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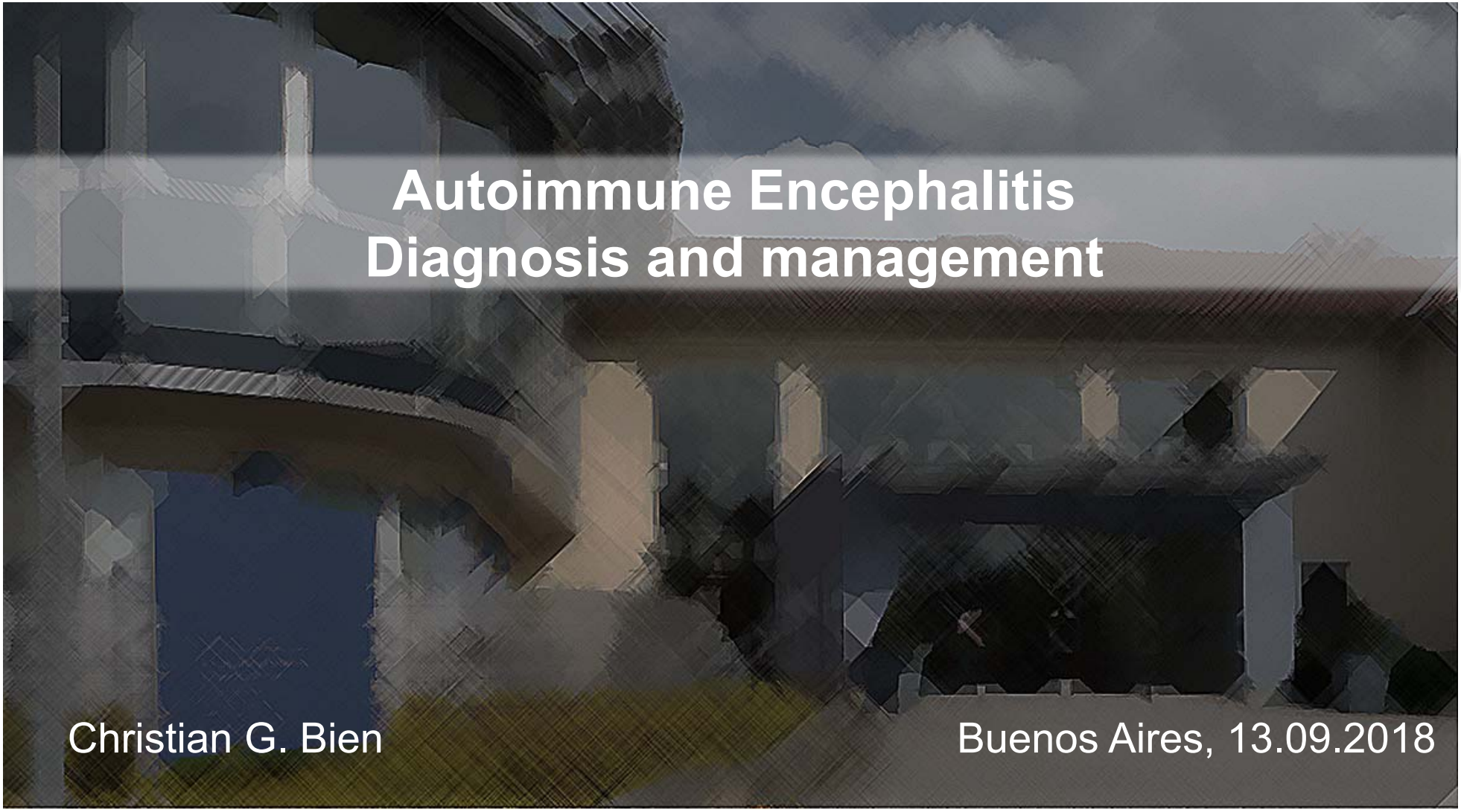
Stiftungsbereich Schulen
Schule für Kranke



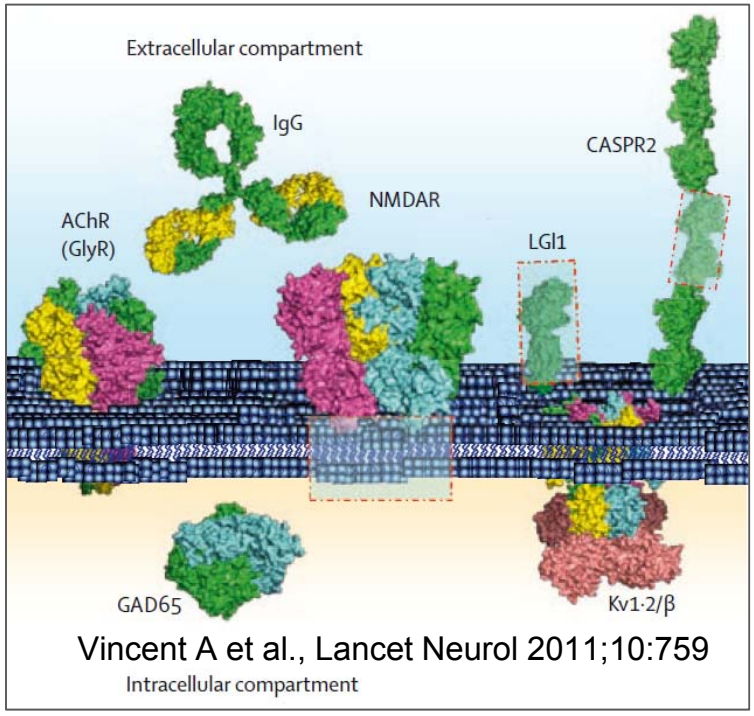
Autoimmune Encephalitis
Diagnosis and management

