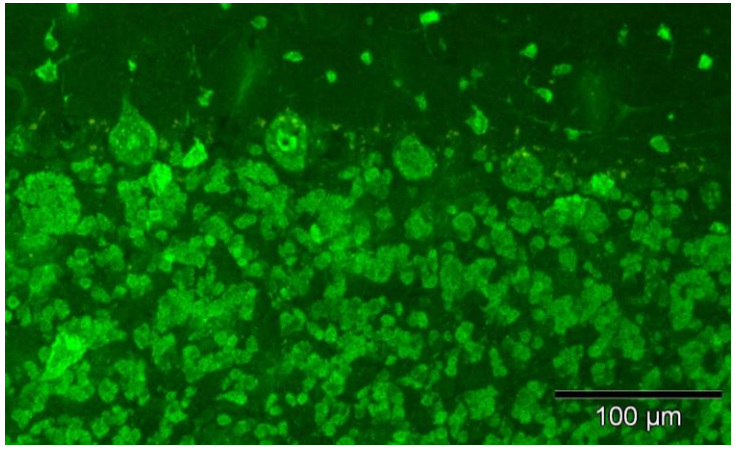
Onconeuronal antibodies and associations with tumours and neurological syndromes

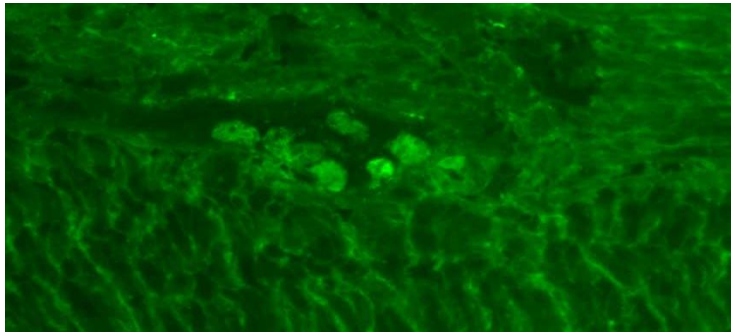


Expression of HuD in tumour tissue and the nervous system



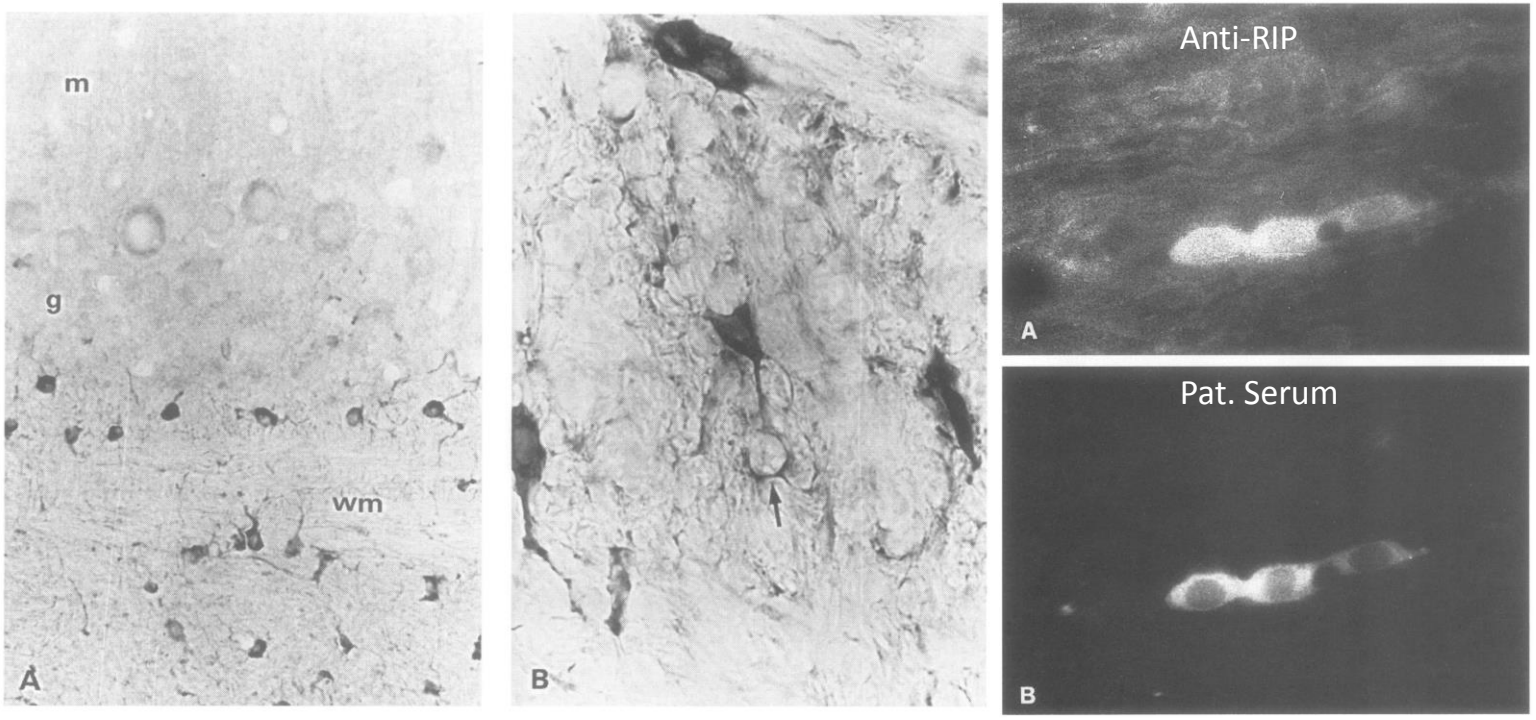
Dysgerminom eines Patienten mit Anti-Hu-postiver PEM





(Graus et al., Brain 2001; 124:1138-1148

CV2 / CRMP5 antibodies bind to oligodendrocytes



Honnorat et al., JNNP 1996;61:270-278

Patients with paraneoplastic chorea in the PNS EuroNetwork registry

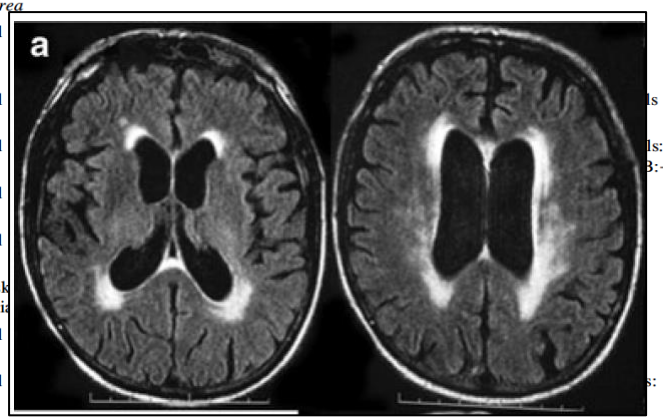
11 of 913 patients had chorea (1.2%)

Table 1 Data of PNS EuroNetwork patients

Case	Sex, age (years)	Type of chorea	Associated syndrome	Tumor and delay[d]	Antibody	CSF	MRI	Response to cancer therapy	Outcome
Definite paraneoplastic chorea									
1	M, 63	Classical					Diffuse leukoencephalopathy. Gadolinium enhancement. After few months lenticular hypointensity	No response	Alive after 5 years
2	M, 54	Classical				ls 5 Prot:58	Normal	Mild response	Death from tumor after 23 months
3[b]	F, 49	Classical				ls:0 Prot: 5 B:+: 9	Diffuse leuko-encephalopathy	Mild response	Death from tumor after 19 months
4	M, 78	Classical					Normal	No response	Death from tumor after 15 months
5	M, 77	Classical					Mild frontal atrophy	No response	Death from tumor after 14 months
6[c]	M, 81	Oral dysk dystoni					Diffuse leuko-encephalopathy	Mild response	Dead after 3 months
7	M, 77	Classical					Normal	No response	Alive after 24 months
8	F, 76	Classical				s: 3 Prot: n.n.	Diffuse leuko-encephalopathy; bilateral hyperintensity of BG (after 4 months)	No therapy	Alive after 18 months
9	M, 65	Oral dyskinesia, slow speech, vocal tics and gnashing of teeth	LE PN	SCLC 4 months after	Hu/ANNA1 CV2/CRMP5	[a]Cells:55 Prot: 1 OB: +	Normal	Good response	Death from PNS after 9 months
10	M, 75	Unilateral chorea	Cognitive disorders	Colon cancer 4 months after	Hu/ANNA1	–	Temporobasal and temporomesial bilateral hyperintensity	No therapy	Death from PNS after 6 months
Possible paraneoplastic chorea									
11	F, 73	Classical chorea		SCLC 17 months before	No Ab	Cells: 1 Prot:40	Normal	No response	
12[b]	F, 59	Cervical dystonia and choreic jerks at left shoulder	Anxiety	Colon cancer 7 months after	No Ab	[a]Cells:1 Prot:60 ↑ IgG index	Normal	No response	Death from tumor after 15 months
13	M, 82	Classical chorea	LE	Colon cancer 6 months after	No Ab	Cells: 3 Prot:49 OB: neg	MRI:NA CT: Normal	No therapy	Death from tumor after 1 month

PN polyneuropathy, *CT* computed tomography, *MRI* magnetic resonance imaging, *OCD* obsessive–compulsive disorder, *LE* limbic encephalitis, *SCLC* small cell lung cancer, *NSCLC* non small cell lung cancer, *CSF* cerebrospinal fluid, *Cell* X cell/mm^3, *Prot* proteins mg/dl, *OB* oligoclonal bands, *IgG* intravenous immunoglobulins, *BG* basal ganglia, *PNS* paraneoplastic neurological syndrome, *NA* not available

[a] Pathologic CSF



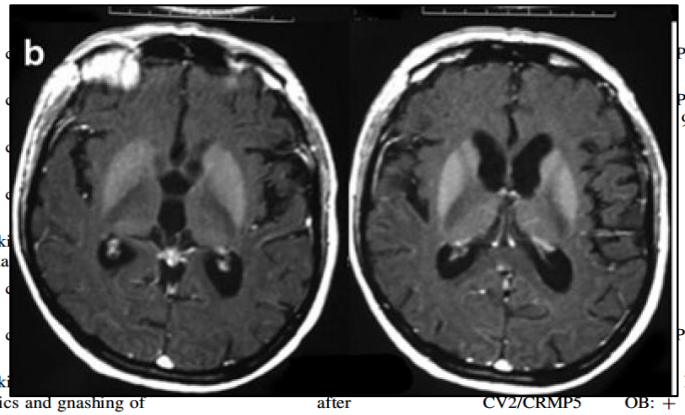
Vigliani et al., Neurol 2011; 258:2058–2068

Patients with paraneoplastic chorea in the PNS EuroNetwork registry

11 of 913 patients had chorea (1.2%)

Table 1 Data of PNS EuroNetwork patients

Case	Sex, age (years)	Type of chorea	Associated syndrome	Tumor and delay[d]	Antibody	CSF	MRI	Response to cancer therapy	Outcome
Definite paraneoplastic chorea									
1	M, 63	Classical chorea	Previous PN	SCLC 1 month after	CV2/CRMP5		Diffuse leukoencephalopathy. Gadolinium enhancement. After few months lenticular hypointensity	No response	Alive after 5 years
2	M, 54	Classical c				Prot:58	Normal	Mild response	Death from tumor after 23 months
3[b]	F, 49	Classical c				Prot: 5 9	Diffuse leuko-encephalopathy	Mild response	Death from tumor after 19 months
4	M, 78	Classical c					Normal	No response	Death from tumor after 15 months
5	M, 77	Classical c					Mild frontal atrophy	No response	Death from tumor after 14 months
6[c]	M, 81	Oral dyski dystonia					Diffuse leuko-encephalopathy	Mild response	Dead after 3 months
7	M, 77	Classical c					Normal	No response	Alive after 24 months
8	F, 76	Classical c				Prot: n.n.	Diffuse leuko-encephalopathy; bilateral hyperintensity of BG (after 4 months)	No therapy	Alive after 18 months
9	M, 65	Oral dyski vocal tics and gnashing of teeth		after	CV2/CRMP5	Prot: 1 OB: +	Normal	Good response	Death from PNS after 9 months
10	M, 75	Unilateral chorea	Cognitive disorders	Colon cancer 4 months after	Hu/ANNA1	–	Temporobasal and temporomesial bilateral hyperintensity	No therapy	Death from PNS after 6 months
Possible paraneoplastic chorea									
11	F, 73	Classical chorea		SCLC 17 months before	No Ab	Cells: 1 Prot:40	Normal	No response	
12[b]	F, 59	Cervical dystonia and choreic jerks at left shoulder	Anxiety	Colon cancer 7 months after	No Ab	[a]Cells:1 Prot:60 ↑ IgG index	Normal	No response	Death from tumor after 15 months
13	M, 82	Classical chorea	LE	Colon cancer 6 months after	No Ab	Cells: 3 Prot:49 OB: neg	MRI:NA CT: Normal	No therapy	Death from tumor after 1 month



PN polyneuropathy, *CT* computed tomography, *MRI* magnetic resonance imaging, *OCD* obsessive–compulsive disorder, *LE* limbic encephalitis, *SCLC* small cell lung cancer, *NSCLC* non small cell lung cancer, *CSF* cerebrospinal fluid, *Cell* X cell/mm^3, *Prot* proteins mg/dl, *OB* oligoclonal bands, *IgG* intravenous immunoglobulins, *BG* basal ganglia, *PNS* paraneoplastic neurological syndrome, *NA* not available

[a] Pathologic CSF

DG ‚Chorea and HD'
21 January 2020

Vigliani et al., Neurol 2011; 258:2058–2068

Patients with paraneoplastic chorea in the PNS EuroNetwork registry

11 of 913 patients had chorea (1.2%)

Table 1 Data of PNS EuroNetwork patients

Case	Sex, age (years)	Type of chorea	Associated syndrome	Tumor and delay[d]	Antibody	CSF	MRI	Response to cancer therapy	Outcome
Definite paraneoplastic chorea									
1	M, 63	Classical chorea	Previous PN	SCLC 1 month after	CV2/CRMP5		Diffuse leukoencephalopathy. Gadolinium enhancement. After few months lenticular hypointensity	No response	Alive after 5 years
2	M, 54	Classical chorea	Myoclonus	SCLC 16 months after	CV2/CRMP5	[a]Cells 5 Prot:58	Normal	Mild response	Death from tumor after 23 months
3[b]	F, 49	Classical chorea	PN Opsoclonus	SCLC 1 month after	Hu/ANNA1	[b]Cells:0 Prot: 5 OB:+: 9	Diffuse leuko-encephalopathy	Mild response	Death from tumor after 19 months
4	M, 78	Classical chorea	–	NSCLC 1 month	CV2/CRMP5	–	Normal	No response	Death from tumor after 15 months
5	M, 77	Classical chorea	–					No response	Death from tumor after 14 months
6[c]	M, 81	Oral dyskinesia cervical dystonia	OCD PN				opathy	Mild response	Dead after 3 months
7	M, 77	Classical chorea	–	after				No response	Alive after 24 months
8	F, 76	Classical chorea	–	Kidney cancer 4 months after	CV2/CRMP5	Cells: 3 Prot: n.n.	Diffuse leuko-encephalopathy; bilateral hyperintensity of BG (after 4 months)	No therapy	Alive after 18 months
9	M, 65	Oral dyskinesia, slow speech, vocal tics and gnashing of teeth	LE PN	SCLC 4 months after	Hu/ANNA1 CV2/CRMP5	[a]Cells:55 Prot: 1 OB: +	Normal	Good response	Death from PNS after 9 months
10	M, 75	Unilateral chorea	Cognitive disorders	Colon cancer 4 months after	Hu/ANNA1	–	Temporobasal and temporomesial bilateral hyperintensity	No therapy	Death from PNS after 6 months
Possible paraneoplastic chorea									
11	F, 73	Classical chorea		SCLC 17 months before	No Ab	Cells: 1 Prot:40	Normal	No response	
12[b]	F, 59	Cervical dystonia and choreic jerks at left shoulder	Anxiety	Colon cancer 7 months after	No Ab	[a]Cells:1 Prot:60 ↑ IgG index	Normal	No response	Death from tumor after 15 months
13	M, 82	Classical chorea	LE	Colon cancer 6 months after	No Ab	Cells: 3 Prot:49 OB: neg	MRI:NA CT: Normal	No therapy	Death from tumor after 1 month

PN polyneuropathy, *CT* computed tomography, *MRI* magnetic resonance imaging, *OCD* obsessive–compulsive disorder, *LE* limbic encephalitis, *SCLC* small cell lung cancer, *NSCLC* non small cell lung cancer, *CSF* cerebrospinal fluid, *Cell* X cell/mm^3, *Prot* proteins mg/dl, *OB* oligoclonal bands, *IgG* intravenous immunoglobulins, *BG* basal ganglia, *PNS* paraneoplastic neurological syndrome, *NA* not available

[a] Pathologic CSF

6/10 patients:
No response to cancer therapy

Vigliani et al., Neurol 2011; 258:2058–2068

Patients with paraneoplastic chorea in the PNS EuroNetwork registry

11 of 913 patients had chorea (1.2%)

Table 1 Data of PNS EuroNetwork patients

Case	Sex, age (years)	Type of chorea	Associated syndrome	Tumor and delay[d]	Antibody	CSF	MRI	Response to cancer therapy	Outcome
Definite paraneoplastic chorea									
1	M, 63	Classical chorea	Previous PN	SCLC 1 month after	CV2/CRMP5		Diffuse leukoencephalopathy. Gadolinium enhancement. After few months lenticular hypointensity	No response	Alive after 5 years
2	M, 54	Classical chorea	Myoclonus	SCLC 16 months	CV2/CRMP5	[a]Cells 5 Prot:58	Normal	Mild response	Death from tumor after 23 months
3[b]					NA1	[b]Cells:0 Prot: 5 OB:+: 9	Diffuse leuko-encephalopathy	Mild response	Death from tumor after 19 months
4					RMP5	–	Normal	No response	Death from tumor after
5					NA1 CRMP5	–	Mild fr		
6[c]					RMP5	–	Diffuse		
7					RMP5		Normal		
8					RMP5	Cells: 3 Prot: n.n.	Diffuse leuko-encephalopathy; bilateral hyperintensity of BG (after 4 months)	No therapy	Alive after 18 months
9					NA1 CRMP5	[a]Cells:55 Prot: 1 OB: +	Normal	Good response	Death from PNS after 9 months
10	M, 75	Unilateral chorea	Cognitive disorders	Colon cancer 4 months after	Hu/ANNA1	–	Temporobasal and temporomesial bilateral hyperintensity	No therapy	Death from PNS after 6 months
Possible paraneoplastic chorea									
11	F, 73	Classical chorea		SCLC 17 months before	No Ab	Cells: 1 Prot:40	Normal	No response	
12[b]	F, 59	Cervical dystonia and choreic jerks at left shoulder	Anxiety	Colon cancer 7 months after	No Ab	[a]Cells:1 Prot:60 ↑ IgG index	Normal	No response	Death from tumor after 15 months
13	M, 82	Classical chorea	LE	Colon cancer 6 months after	No Ab	Cells: 3 Prot:49 OB: neg	MRI:NA CT: Normal	No therapy	Death from tumor after 1 month

PN polyneuropathy, *CT* computed tomography, *MRI* magnetic resonance imaging, *OCD* obsessive–compulsive disorder, *LE* limbic encephalitis, *SCLC* small cell lung cancer, *NSCLC* non small cell lung cancer, *CSF* cerebrospinal fluid, *Cell* X cell/mm^3, *Prot* proteins mg/dl, *OB* oligoclonal bands, *IgG* intravenous immunoglobulins, *BG* basal ganglia, *PNS* paraneoplastic neurological syndrome, *NA* not available

[a] Pathologic CSF

Typical CSF finding in PNS:

- CSF pleocytosis: ~40%
- Protein increased: ~66%
- OCBs positive: ~66%
- Normal: ~10%

Psimaras et al., JNNP 2010, 81(1):42-5

4/7 patients:
Inflammatory CSF changes

Vigliani et al., Neurol 2011; 258:2058–2068

Patients with paraneoplastic chorea in the PNS EuroNetwork registry

11 of 913 patients had chorea (1.2%)

Table 1 Data of PNS EuroNetwork patients

Case	Sex, age (years)	Type of chorea	Associated syndrome	Tumor and delay[d]	Antibody	CSF	MRI	Response to cancer therapy	Outcome
Definite paraneoplastic chorea									
1	M, 63	Classical chorea	Previous PN	SCLC 1 month after	CV2/CRMP5		Diffuse leukoencephalopathy. Gadolinium enhancement. After few months lenticular hypointensity	No response	Alive after 5 years
2	M, 54	Classical chorea	Myoclonus	SCLC 16 months after	CV2/CRMP5	[a]Cells 5 Prot:58	Normal	Mild response	Death from tumor after 23 months
3[b]	F, 49	Classical chorea	PN Opsoclonus	SCLC 1 month after	Hu/ANNA1	[b]Cells:0 Prot: 5 OB:+: 9	Diffuse leuko-encephalopathy	Mild response	Death from tumor after 19 months
4	M, 78	Classical chorea	–	NSCLC 1 month after	CV2/CRMP5	–	Normal	No response	Death from tumor after 15 months
5	M, 77	Classical chorea	–	SCLC 3 months after	Hu/ANNA1 CV2/CRMP5	–	Mild frontal atrophy	No response	Death from tumor after 14 months
6[c]	M, 81	Oral dyskinesia cervical dystonia	OCD PN	SCLC 1 month before	CV2/CRMP5	–	Di	esponse	Dead after 3 months
7	M, 77	Classical chorea	–	SCLC 7 months after	CV2/CRMP5		No	ponse	Alive after 24 months
8	F, 76	Classical chorea	–	Kidney cancer 4 months after	CV2/CRMP5	Cells: 3 Prot: n.n.	Diffuse leuko-encephalopathy; bilateral hyperintensity of BG (after 4 months)	No therapy	Alive after 18 months
9	M, 65	Oral dyskinesia, slow speech, vocal tics and gnashing of teeth	LE PN	SCLC 4 months after	Hu/ANNA1 CV2/CRMP5	[a]Cells:55 Prot: 1 OB: +	Normal	Good response	Death from PNS after 9 months
10	M, 75	Unilateral chorea	Cognitive disorders	Colon cancer 4 months after	Hu/ANNA1	–	Temporobasal and temporomesial bilateral hyperintensity	No therapy	Death from PNS after 6 months
Possible paraneoplastic chorea									
11	F, 73	Classical chorea		SCLC 17 months before	No Ab	Cells: 1 Prot:40	Normal	No response	
12[b]	F, 59	Cervical dystonia and choreic jerks at left shoulder	Anxiety	Colon cancer 7 months after	No Ab	[a]Cells:1 Prot:60 ↑ IgG index	Normal	No response	Death from tumor after 15 months
13	M, 82	Classical chorea	LE	Colon cancer 6 months after	No Ab	Cells: 3 Prot:49 OB: neg	MRI:NA CT: Normal	No therapy	Death from tumor after 1 month

PN polyneuropathy, *CT* computed tomography, *MRI* magnetic resonance imaging, *OCD* obsessive–compulsive disorder, *LE* limbic encephalitis, *SCLC* small cell lung cancer, *NSCLC* non small cell lung cancer, *CSF* cerebrospinal fluid, *Cell* X cell/mm^3, *Prot* proteins mg/dl, *OB* oligoclonal bands, *IgG* intravenous immunoglobulins, *BG* basal ganglia, *PNS* paraneoplastic neurological syndrome, *NA* not available

[a] Pathologic CSF

Grim prognosis

Vigliani et al., Neurol 2011; 258:2058–2068

Patients with paraneoplastic chorea in the PNS EuroNetwork registry

11 of 913 patients had chorea (1.2%)

Table 1 Data of PNS EuroNetwork patients

Case	Sex, age (years)	Type of chorea	Associated syndrome	Tumor and delay[d]	Antibody	CSF	MRI	Response to cancer therapy	Outcome
Definite paraneoplastic chorea									
1	M, 63	Classical chorea	Previous PN	SCLC 1 month after	CV2/CRMP5		Diffuse leukoencephalopathy. Gadolinium enhancement. After few months lenticular hypointensity	No response	Alive after 5 years
2	M, 54	Classical chorea	Myoclonus	SCLC 16 months after	CV2/CRMP5	[a]Cells 5 Prot:58	Normal	Mild response	Death from tumor after 23 months
3[b]	F, 49	Classical chorea	PN Opsoclonus	SCLC 1 month after	Hu/ANNA1	[b]Cells:0 Prot: 5 OB:+: 9	Diffuse leuko-encephalopathy	Mild response	Death from tumor after 19 months
4	M, 78	Classical chorea	–	NSCLC 1 month after	CV2/CRMP5	–	Normal	No response	Death from tumor after 15 months
5	M, 77	Classical chorea	–	SCLC 3 months after	Hu/ANNA1	–	Mild frontal atrophy	No response	Death from tumor after 14 months
6[c]	M, 81	Oral dyskinesia cervical dystonia	OCD PN	SCLC 1 month before			e leuko-encephalopathy	Mild response	Dead after 3 months
7	M, 77	Classical chorea	–	SCLC 7 months after			Normal	No response	Alive after 24 months
8	F, 76	Classical chorea	–	Kidney cancer 4 months after	CV2/CRMP5	Cells: 3 Prot: n.n.	Diffuse leuko-encephalopathy; bilateral hyperintensity of BG (after 4 months)	No therapy	Alive after 18 months
9	M, 65	Oral dyskinesia, slow speech, vocal tics and gnashing of teeth	LE PN	SCLC 4 months after	Hu/ANNA1 CV2/CRMP5	[a]Cells:55 Prot: 1 OB: +	Normal	Good response	Death from PNS after 9 months
10	M, 75	Unilateral chorea	Cognitive disorders	Colon cancer 4 months after	Hu/ANNA1	–	Temporobasal and temporomesial bilateral hyperintensity	No therapy	Death from PNS after 6 months
Possible paraneoplastic chorea									
11	F, 73	Classical chorea		SCLC 17 months before	No Ab	Cells: 1 Prot:40	Normal	No response	
12[b]	F, 59	Cervical dystonia and choreic jerks at left shoulder	Anxiety	Colon cancer 7 months after	No Ab	[a]Cells:1 Prot:60 ↑ IgG index	Normal	No response	Death from tumor after 15 months
13	M, 82	Classical chorea	LE	Colon cancer 6 months after	No Ab	Cells: 3 Prot:49 OB: neg	MRI:NA CT: Normal	No therapy	Death from tumor after 1 month