Christian G. Bien

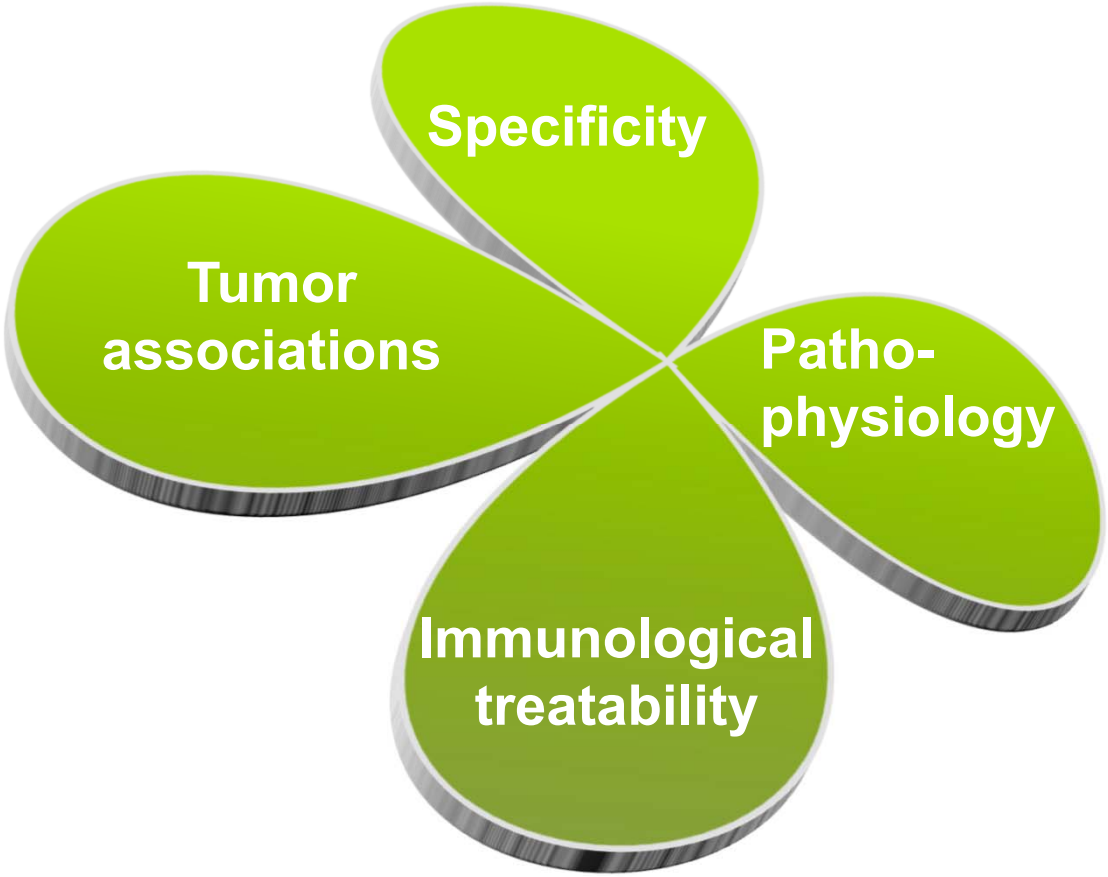
Buenos Aires, 13.09.2018

Autoimmune encephalitis

Four reasons why the neural antibodies are a success story

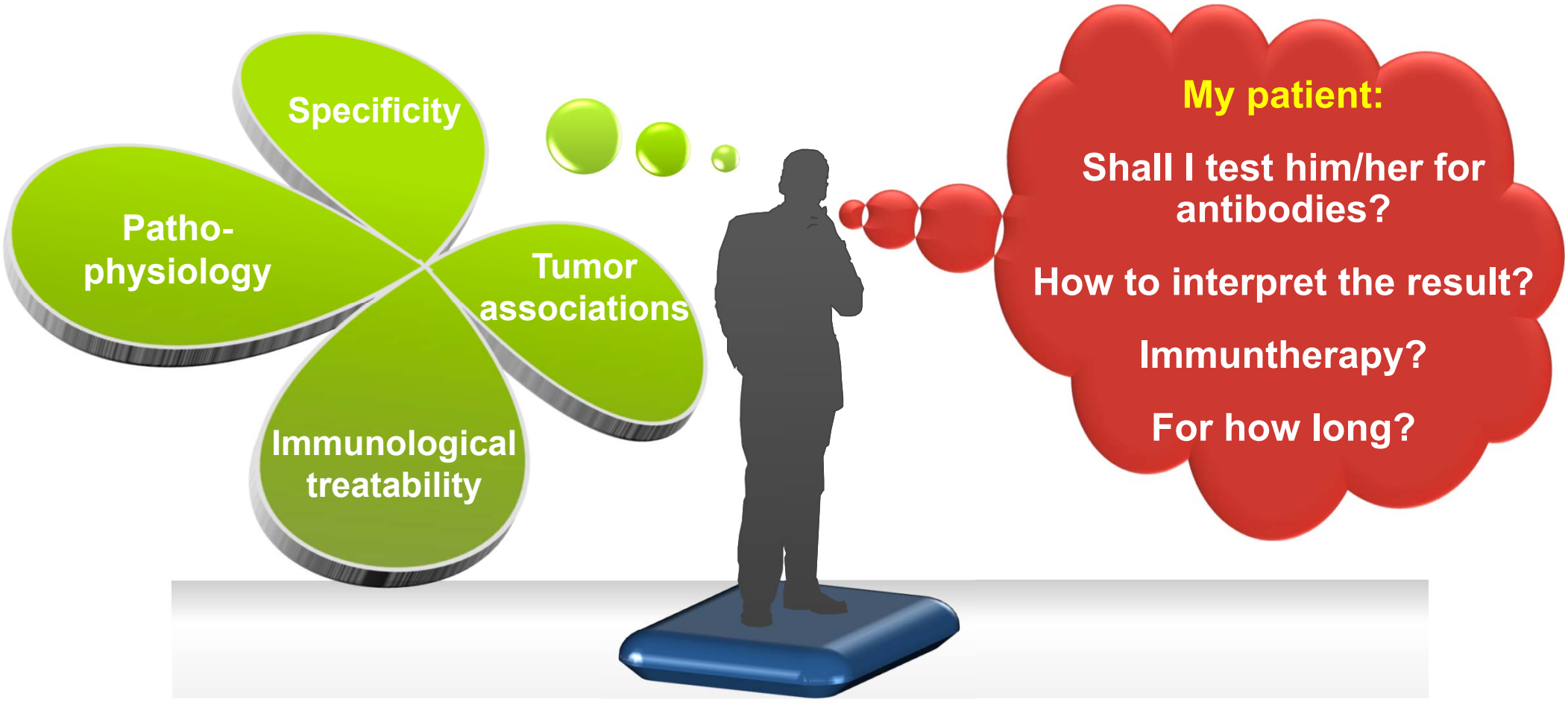


Vincent A et al., Lancet Neurol 2011;10:759



Autoimmune encephalitis

What goes through our heads being clinical neurologists



Autoimmune encephalitis

Traditional order

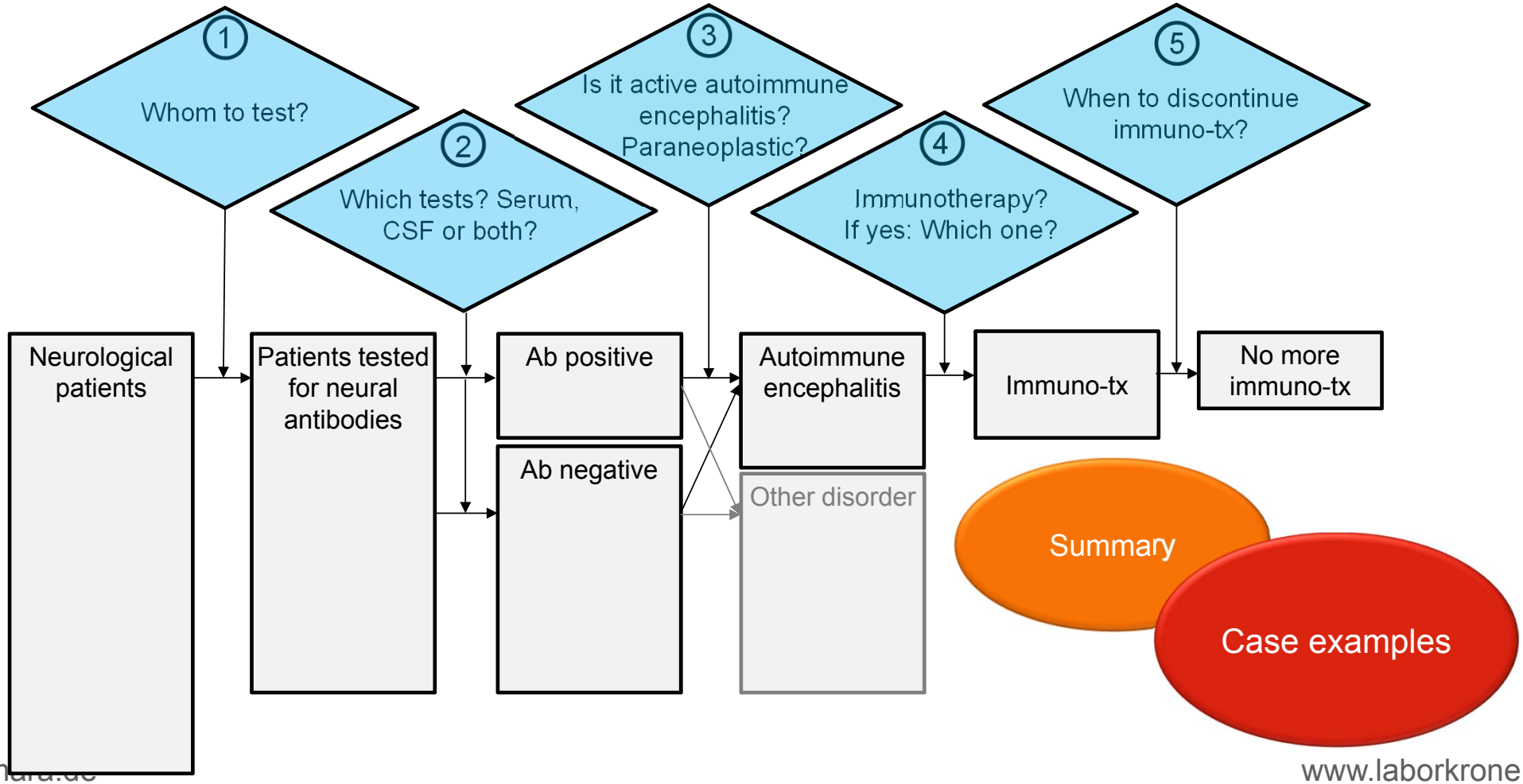
1. Etiology and pathogenesis
2. Epidemiology
3. Clinical characteristics
4. Diagnosis
5. Treatment
6. Prognosis, outcome