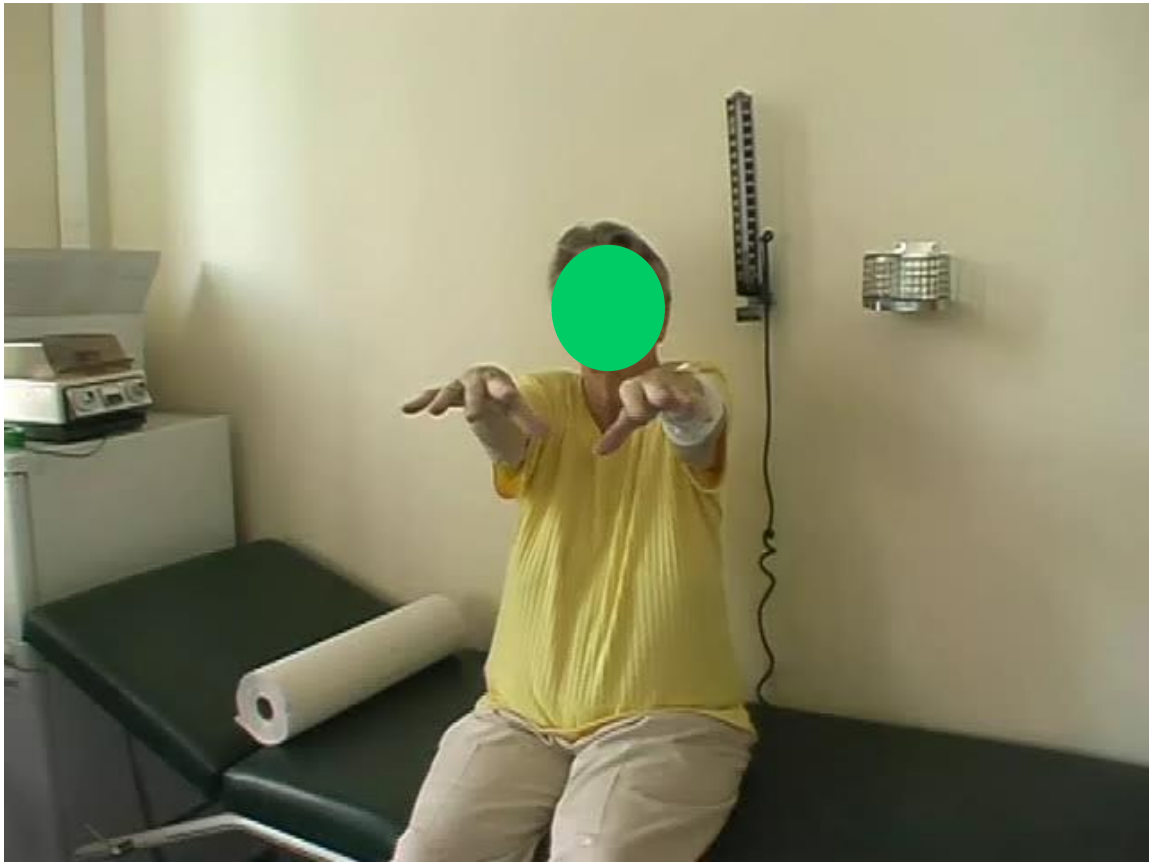
3/13 Neuropathy

PN polyneuropathy, *CT* computed tomography, *MRI* magnetic resonance imaging, *OCD* obsessive–compulsive disorder, *LE* limbic encephalitis, *SCLC* small cell lung cancer, *NSCLC* non small cell lung cancer, *CSF* cerebrospinal fluid, *Cell* X cell/mm^3, *Prot* proteins mg/dl, *OB* oligoclonal bands, *IgG* intravenous immunoglobulins, *BG* basal ganglia, *PNS* paraneoplastic neurological syndrome, *NA* not available

[a] Pathologic CSF

Vigliani et al., Neurol 2011; 258:2058–2068

Chorea in PNS: Is it really chorea?



What to you think that this patient mostly probably has?

Q3- What to you think that this patient mostly probably has?

a. Classical chorea with slight lateralisation to the left
b. Myoclonus
c. Pseudoathetosis due to sensory deafferentiation
d. Cerebellar ataxia

Management of patients with PNS

Search for the underlying neoplasm:
every 6 months for up to 5 years
CT /US depending on suspected tumor entity, FDG-PET

Tumor therapy (surgery, chemotherapy)

Immunosuppression

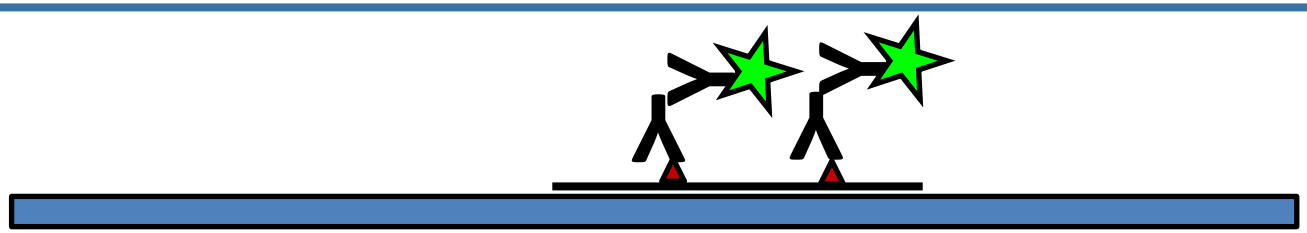
CNS:

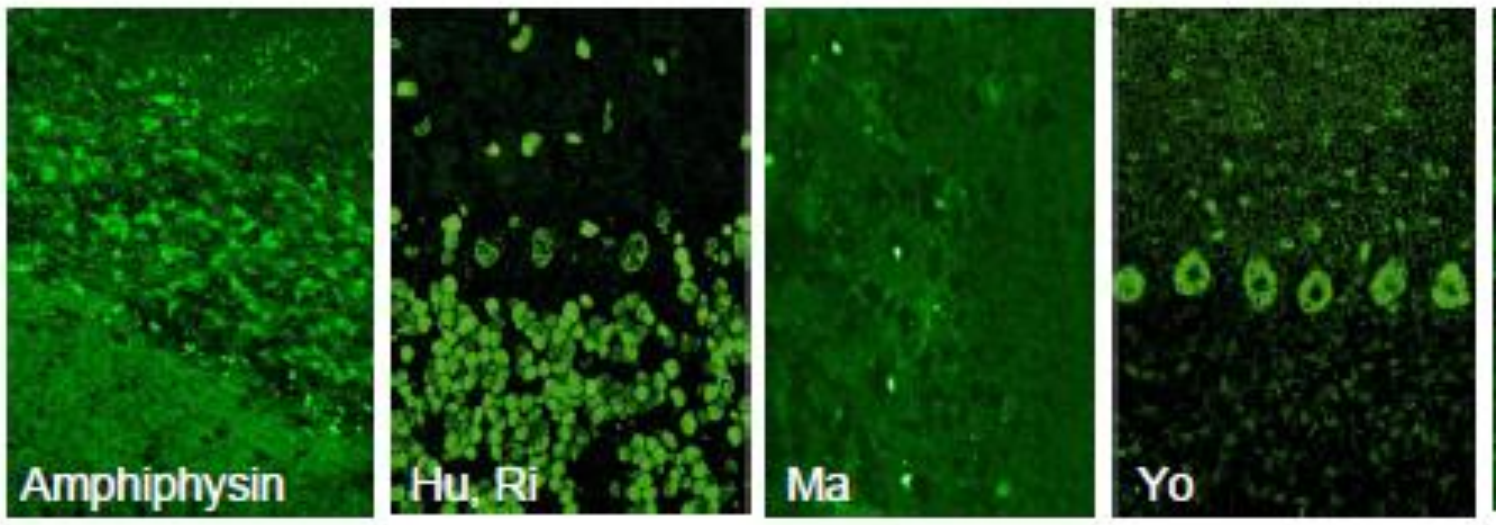
- Methylprednisolone 5 x 1g
- If no response within 2 weeks:
- Cyclophosphamide (750-1000 mg/m^2 every 4 w.), Alternatively rituximab

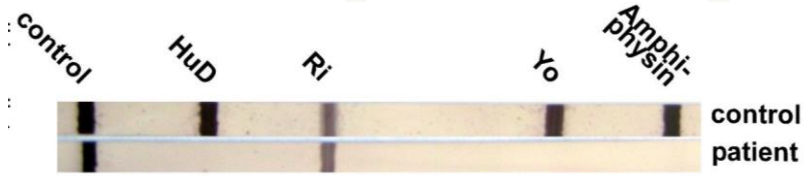
PNS

- Alternatives are IVIG or plasma exchange

How to test for onconeural antibodies?





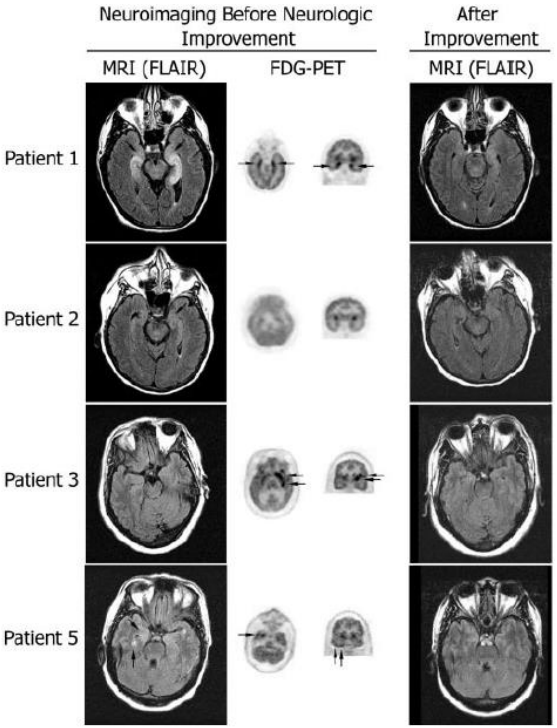


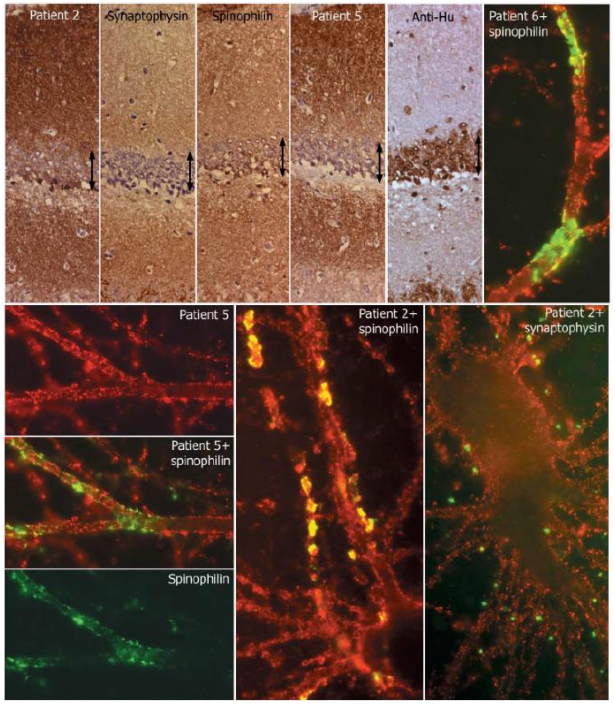
In ~20% of all PNS no onconeural antibodies are present

(Giometto et al., Arch Neurol 2010 ; 67 : 330 – 335)

Chorea in autoimmune encephalitis associated with antibodies against neuronal surface proteins

Discovery of neuropil antibodies in patients with therapy-reponsive limbic encephalitis





Ances et al. Brain 2005; 128: 1764-1777

Potentially paraneoplastic autoimmune encephalitides with antibodies against neuronal surface antigen

Year	Target antigen	Tumour	
2007[1]	NMDA-Rezeptor	30-50%	Ovary (teratoma)
2009[2]	AMPA receptor	70%	Lung,breast,thymoma
2010[3]	$GABA_B$ receptor	60%	SCLC
2004[4]	VGKC complex (obsolete)		
- 2010[5]	LGI1	0[5]-11[6]%	SCLC, thymoma
- 2010[5]	CASPR2	up to 40%	Thymoma
2013[7]	DPPX	n.k.	
2014[8,9]	$GABA_A$ receptor	40%	thymoma, SCLC
2014[10]	IgLON5	n.k.	
2016[11]	Neurexin-3α	n.k.	

[1]Dalmau et al., Ann Neurol. 2007; 61: 25–36. [2]*Lai et al.,* Ann Neurol 2009; 65: 424 – 434. [3]Lancaster et al., Lancet Neurol. 2010; 9: 67–76. [4]Vincent A, Brain 2004; 127: 701–12. [5]Irani et al., Brain 2010; 133: 2734–2748, [6]Van Sonderen et al. Neurology. 2016 Oct 4;87(14):1449-1456, [7]Boronnat et al., Ann Neurol 2013;73:120–128, [8]Petit-Pedrol et al., Lancet Neurol 2014;13(3):276-86, [9]Spatola et al., Neurology 2017, epub Feb 15, [10]Sabater et al., Lancet Neurol 2014;13(6):575-86, [11]Gresa-Arribas et al., Neurology. 2016 Jun 14;86(24):2235-42.

Reportedly associated with chorea (Balint et al., Brain 2018: 141; 13–36)

Potentially paraneoplastic autoimmune encephalitides with antibodies against neuronal surface antigen

Year	Target antigen	Tumour	
2007[1]	NMDA-Rezeptor	30-50%	Ovary (teratoma)
2009[2]	AMPA receptor	70%	Lung,breast,thymoma
2010[3]	$GABA_B$ receptor	60%	SCLC
2004[4]	VGKC complex (obsolete)		
- 2010[5]	LGI1	0[5]-11[6]%	SCLC, thymoma
- 2010[5]	CASPR2	up to 40%	Thymoma
2013[7]	DPPX	n.k.	
2014[8,9]	$GABA_A$ receptor	40%	thymoma, SCLC
2014[10]	IgLON5	n.k.	
2016[11]	Neurexin-3α	n.k.	