"Autoimmune encephalitis in children and adolescents"
Today, 4:30 pm!

"Diagnosis and Management"

Autoimmune encephalitis

Patient flow and the questions to the neurologist



Krankenhaus **MARA**

Autoimmune encephalitis

Titelmasterformat durch Klicken bearbeiten

Epilepsy Center Bethel, Bielefeld
130 beds + 35 epilepsy rehab beds
2900 in-patient cases per year
Mean duration of stay: 16 days
Adults/children = 60%/40%

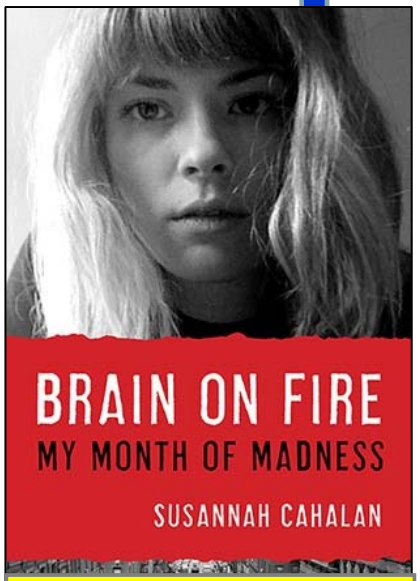
Laboratory Krone, Bad Salzuflen
Antibody diagnostics
Approximately 3000 patients per year tested

Autoimmune encephalitis

Whom to test

Whom to test

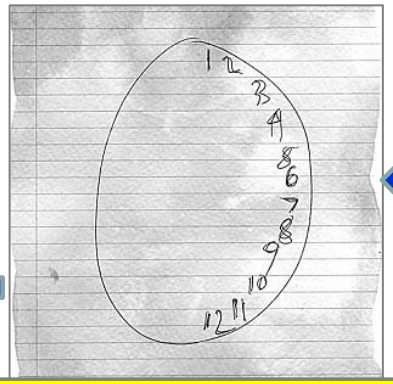
Approach 1: The unusual combination of features



Psychosis

Seizures

Dr. Souhel Najjar



Neglect to the left

Anti-NMDAR-Enzephalitis

Cahalan S: Brain of Fire. My Month of Madness. Free Press/New York 2012

Whom to test

Approach 1: The unusual combination of features

Cahalan S: Brain of Fire. My Month of Madness. Free Press/New York 2012 - Netflix

Whom to test

Approach 2: Checklist to identify ab positive cases

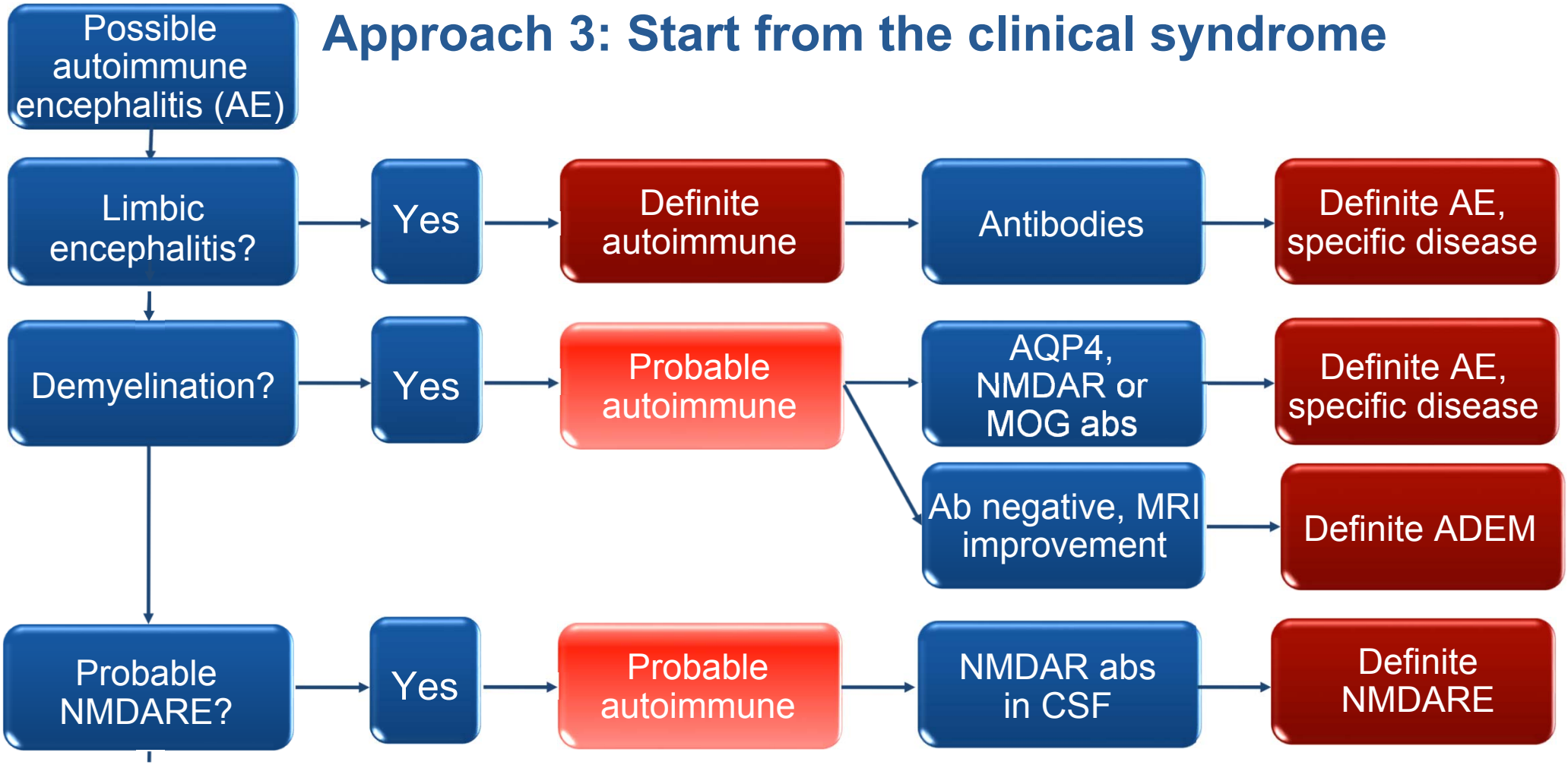
1	New onset progressive mental status changes over 1-6 mo *or* new onset seizures	2	Facial dyskinesias, to be scored in the absence of faciobrachial dystonic seizures
1	Neuropsychiatric changes; agitation, aggressiveness, emotional lability	2	Seizures refractory to ≥2 AED
1	Autonomic dysfunction	2	CSF: protein >50 mg/dL and/or >5 cells/µl
2	Viral prodrome	2	Brain MRI suggesting encephalitis
3	Faciobrachial dystonic seizures	2	Systemic cancer diagnosed within 5 years of neurological symptom onset