[1]Dalmau et al., Ann Neurol. 2007; 61: 25–36. [2]*Lai et al.,* Ann Neurol 2009; 65: 424 – 434. [3]Lancaster et al., Lancet Neurol. 2010; 9: 67–76. [4]Vincent A, Brain 2004; 127: 701–12. [5]Irani et al., Brain 2010; 133: 2734–2748, [6]Van Sonderen et al. Neurology. 2016 Oct 4;87(14):1449-1456, [7]Boronnat et al., Ann Neurol 2013;73:120–128, [8]Petit-Pedrol et al., Lancet Neurol 2014;13(3):276-86, [9]Spatola et al., Neurology 2017, epub Feb 15, [10]Sabater et al., Lancet Neurol 2014;13(6):575-86, [11]Gresa-Arribas et al., Neurology. 2016 Jun 14;86(24):2235-42.

Very rare, chorea/dyskinesia associated with severe encephalitis

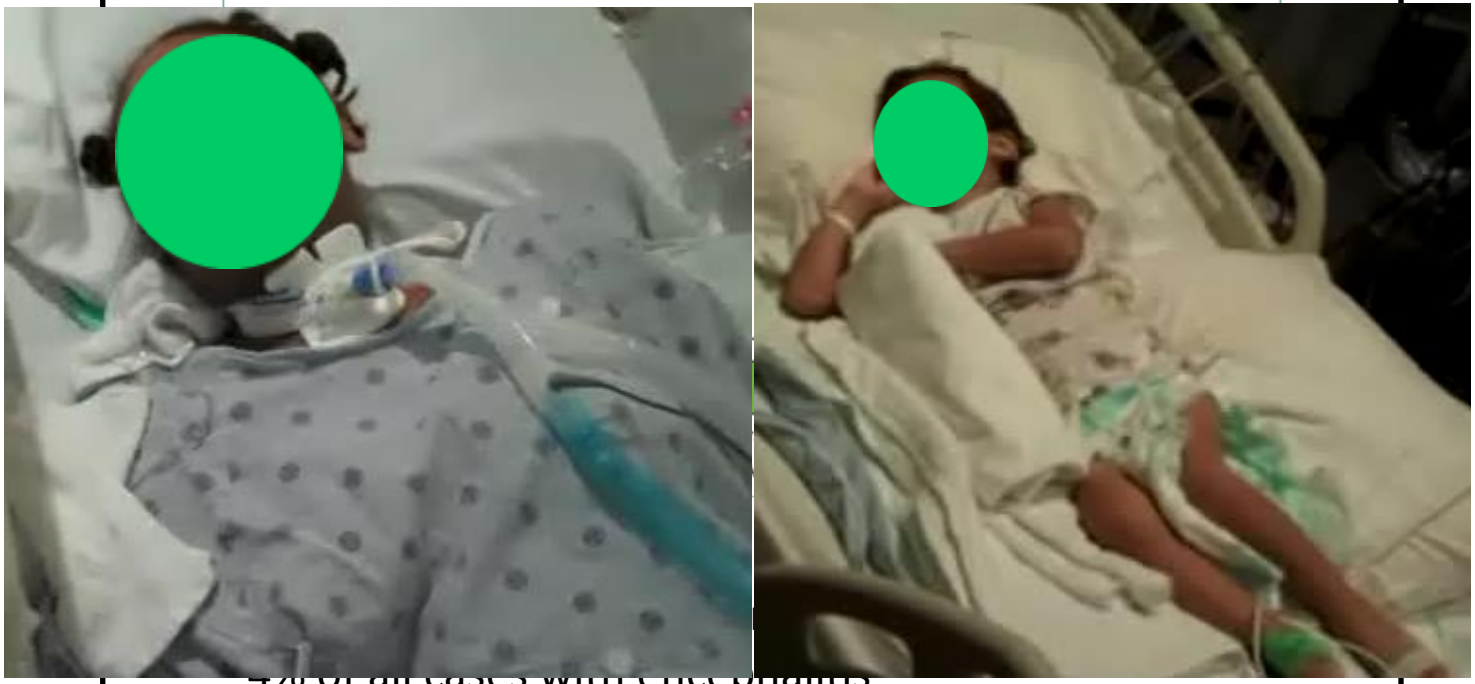
Potentially paraneoplastic autoimmune encephalitides with antibodies against neuronal surface antigen

Year	Target antigen	Tumour	
2007[1]	NMDA-Rezeptor	30-50%	Ovary (teratoma)
2009[2]	AMPA receptor	70%	Lung,breast,thymoma
2010[3]	$GABA_B$ receptor	60%	SCLC
2004[4]	VGKC complex (obsolete)		
- 2010[5]	LGI1	0[5]-11[6]%	SCLC, thymoma
- 2010[5]	CASPR2	up to 40%	Thymoma
2013[7]	DPPX	n.k.	
2014[8,9]	$GABA_A$ receptor	40%	thymoma, SCLC
2014[10]	IgLON5	n.k.	
2016[11]	Neurexin-3α	n.k.	

[1]Dalmau et al., Ann Neurol. 2007; 61: 25–36. [2]*Lai et al.,* Ann Neurol 2009; 65: 424 – 434. [3]Lancaster et al., Lancet Neurol. 2010; 9: 67–76. [4]Vincent A, Brain 2004; 127: 701–12. [5]Irani et al., Brain 2010; 133: 2734–2748, [6]Van Sonderen et al. Neurology. 2016 Oct 4;87(14):1449-1456, [7]Boronnat et al., Ann Neurol 2013;73:120–128, [8]Petit-Pedrol et al., Lancet Neurol 2014;13(3):276-86, [9]Spatola et al., Neurology 2017, epub Feb 15, [10]Sabater et al., Lancet Neurol 2014;13(6):575-86, [11]Gresa-Arribas et al., Neurology. 2016 Jun 14;86(24):2235-42.

Common, chorea/dyskinesias also associated with severe encephalitis

Encephalitis with NMDAR antibodies affect young patients



4% of all cases with encephalitis

[1]Prüss et al., Neurology 2010; 75:1735–1739,[2]Granerod et al., Lancet Infect Dis 2010;10: 835–44

Baizabal-Carvallo Mov Disord. 2013 Apr;28(4):543-7.

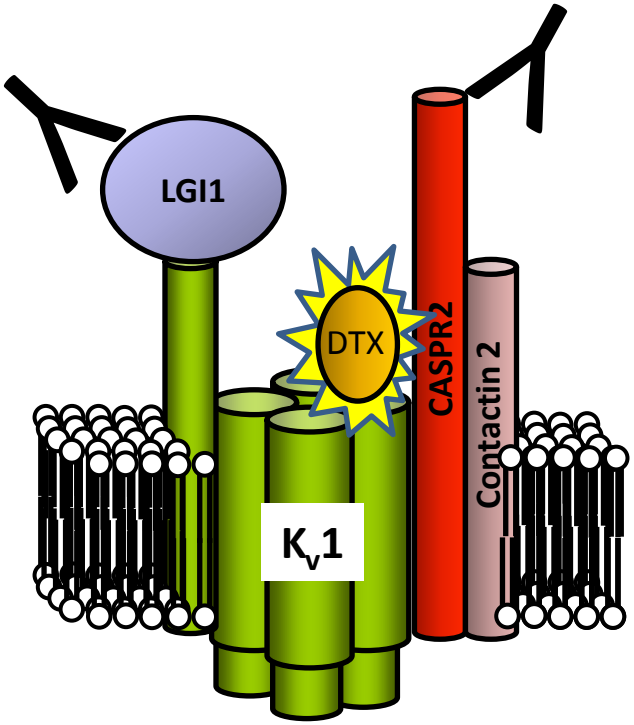
Potentially paraneoplastic autoimmune encephalitides with antibodies against neuronal surface antigen

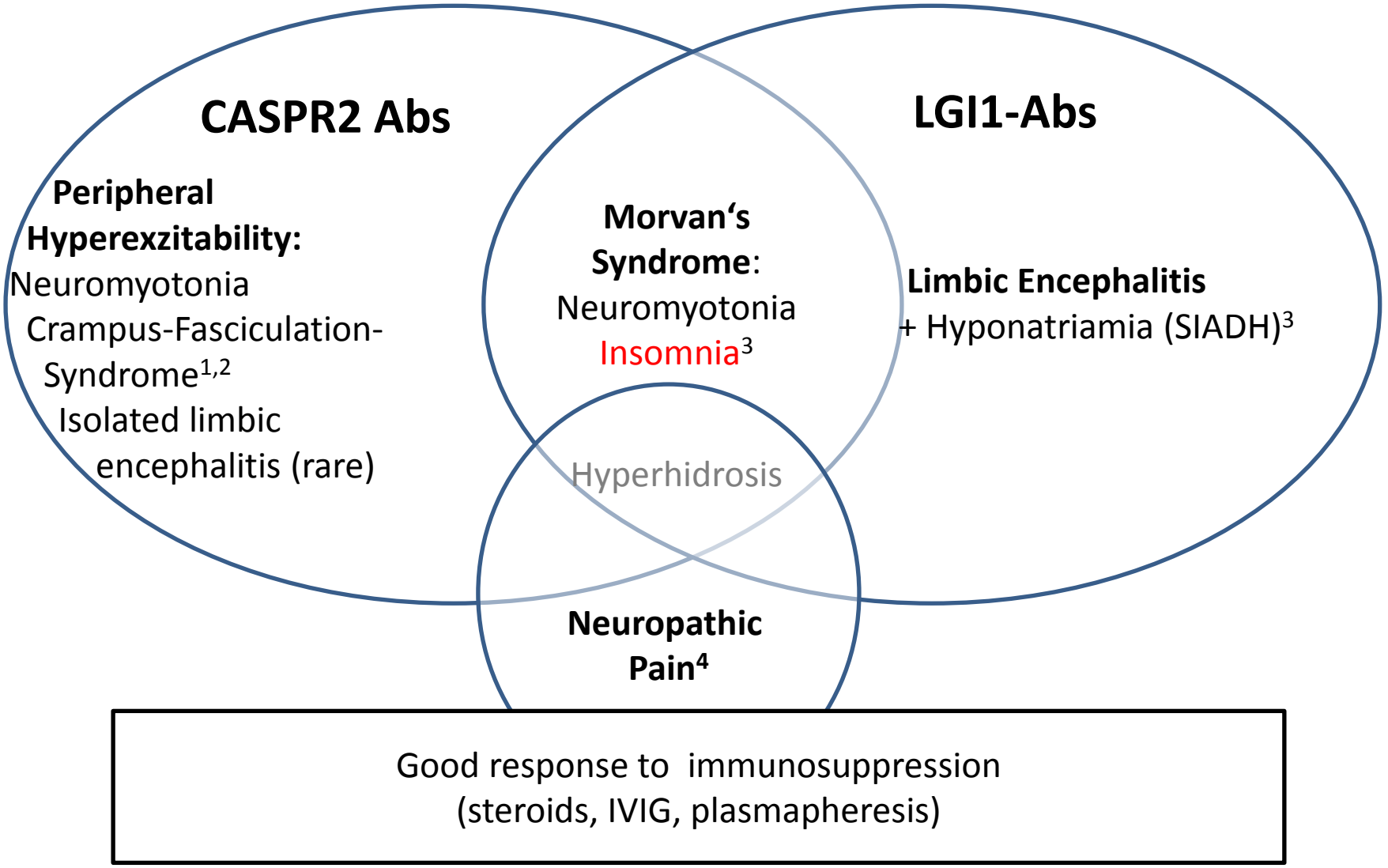
Year	Target antigen	Tumour	
2007[1]	NMDA-Rezeptor	30-50%	Ovary (teratoma)
2009[2]	AMPA receptor	70%	Lung,breast,thymoma
2010[3]	$GABA_B$ receptor	60%	SCLC
2004[4]	VGKC complex (obsolete)		
- 2010[5]	LGI1	0[5]-11[6]%	SCLC, thymoma
- 2010[5]	CASPR2	up to 40%	Thymoma
2013[7]	DPPX	n.k.	
2014[8,9]	$GABA_A$ receptor	40%	thymoma, SCLC
2014[10]	IgLON5	n.k.	
2016[11]	Neurexin-3α	n.k.	

[1]Dalmau et al., Ann Neurol. 2007; 61: 25–36. [2]*Lai et al.,* Ann Neurol 2009; 65: 424 – 434. [3]Lancaster et al., Lancet Neurol. 2010; 9: 67–76. [4]Vincent A, Brain 2004; 127: 701–12. [5]Irani et al., Brain 2010; 133: 2734–2748, [6]Van Sonderen et al. Neurology. 2016 Oct 4;87(14):1449-1456, [7]Boronnat et al., Ann Neurol 2013;73:120–128, [8]Petit-Pedrol et al., Lancet Neurol 2014;13(3):276-86, [9]Spatola et al., Neurology 2017, epub Feb 15, [10]Sabater et al., Lancet Neurol 2014;13(6):575-86, [11]Gresa-Arribas et al., Neurology. 2016 Jun 14;86(24):2235-42.