If Ab-Prevalence-in-Epilepsy-and-Encephalopathy (APE) score ≥4: positive ab result likely (sensitivity >90% and specificity >70%)

Modified from Dubey D et al., J Neuroimmunol 2018;323:62 (see also Dubey D et al., Epilepsia 2017;58:1181)

Whom to test?

Approach 3: Start from the clinical syndrome



Modified from Graus F et al., Lancet Neurol 2016;15:391

Whom to test

Approach 3: Start from the syndrome

Possible autoimmune encephalitis	Limbic encephalitis	Probable anti-NMDA receptor encephalitis
Subacute (<3 mo) cognitive problems (memory, consciousness, lethargy, personality change) *or* psychiatric symptoms	Subacute (<3 mo) memory problems *or* seizures *or* psychiatric limbic disorder	Subacute (<3 mo) onset of ≥4 : - Abnormal behavior or cognition - Speech dysfunction (pressured speech, verbal reduction, mutism) - Seizures - Movement disorder - Decreased level of consciousness - Autonomic dysfunction or central hypoventilation - *Teratoma can replace 1 point* - *With NMDAR CSF abs, 1 pt is enough*
≥1 of the following: - New focal CNS fi ndings - New onset seizures - CSF: >5 cells/µl - MRI suggestive	Bilateral mediotemporal: MRI-T2/FLAIR signal↑ *or* FDG-PET signal↑	≥1 of the following: - EEG: focal or diffuse slowing, ETP or extreme delta brush - CSF >5 cells/µl or oligoclonal bands
Exclusion of alternative causes: - CNS infection - Septic or metabolic encephalopathy - Intoxication - Brain tumor	≥1 of the following: - CSF >5 cells/µl - EEG: temporal ETP or slowing	Exclusion of alternative causes
	Exclusion of alternative causes	

Bickerstaff brainstem encephalitis | **ADEM** | **Hashimoto** | **Ab-negative but probable autoimmune encephalitis**

Modified from Graus F et al., Lancet Neurol 2016;15:391

Whom to test

Filters for antibody testing?

Suggested filters (Who should probably not be tested)

- Long disease duration (>5 y)
- If you can‘t align the clinical presentation with any autoimmune syndrome
- Generalized epilepsies
- Patients with psychogenic seizures

No good filters

- Normal CSF
- Negative MRI

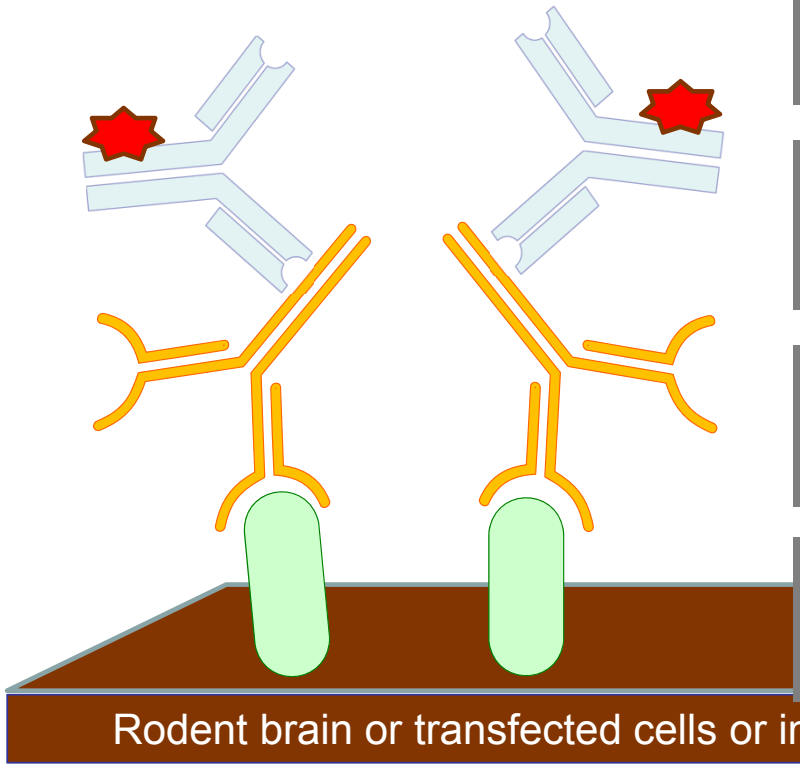
Autoimmune encephalitis

Which tests?

Serum, CSF, both?

Which tests? Which material?

General principle of antibody detection



Dye, coupled to secondary antibody

"Secondary ab" from animal, directed against human IgG gerichtet

Antibodies from patient's blood or CSF

Antigen, e.g. NMDAR or LGI1

Rodent brain or transfected cells or immunoblot

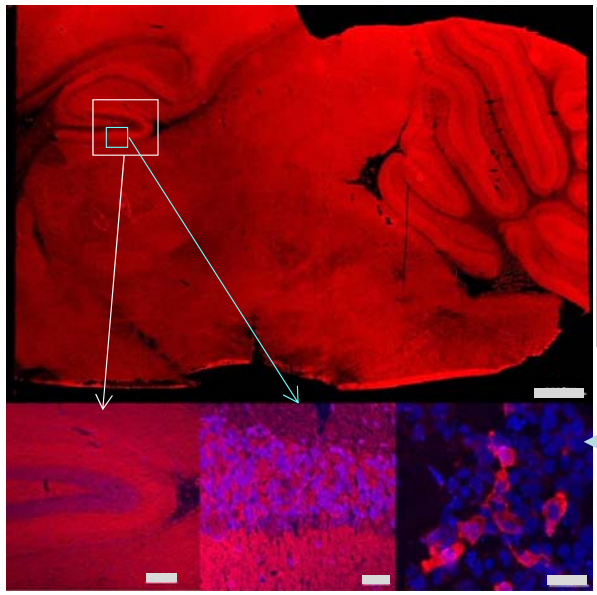
Krankenhaus **MARA**

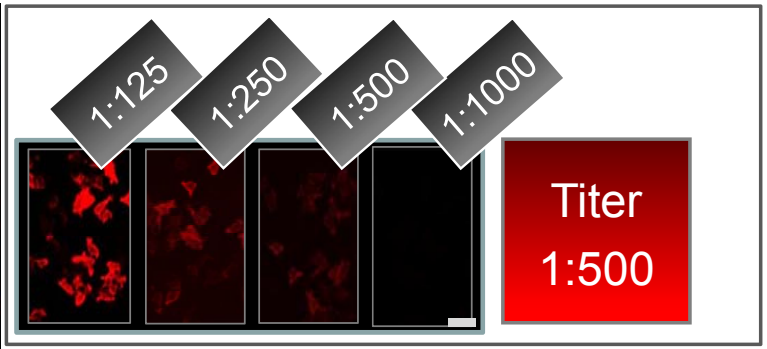
Which tests? Which material?

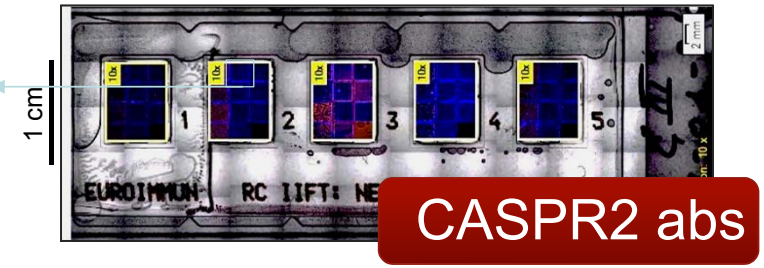
A modern comprehensive testing

Antigens on cell surfaces (NMDAR …)

- Indirect immunofluorescene on mouse brain
- Panels with cell-based assays



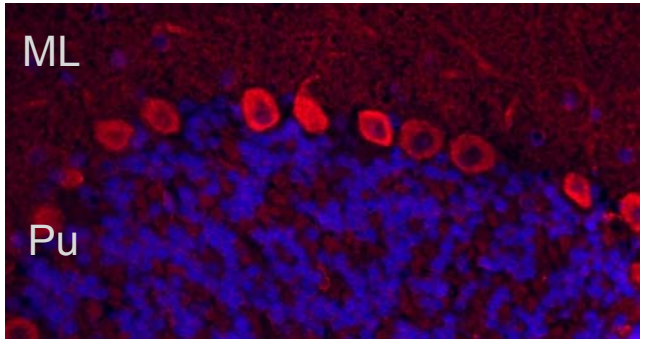




CASPR2 abs

Intracellular antigens

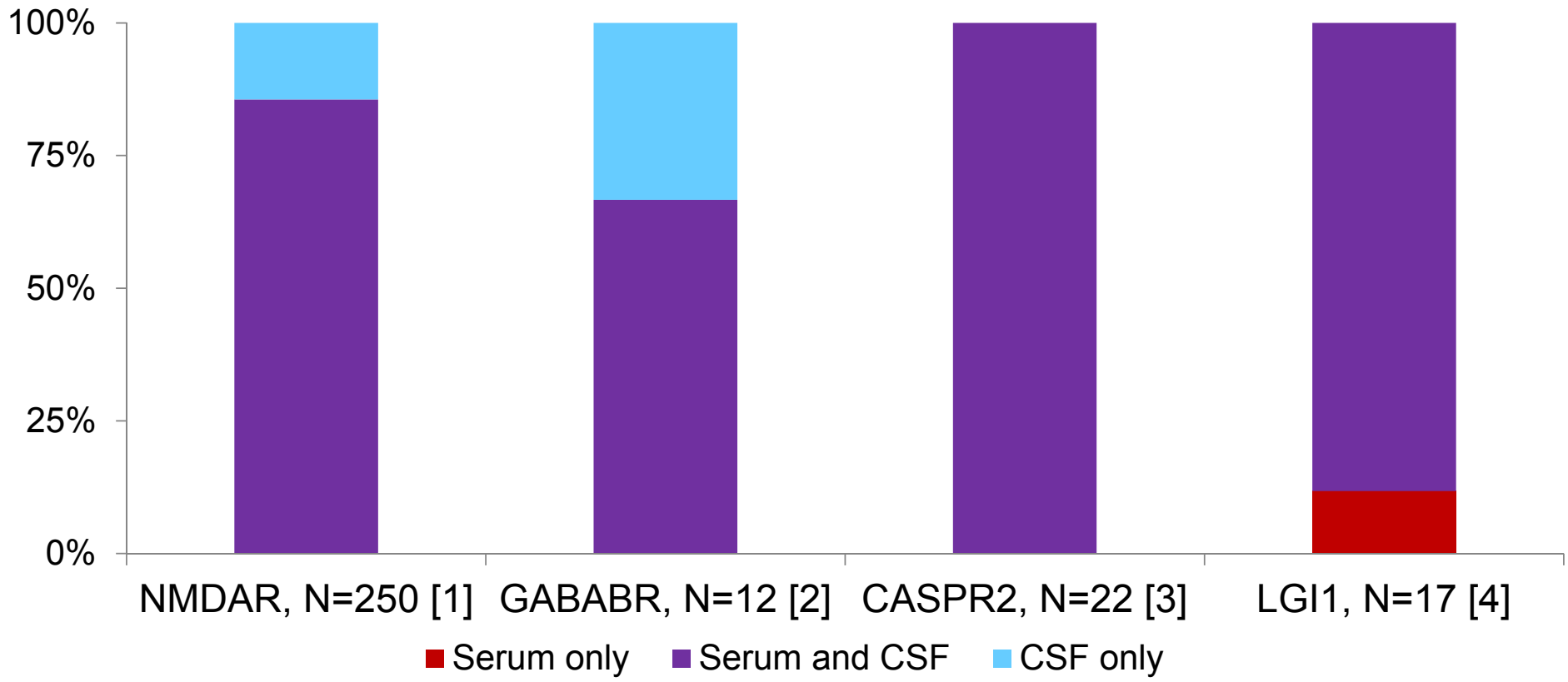
- IIF on mouse brain
- Immunoblot



Yo abs

Which tests? Which material?

Serum, CSF or both? Experience from serum-CSF pairs



[1] Gresa-Arribas N et al., Lancet Neurol 2014;13:167; [2] Höftberger R et al., Neurology 2013;81:1500; [3] van Sonderen A et al., Neurology 2016;87:521; [4] van Sonderen A et al., Neurology 2016;87:1;

Autoimmune encephalitis

Is it active autoimmune encephalitis?

Is it paraneoplastic?