Rather common, protracted course and prominent chorea possible

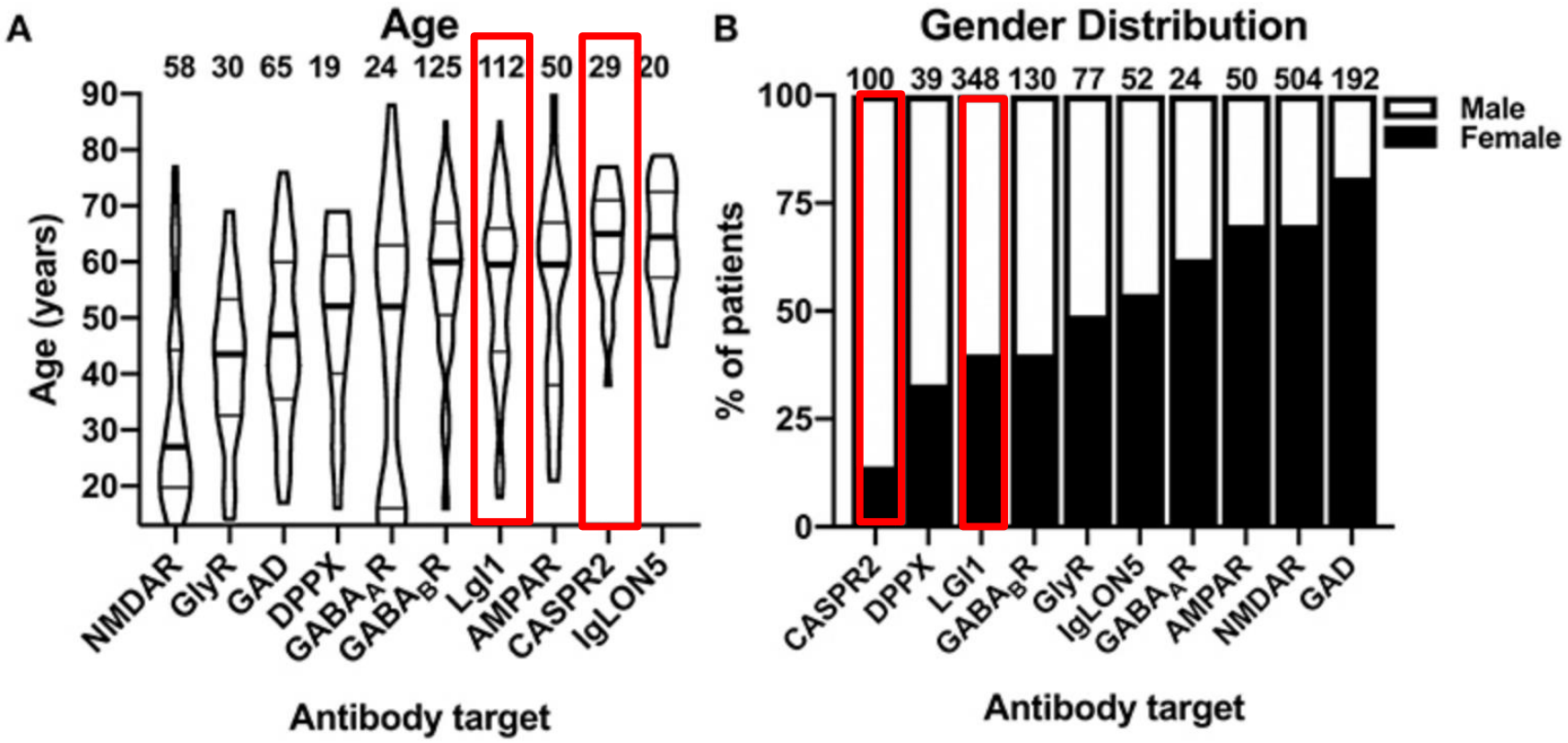
CASPR2 and LGI1 antibodies, formerly known as VGKC





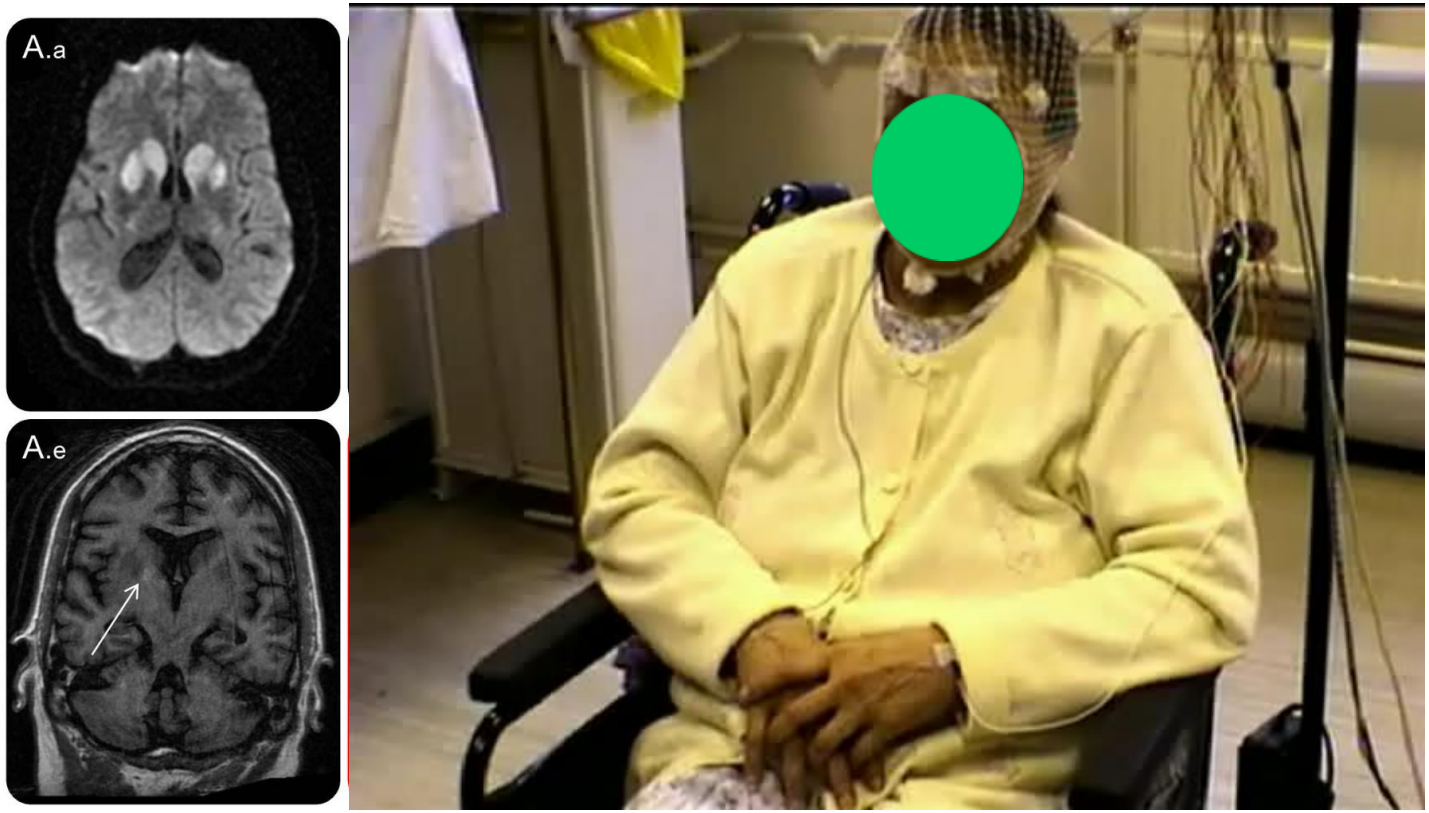
[1]Hart et al., Brain 2002; 125:1887-1895, [2]Irani et al., Brain 2010: 133; 2734–2748,
[3]Irani et al., Ann Neurol 2011;69:892–900, [4]Klein et al., Neurology 2012; 79: 1136-44.

Older age and male predominance in autoimmune encephalitis associated with either CASPR2 or LGI1 antibodies



Blinder & Lewerenz Front Neurol 2019 Jul 25;10:804.

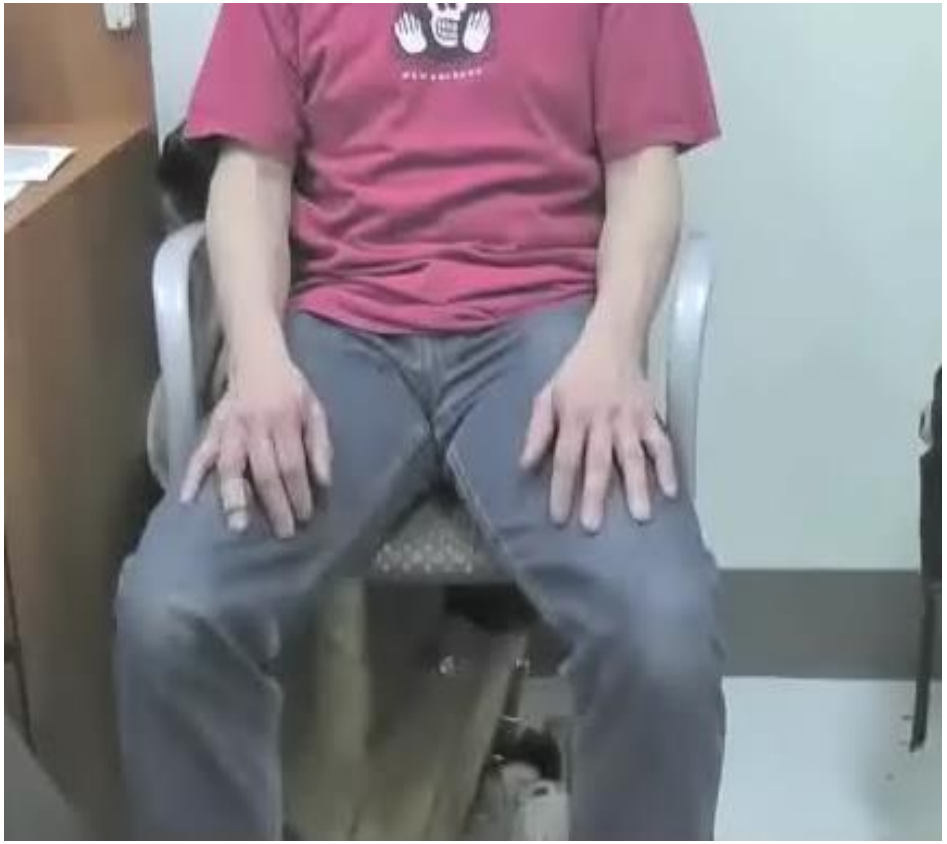
Basal ganglia abnormalities in some patients with autoimmune encephalitis associated with LGI1 antibodies



(A) Brain MRI obtained during relapse: (A.a) Prominent restricted diffusion and (A.b) apparent diffusion coefficient correlate with changes in the bilateral basal ganglia. (A.c) T2 fluid-attenuated inversion recovery (FLAIR) hyperintensities in the same "restricted diffusion" distribution. (A.d) FLAIR normal hippocampal size. (A.e) Coronal sequence showing T1 hyperintensities in the right basal ganglia. (A.f) 18F-fluorodeoxyglucose (18F-FDG) PET/CT. Intense 18F-FDG uptake is noted in the bilateral basal ganglia, asymmetric FDG uptake within the left medial temporal lobe. (B) Follow-up brain MRI: (B.a, B.b) 16 months after the onset of symptoms. Axial T2 FLAIR shows prominent caudate nuclei atrophy and bilateral hippocampal atrophy (arrowheads).

- Irani et al. Ann Neurol. 2011 May;69(5):892-900.