Autoimmune epilepsy

Estimation question to the audience

How many percent of patients have antibodies:

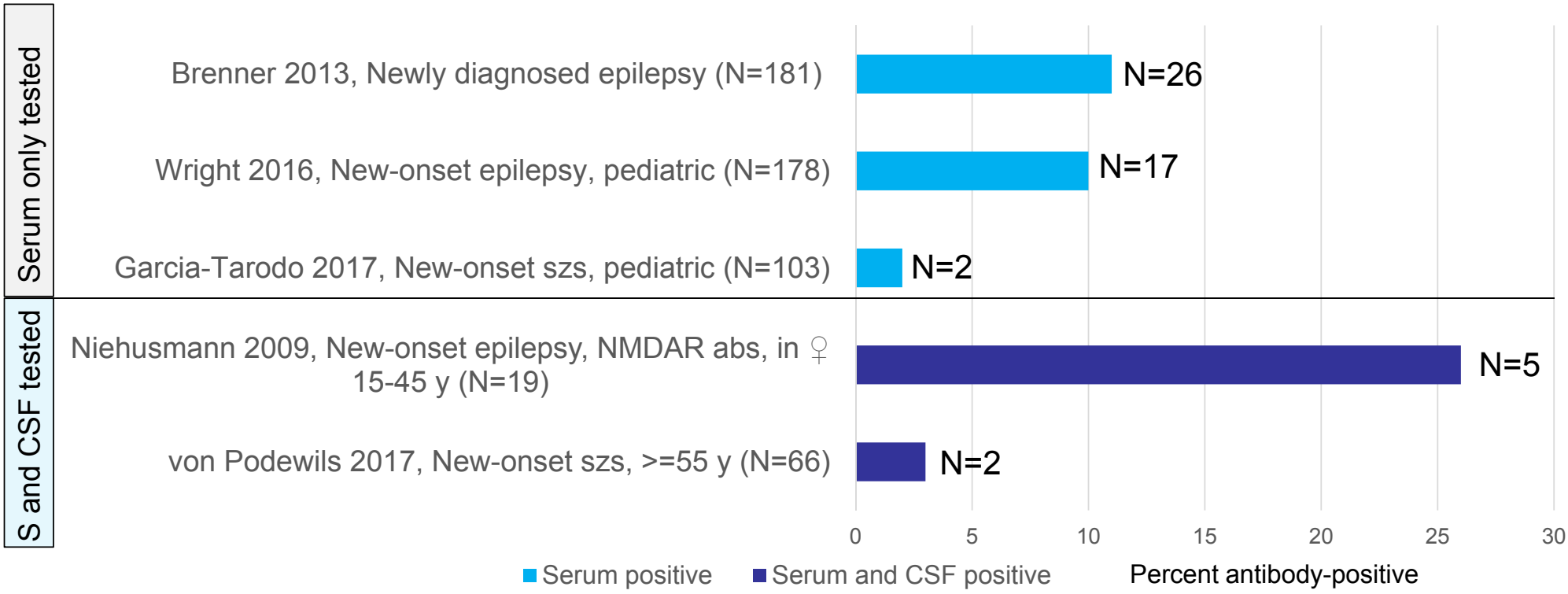
- … with recent onset seizures?
- ... with chronic temporal lobe epilepsy?

Is it active autoimmune encephalitis?

New-onset seizures

Is it active autoimmune encephalitis?

How frequently encountered in new onset-seizures?



von Podewils F et al., Epilepsia 2017;58:1542; Niehusmann P et al., Arch Neurol 2009;66:458; Brenner T et al., Epilepsia 2013;54:1028; Garcia-Tarodo S et al., Eur J Paediatr Neurol 2018;22:396; Wright S et al., Epilepsia 2016;57:823

Is it active autoimmune encephalitis?

Brenner study: high prevalence >16 y – from today's perspective

Patients and Methods

- Clinic cohort, CC - established epilepsies: N=235
- Newly diagnosed cohort, NDC: N=181
- Controls (healthy, OND, autoimmune disorders) : N=148

No specific syndrome

Results

	VGKC	GAD	NMDAR	Gly-R	VGKC/GlyR	Sum
CC	8 (3%)	4 (2%)	3 (1%)	10 (4%)	1 (0.4%)	26 (11%)
NDC	12 (7%)	3 (2%)	4 (2%)	1 (1%)	0	20 (11%)
Controls	2 (1%)	0	0	0	0	2 (1%)

P<0.001

LGI1-/CASPR2-antibody negative, non-specific

Titers? (Low titres neurologically irrelevant)

CSF? Serum only would be non-specific

Titres? <1:50 non-specific

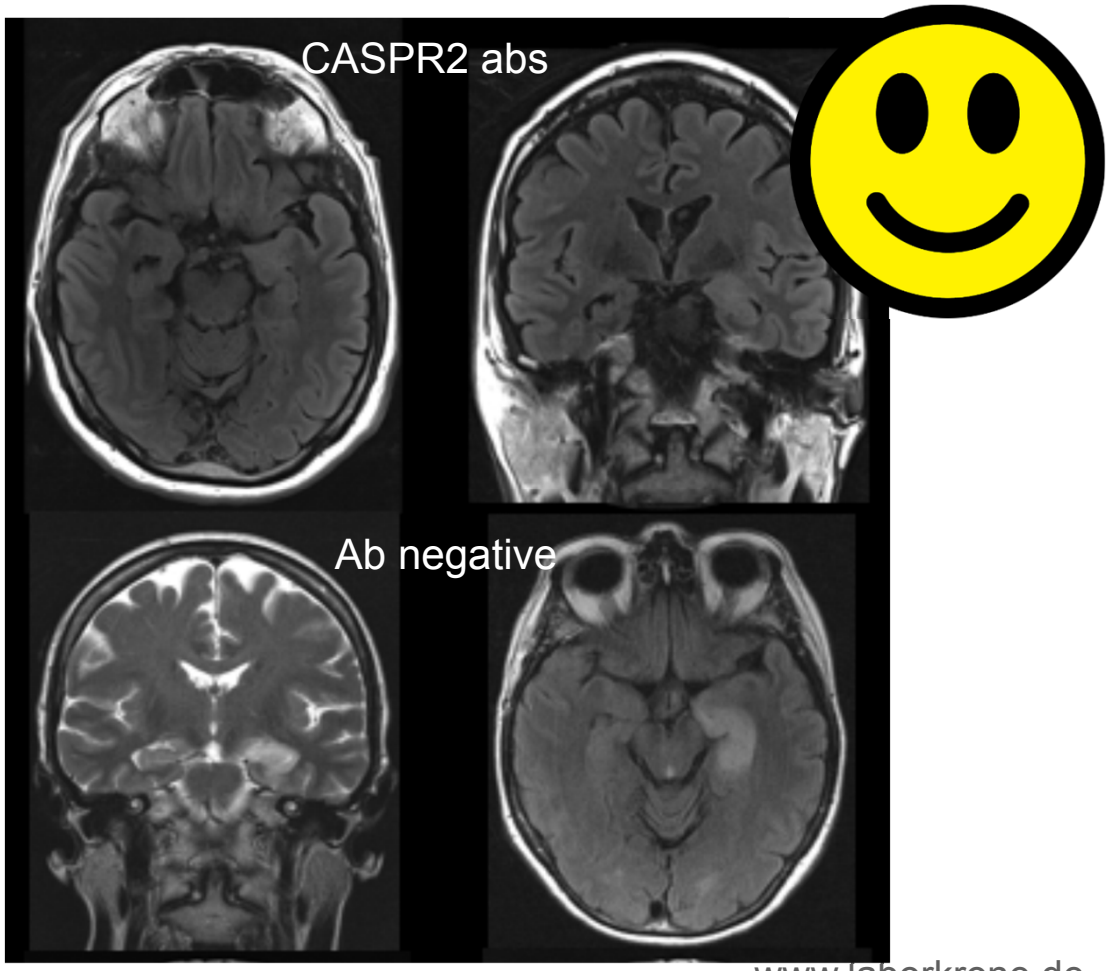
Is it active autoimmune encephalitis?

von Podewils: Prospective serum-CSF study in patients ≥55 yrs

- N=66
- ≥1 seizure in last 6 months
- No obvious cause
- Only specific antibodies were counted

- High-titre CASPR2 abs in serum and CSF, MRI: limbic encephalitis, N=2 (3%)
- Ab negative limbic encephalitis, N=2
- All 4 had memory problems

- 3/4 received corticosteroids; 4/4 received levetiracetam
- After 14-32 months: All sz-free, normal memory



von Podewils F et al., Epilepsia 2017;58:1542

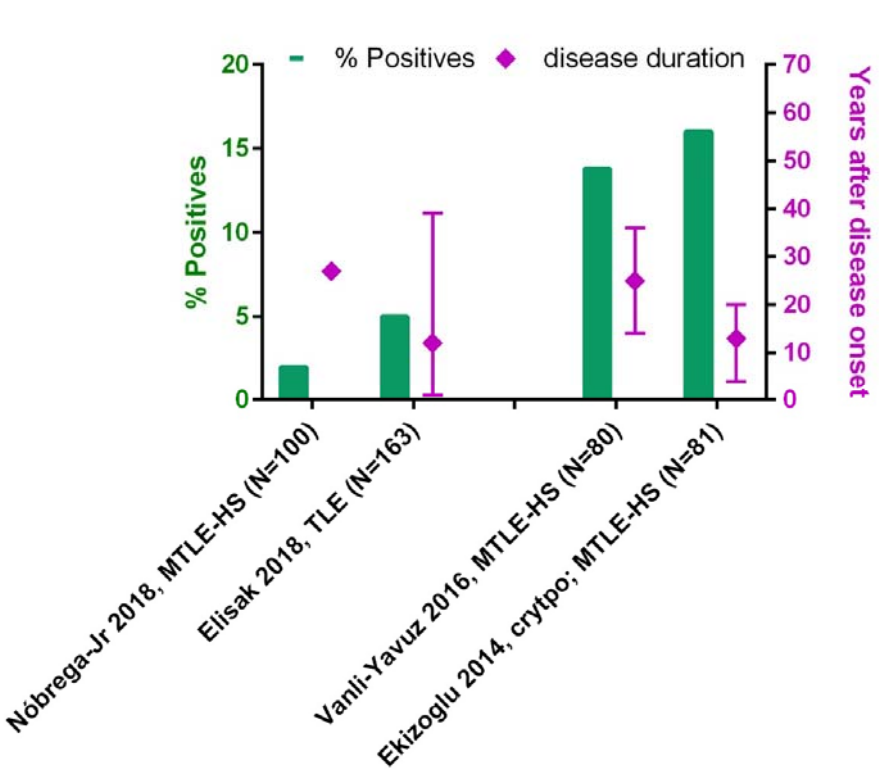
Is it active autoimmune encephalitis?

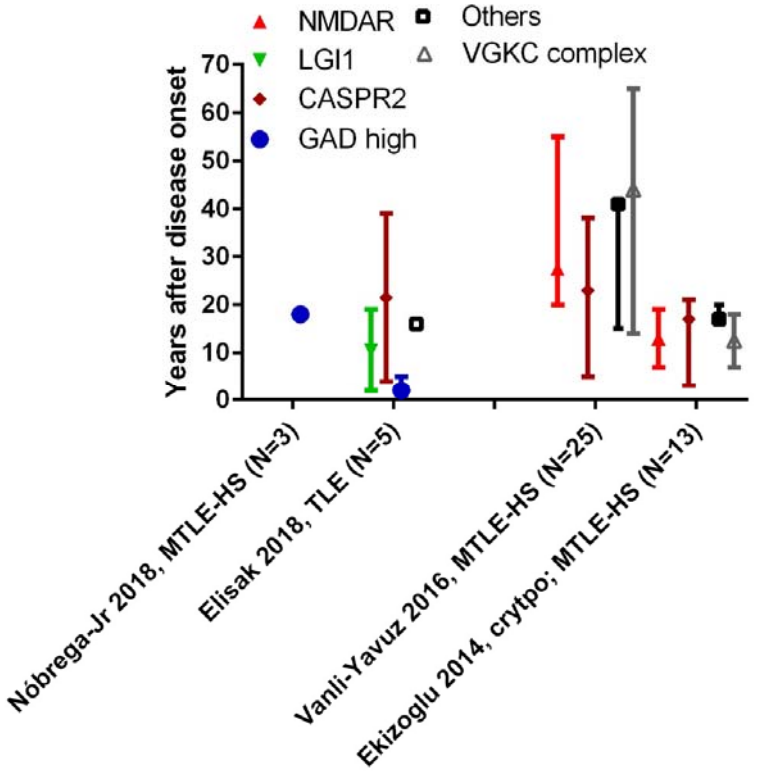
Chronic epilepsy

Krankenhaus **MARA**

Is it active autoimmune encephalitis?

Four serum studies in TLE series

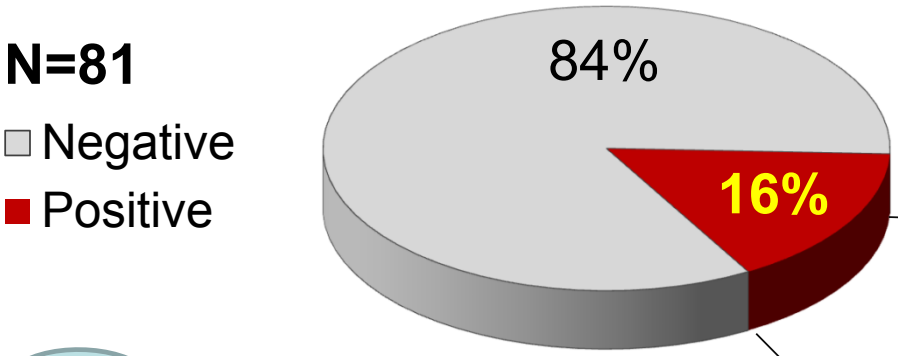




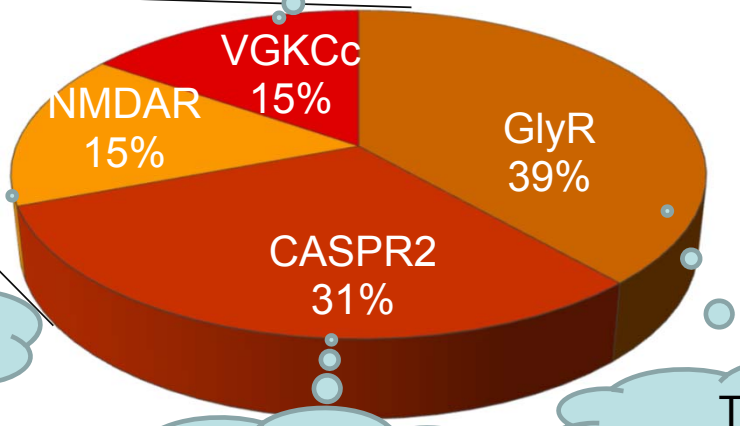
Nóbrega-Jr AW et al., Epilepsia 2018;59:e152; Elisak M et al., Seizure in press;
Vanli-Yavuz EN et al., JNNP 2016;87:684; Ekizoglu E et al., Epilepsia 2014;55:414

Is it active autoimmune encephalitis?

Focal epilepsies of unclear origin or MTLE-HS



LGI1-/CASPR2-
ab negative, non-specific



Immunotherapy w/o
convincing response
(N=3)

CSF? Serum-only
non-specific

Histopathology: no
encephalitis (N=3)

Titres?
<1:128 non-specific

Titres?
<1:50 non-specific

Specificity and relevance not clear for all positives

Ekizoglu E et al., Epilepsia 2014;55:414

Is it active autoimmune encephalitis?