Chorea in autoimmune encephalitis with LGI1 antibodies is rare

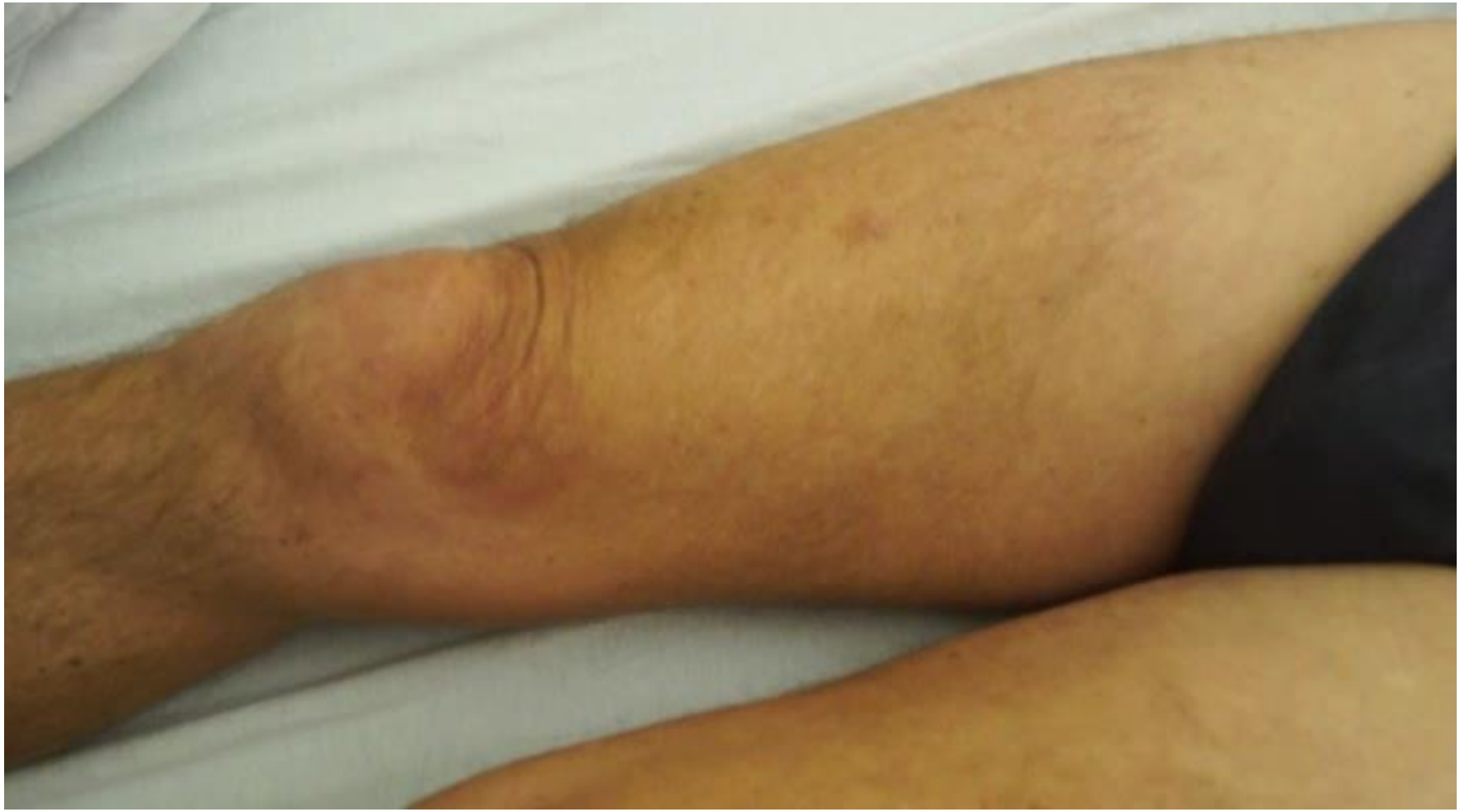


Ramdhani & Frucht, Tremor Other Hyperkinet Mov 2014; 8:4

Characteristics	Values
Male, n (%)	25/38 (66)
Age at onset, y, median (IQR, range)	64 (60-69, 31-84)
Time to maximum disease severity, wk (IQR, range)	22 (8-32, 2-150)
Clinical syndrome, n (%)	
Limbic encephalitis	34 (90)
Morvan syndrome[a]	3 (8)
Epilepsy	1 (3)
Seizures, n (%)	34 (90)
Memory deficit, n (%)	37 (97)
Disorder of behavior, n (%)	34 (90)
Spatial disorientation, n (%)	17/33 (52)
Insomnia, n (%)	20/31 (65)
Weight loss, n (%)	9/33 (27)
Autonomic dysfunction, n (%)	15/32 (47)
Pain, n (%)	3/34 (9)
Peripheral nervous system symptoms, n (%)	5/32 (16)
Hyponatremia, n (%)	24/37 (65)
CSF, n (%)	
Cell count >5 cells/μL	5/32 (16) (max 88 cells/μL)
Protein >0.58 g/L	5/32 (16)
EEG, n (%)	
Focal slowing	9/36 (25)
Epileptic	11/36 (31)
MRI at presentation, n (%)	
Unilateral hippocampal lesion	21/35 (60)
Bilateral hippocampal lesion	5/35 (14)
Normal	9/35 (26)

Van Sonderen et al., Neurology. 2016 Oct 4;87(14):1449-1456

Chorea in autoimmune encephalitis with CASPR2 antibodies



Potentially paraneoplastic autoimmune encephalitides with antibodies against neuronal surface antigen

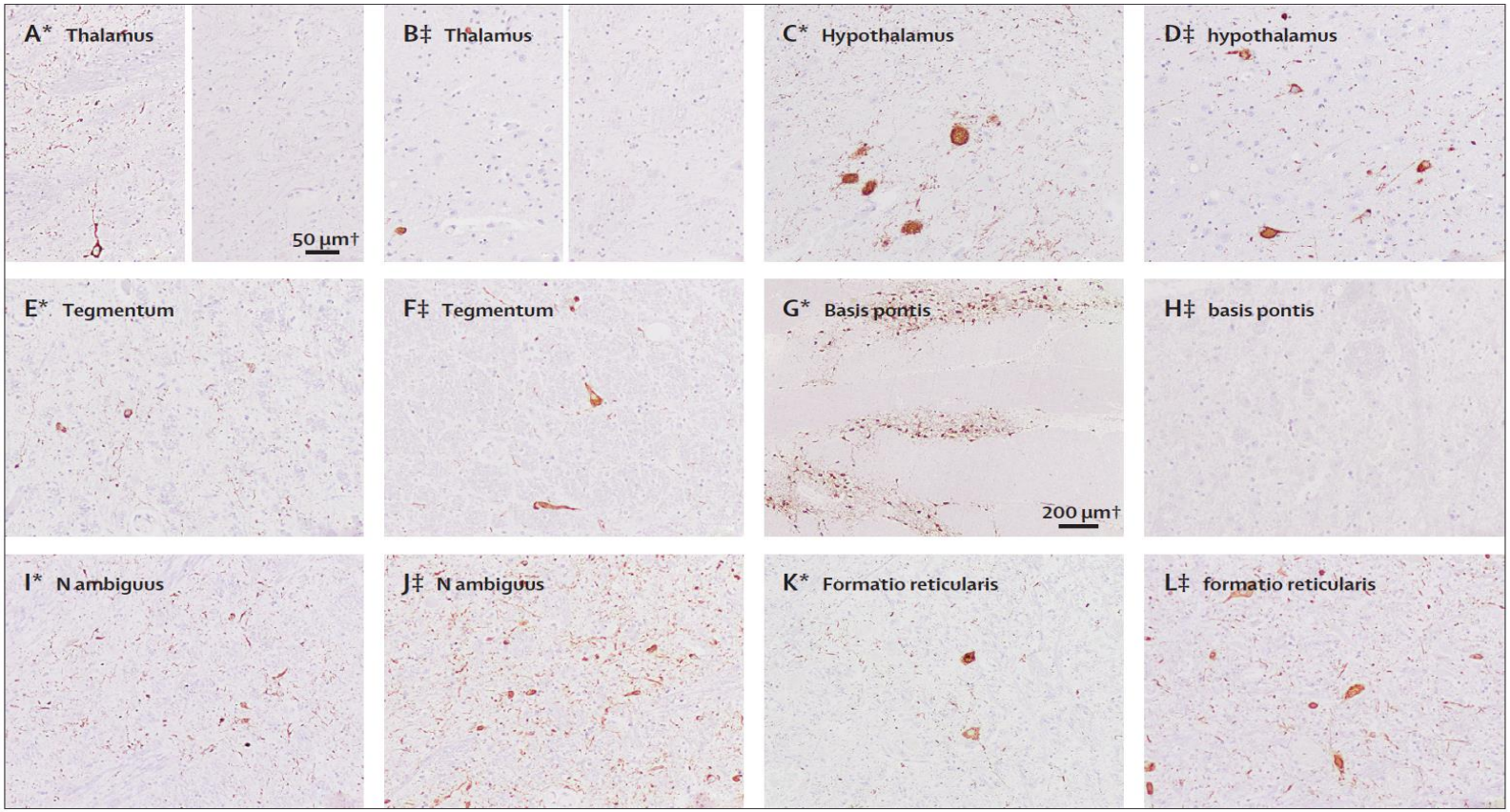
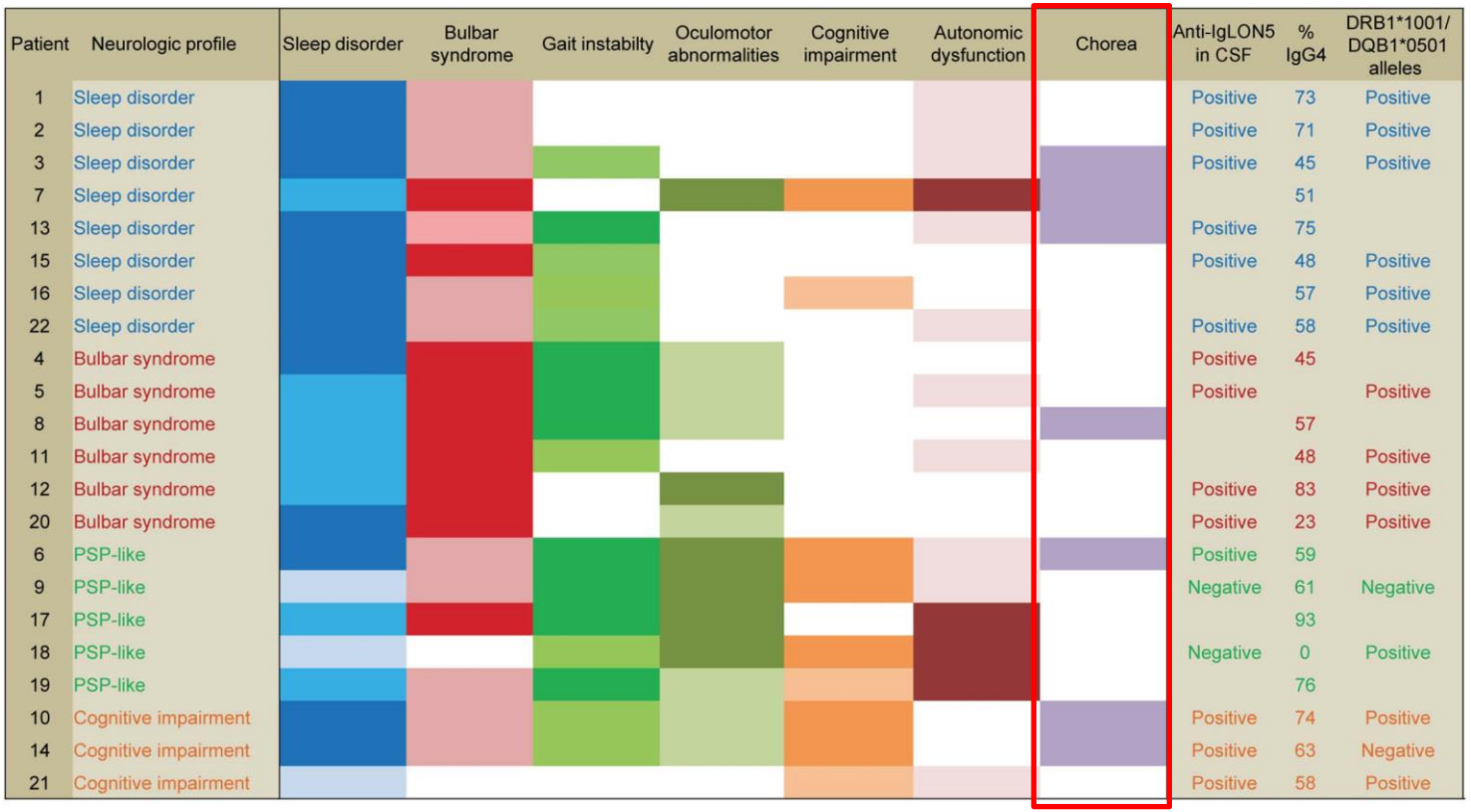


Figure 5: **Distribution of tau pathology**
Moderate amounts of AT8-immunoreactive neuropil threads and neurofibrillary tangles are detected in hypothalamic nuclei (C, D; posterior hypothalamic nucleus) and anterior thalamus (A, B [left panels]), but are completely absent in lateral and posterior thalamic neurons of both cases (A, B [right panels]). Although the pontine tegmentum is mildly (F) and moderately (E) affected in patients seven and two, respectively, neurons of nucleus propii of basis pontis show extensive tau pathology mainly in form of pretangles (G), which is not noted in patient seven (H). By contrast, prominent pathological change in nucleus ambiguus is detected in patient seven (J), and less in patient two (I) and to a lesser extent in magnocellular nuclei of the formatio reticularis in both cases (K, L). *Patient two. †The scale bar is 50 µm for all panels except panel G, for which the bar is 200 µm. ‡Patient seven.

Chorea is frequent in IgLON5 encephalopathy



7/22 of patients had chorea

Sabater et al. Lancet Neurol 2014; 13: 575–86

Frequency of chorea in IgLON5 encephalopathy

	Patient one	Patient two	Patient three	Patient four	Patient five	Patient six	Patient seven	Patient eight
Outcome	No change	No change. Sudden death at home while asleep	No change	No change. Sudden death at home	No change. Sudden death during wakefulness	No change. Died in the intensive care unit during wakefulness	No change. Sudden death at home while asleep	Improved. Discharged from the intensive care unit. Sudden death during wakefulness

Sabater et al. Lancet Neurol 2014; 13: 575–86

Management of autoimmune encephalitis with neuronal surfact antibodies

- Autoimmune encephalitides frequently respond to immunotherapy
- Early treatment is associated with better prognosis ->
- High clinical suspicion should trigger treatment!

A clinical approach to diagnosis of autoimmune encephalitis

Francesc Graus, Maarten J Titulaer, Ramani Balu, Susanne Benseler, Christian G Bien, Tania Cellucci, Irene Cortese, Russell C Dale, Jeffrey M Gelfand, Michael Geschwind, Carol A Glaser, Jerome Honnorat, Romana Höftberger, Takahiro Iizuka, Sarosh R Irani, Eric Lancaster, Frank Leypoldt, Harald Prüss, Alexander Rae-Grant, Markus Reindl, Myrna R Rosenfeld, Kevin Rostásy, Albert Saiz, Arun Venkatesan, Angela Vincent, Klaus-Peter Wandinger, Patrick Waters, Josep Dalmau

Encephalitis is a severe inflammatory disorder of the brain with many possible causes and a complex differential diagnosis. Advances in autoimmune encephalitis research in the past 10 years have led to the identification of new syndromes and biomarkers that have transformed the diagnostic approach to these disorders. However, existing criteria for autoimmune encephalitis are too reliant on antibody testing and response to immunotherapy, which might delay the diagnosis. We reviewed the literature and gathered the experience of a team of experts with the aims of developing a practical, syndrome-based diagnostic approach to autoimmune encephalitis and providing guidelines to navigate through the differential diagnosis. Because autoantibody test results and response to therapy are not available at disease onset, we based the initial diagnostic approach on neurological assessment and conventional tests that are accessible to most clinicians. Through logical differential diagnosis, levels of evidence for autoimmune encephalitis (possible, probable, or definite) are achieved, which can lead to prompt immunotherapy.

Lancet Neurol 2016; 15: 391–404

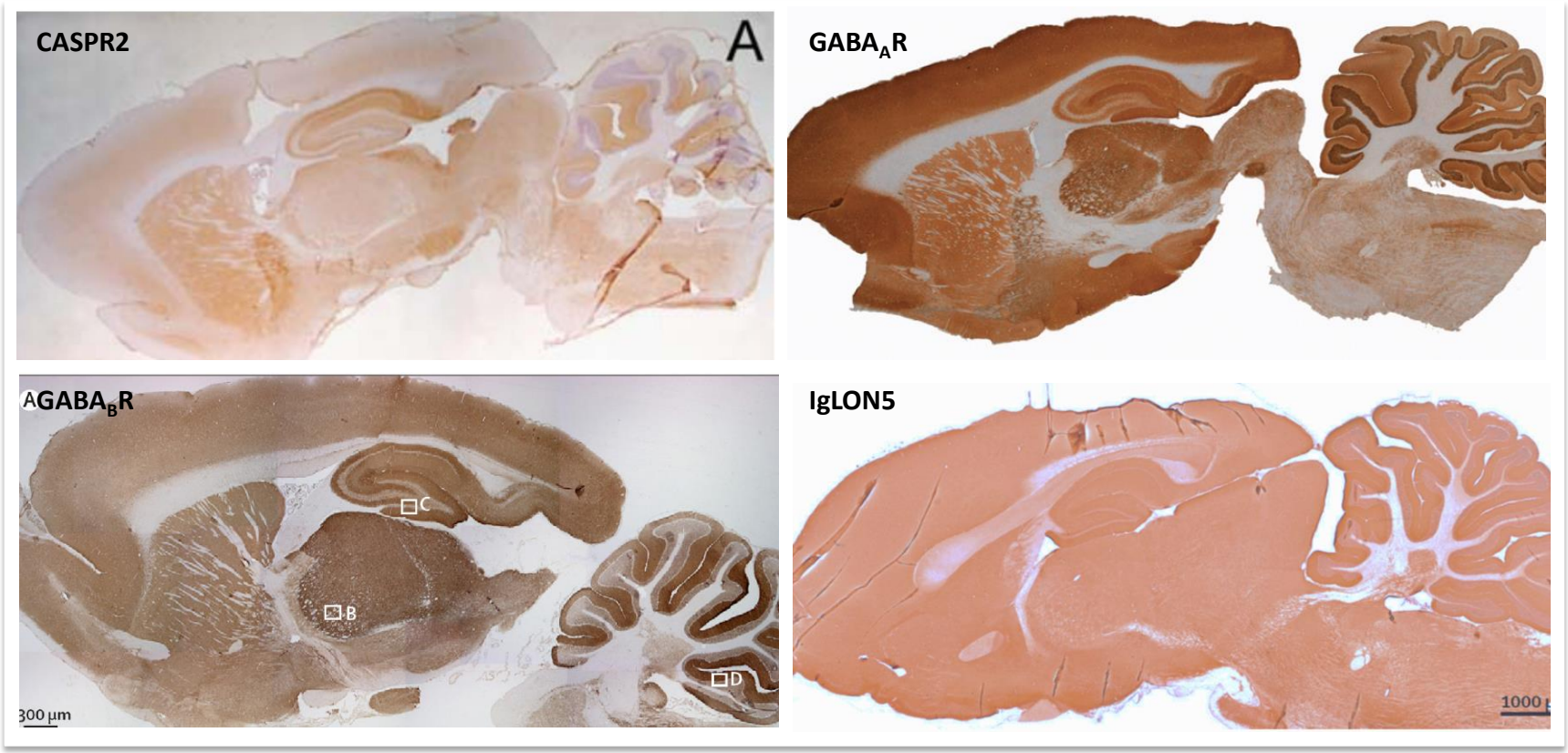
Published Online
February 19, 2016
http://dx.doi.org/10.1016/S1474-4422(15)00401-9

See Comment page 349

Neuroimmunology Program, Institut d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain (Prof F Graus MD, Prof M R Rosenfeld MD,

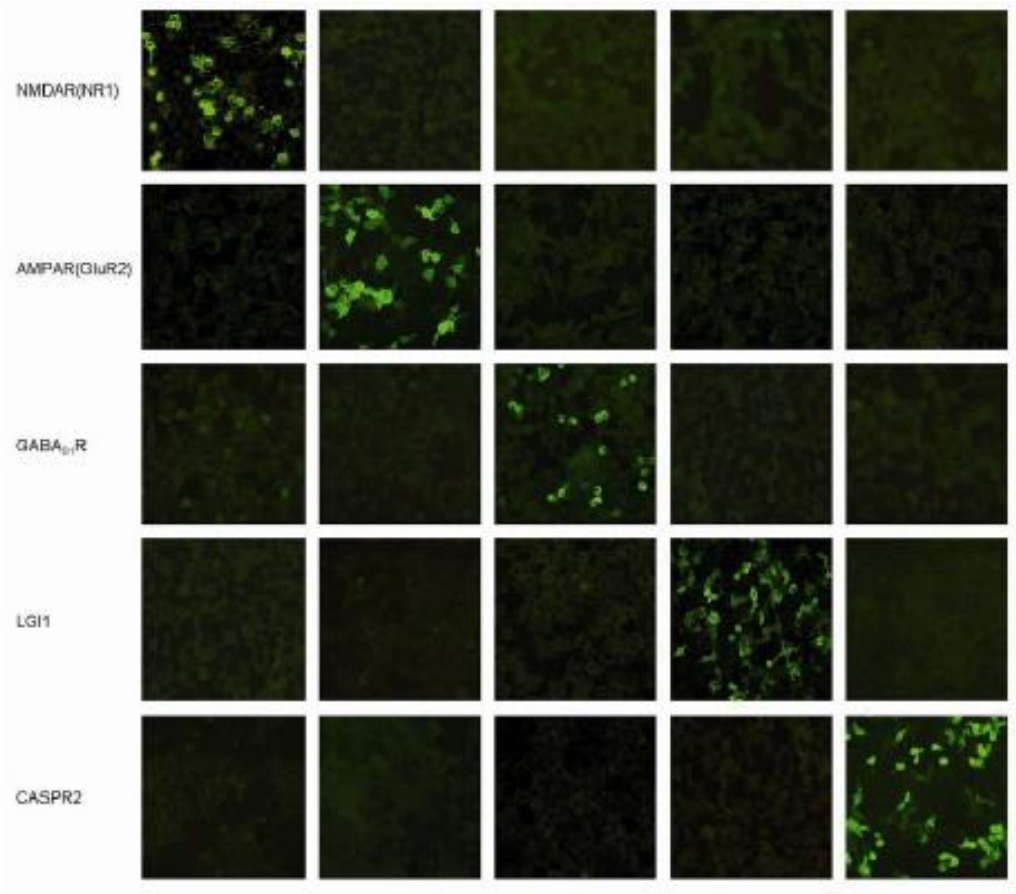
DG ,Chorea and HD

Testing for antibodies against neuronal surface antigens



Lancaster et al., Ann Neurol 2011;69:303–311, Petit-Pedrol et al., Lancet Neurol 2014;13(3):276-86, Lancaster et al., Lancet Neurol. 2010 January ; 9(1): 67–76, Sabater et al., Lancet Neurol 2014;13(6):575-86

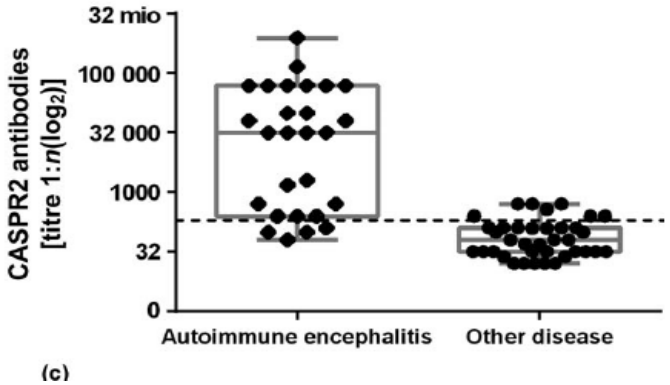
Cell-based assay as specific test

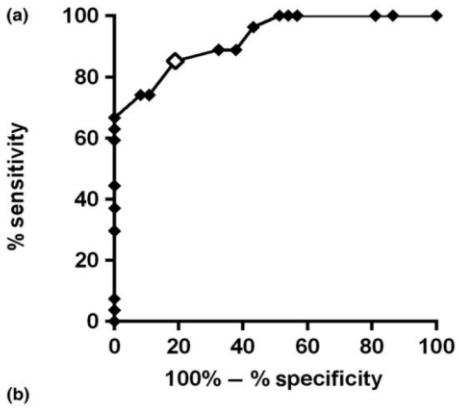


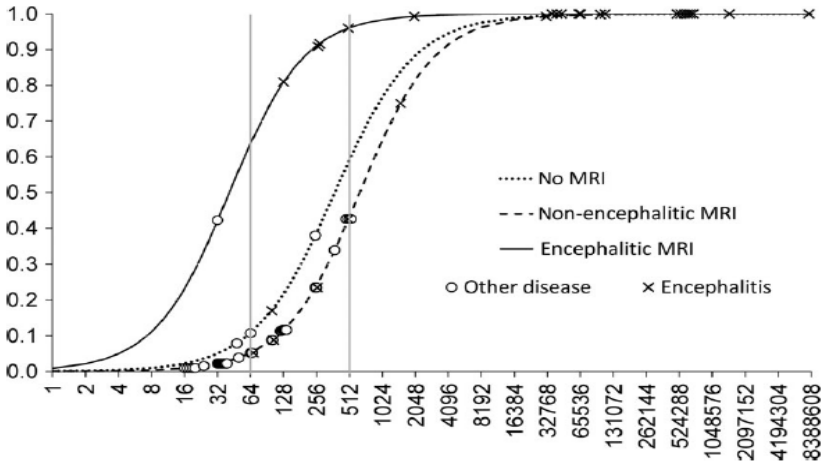
Wandinger et al., J Lab Med 2011

EUROIMMUN

Low titre CASPR2 antibodies can unrelated to neurological symptomes



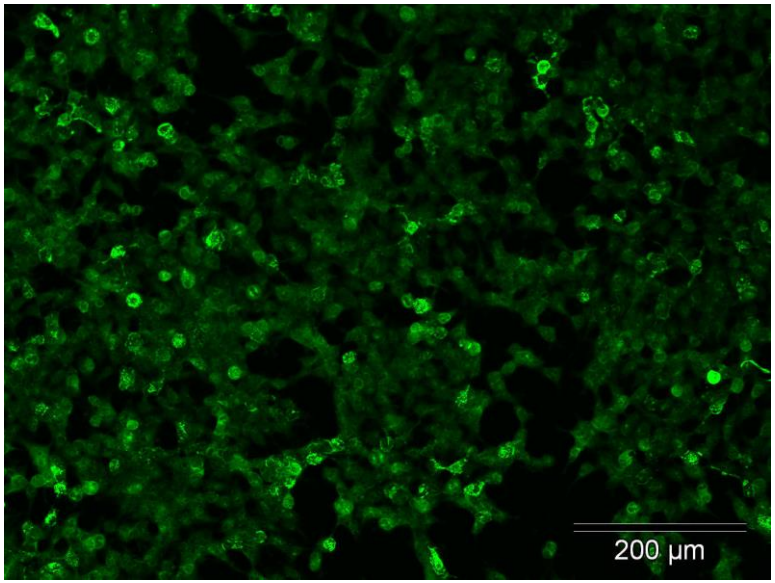


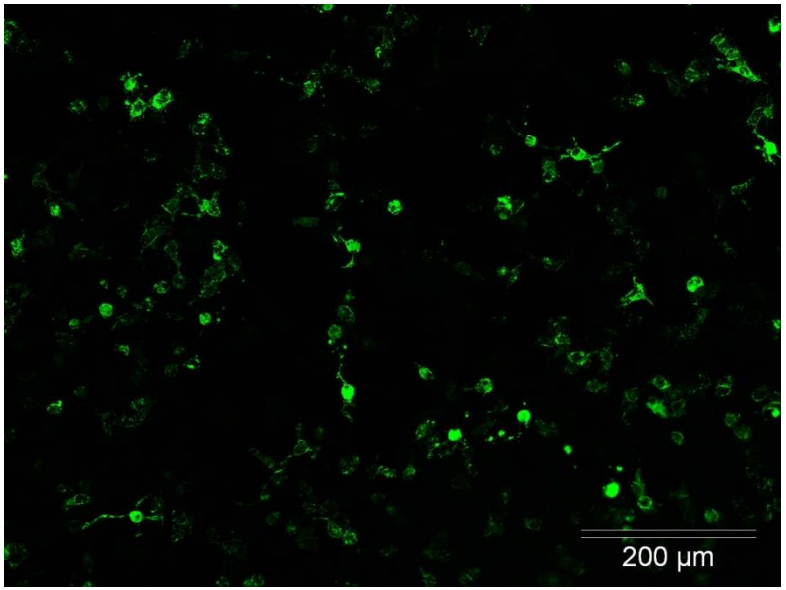


Bien et al., Eur J Neurol. 2017 Jan;24(1):175-186

Testing for NMDAR antibodies should always include serum

Detection of NMDAR antibodies in CSF is more sensitive than in serum (100% vs 85%, N=250)

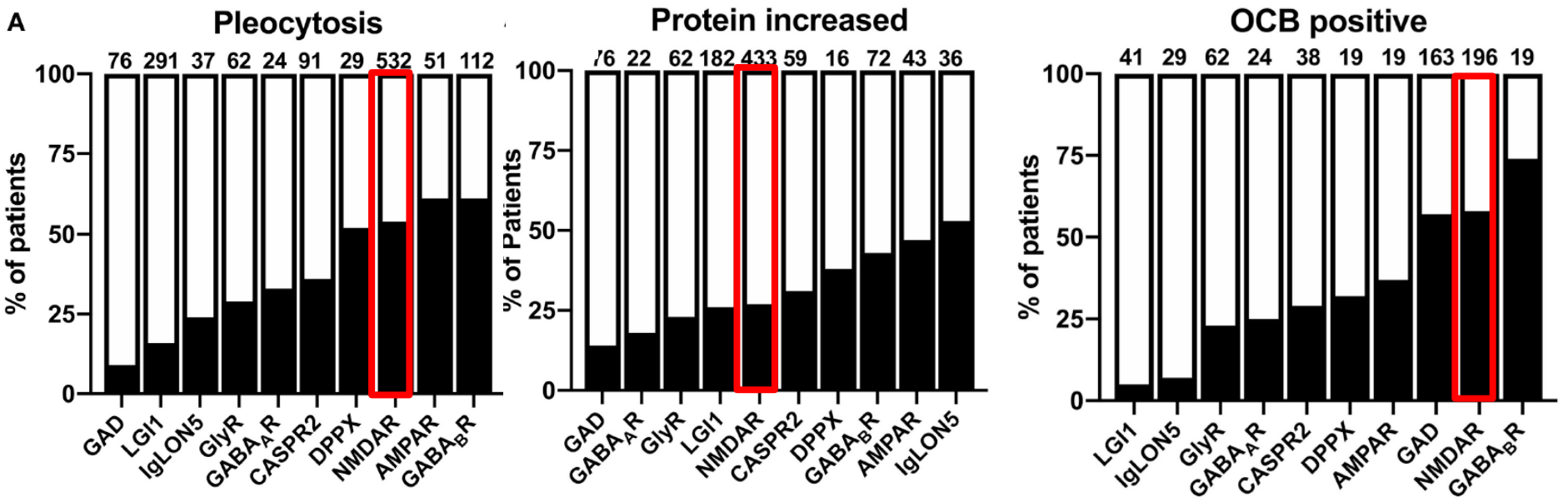




Titer : Serum 1:100, CSF 1:100

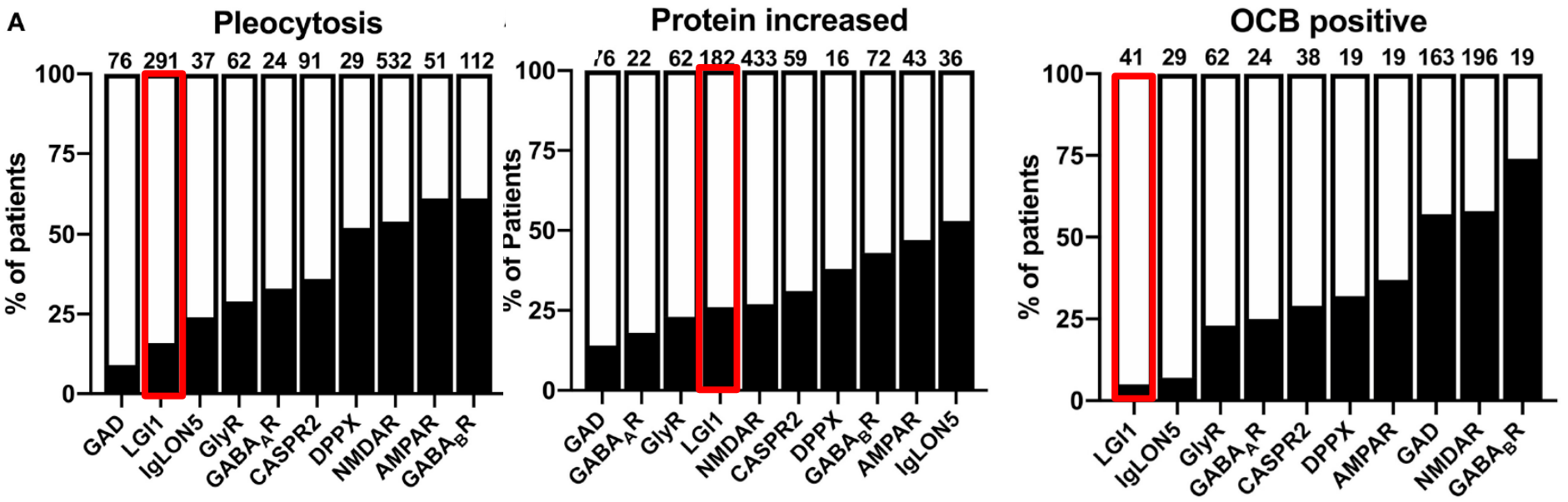
Dalmau, Lancet Neurol. 2011; 10: 63–74,
Titulaer et al., Lancet Neurology 2013; 12: 157-165

Frequency of cerebrospinal fluid abnormalities in auto-immune encephalitides potentially associated with chorea



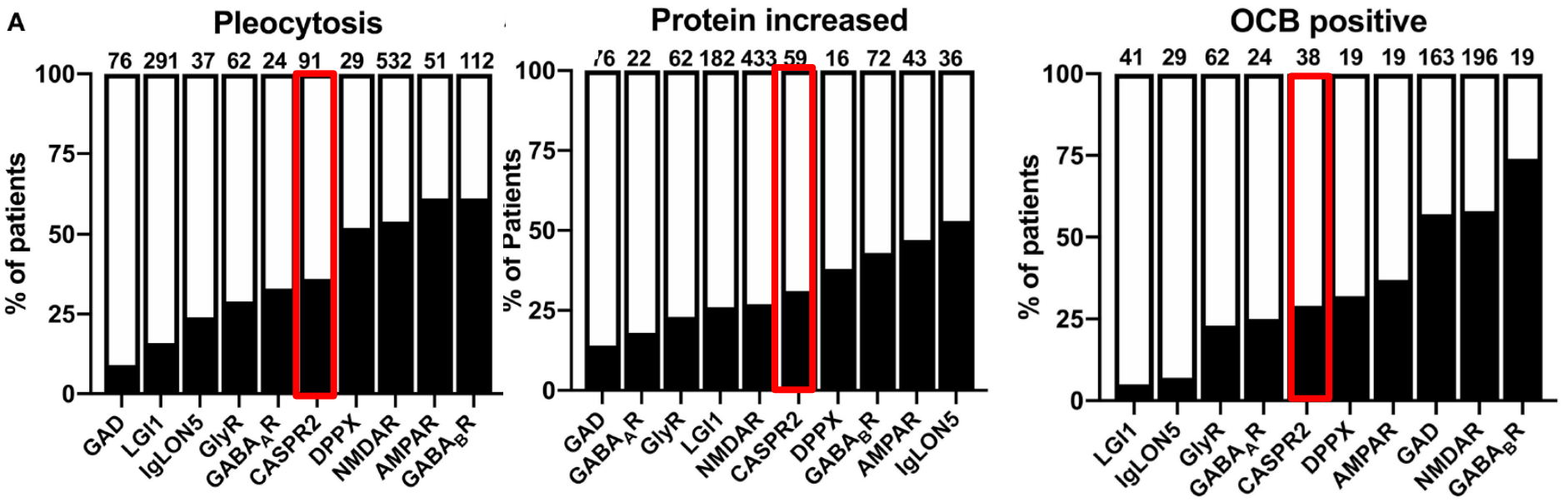
Blinder & Lewerenz Front Neurol 2019 Jul 25;10:804.

Frequency of cerebrospinal fluid abnormalities in auto-immune encephalitides potentially associated with chorea



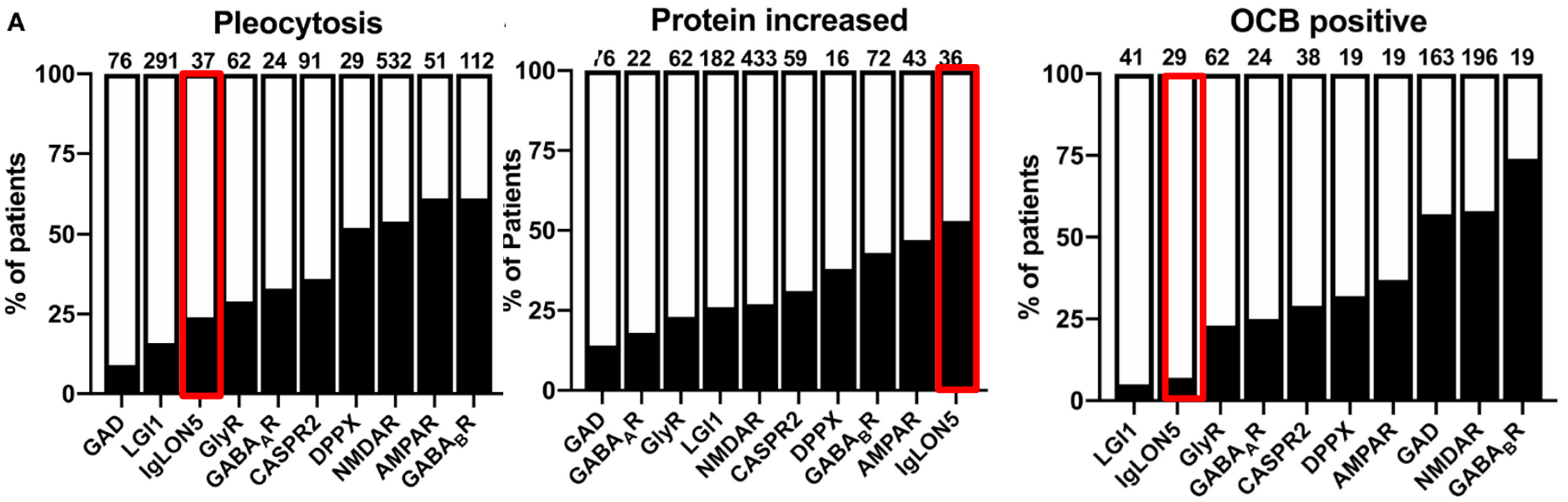
Blinder & Lewerenz Front Neurol 2019 Jul 25;10:804.

Frequency of cerebrospinal fluid abnormalities in auto-immune encephalitides potentially associated with chorea



Blinder & Lewerenz Front Neurol 2019 Jul 25;10:804.

Frequency of cerebrospinal fluid abnormalities in auto-immune encephalitides potentially associated with chorea



Blinder & Lewerenz Front Neurol 2019 Jul 25;10:804.

Q4-Which answer is not correct?

Immune-mediated chorea with detection of brain-specific antibodies

a. warrants immediate immune-modulatory therapy
b. might be associated with different types of tumors, depending on the identified antibody
c. has a poor prognosis
d. cannot be excluded by normal routine CSF findings

Q5-Which statement is not correct?

a. Chorea associated with IgLON5 or Caspr2 antibodies might be associated with sleep dysturbances

b. Fasciculations are mostly found in patients with Caspr2 antibodies

c. Testing serum is sufficient to diagnose autoimmune-encephalitis associated with NMDAR antibodies

d. Positive Caspr2 antibodies in serum can occur without association with a immune-mediated CNS disease

Key Points /Conclusions

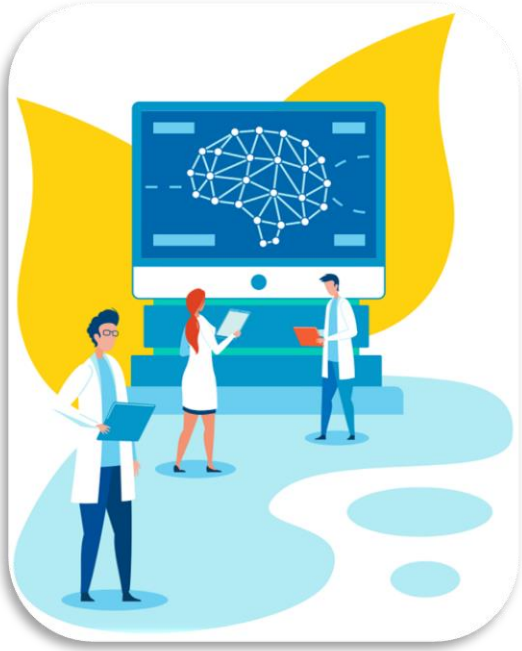
- Autoimmune chorea rarely is often associated with other clinical or laboratory findings that hint to the correct diagnosis
- Rheumatological test and CSF analysis including antineuronal/onconeuronal antibodies should be included in the work-up of unexplained non-hereditary chorea
- Immunotherapy in many cases is beneficial

European Reference Network
for rare or low prevalence complex diseases
Network Neurological Diseases (ERN-RND)

ean european academy of neurology

European Reference Network
for rare or low prevalence complex diseases
Network Neuromuscular Diseases (ERN EURO-NMD)

Joint webinar series



THANK YOU

Next Webinar: ‚Introduction into Leukodystrophies‘
28 January 2020, 15-16h CET