The Elišák study: chronic TLE (>1 y, N=163)

High-titre CASPR2 abs, N=2
4 y and 39 y disease duration
Sz free upon immuno-tx: ½ patients

High-titre GAD abs, N=3
1, 2, 5 y disease duration
≥50% sz reduction upon immuno-tx: 1/3 patients

LGI1 abs, N=2
2, 19 y disease duration
Sz free upon immuno-tx: 1/1 patient

$GABA_BR$ abs, N=1
16 y disease duration, no tumour

Ma2 abs, N=1
6 y disease duration, no tumour
≥50% Sz reduction to immuno-tx, 1/1 patient

8/163 **(5%)** positive for specific abs, all probably fulfilling Graus' criteria for "limbic encephalitis"

3/6 (50%) responded to immuno-tx: 2/6 sz free (2, 4 y disease duration), 1/6 ≥50% sz reduction (2 y)

Elisak et al., Seizure in press. Graus F et al., Lancet Neurol 2016;15:391

Is it active autoimmune encephalitis?

„High-rank antibodies “ vs. „grey cases“

	Syndrom-Spezifität	Spezifität bestätigt	Immunologische Therapierbarkeit
High-rank antibodies against…			
NMDAR in CSF	+	+	+
LGI1	+	+	+
CASPR2 ≥1:128 in serum	+	+	+
AMPAR	+	+	+/-
$GABA_BR$	+	+	+/-
DPPX	+	+	+/-
Grey cases, antibodies against …			
Onconeural antigens	+	+	-
GAD65	+	+	-
IgLON5	+/-	+/-	-
Neurexin 3α	+	-	?
Glycin-R	+/-	-	+/-
mGluR5	+/-	-	?
VGKC-complex, not LGI1, CASPR2	-		+/-
NMDAR in serum only	-		?
CASPR2 <1:128 in serum	-- (exception: Morvan/neuromytonia)		?
$GABA_AR$	?		+/-

Modified from: Bien CG & Holtkamp M, Epilepsy Curr 2017;17:134

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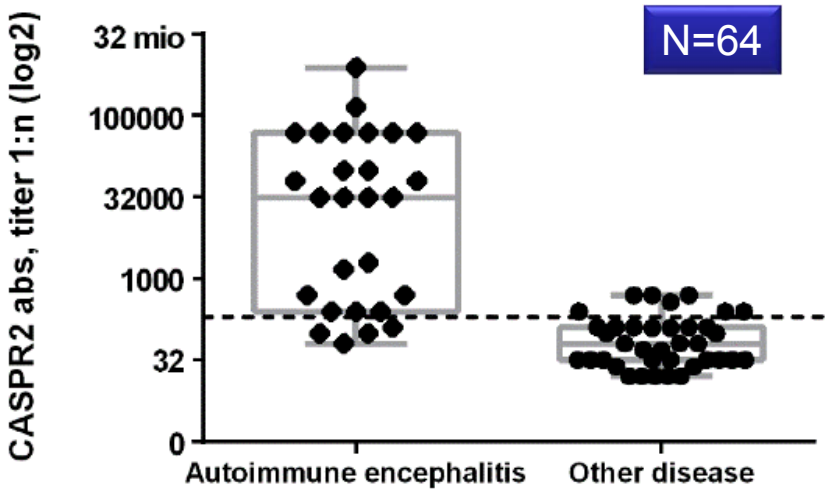
Is it active autoimmune encephalitis?

Specificity by establishing titer cut-offs

CASPR2 antibodies

CASPR2 ab serum titer:
Autoimmune encephalitis
vs. other disease



Bien CG et al., Eur J Neurol 2017;24:175

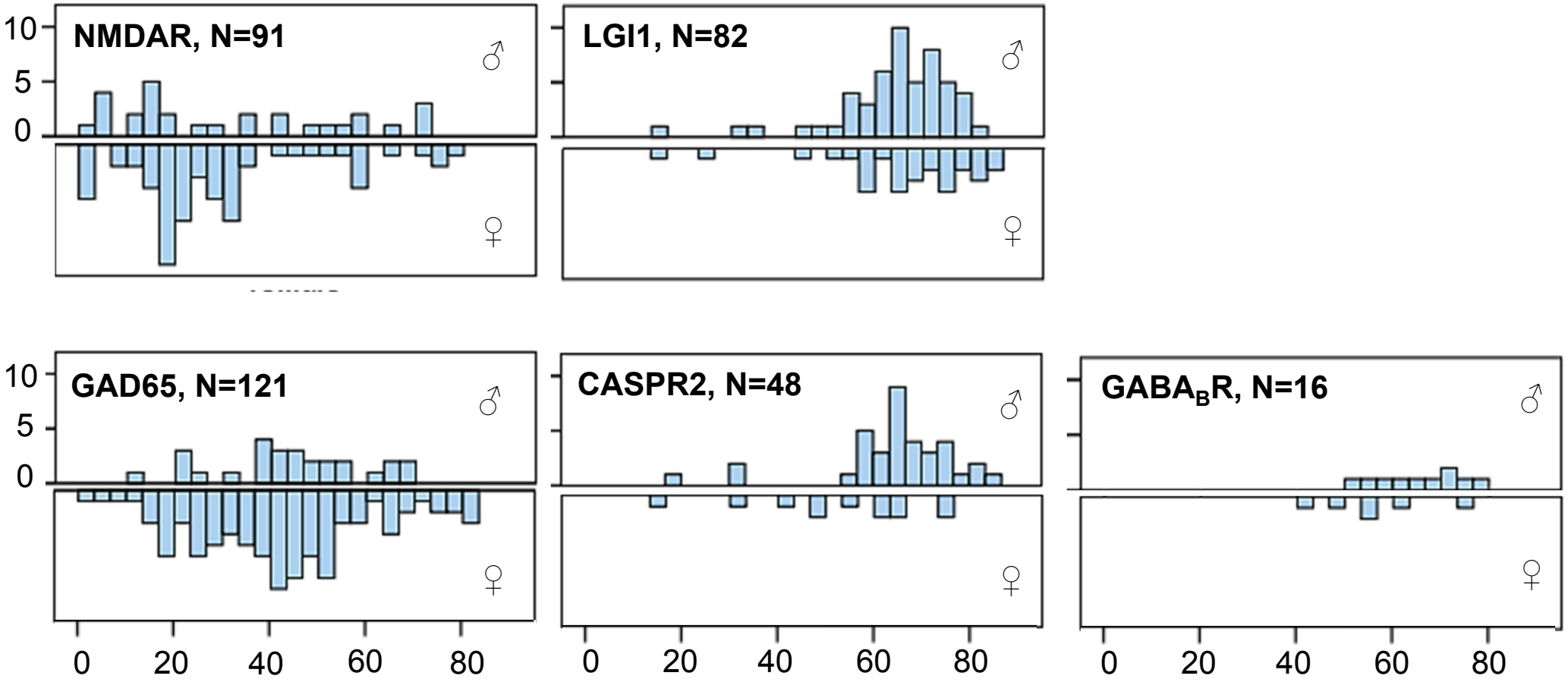
Is it active autoimmune encephalitis?

Plausibility check I: Congruence antibody - syndrome

Antigen	Typical syndromes
NMDAR	• Encephalopathy (multiple areas of CNS affected)
LGI1	• Faciobrachial dystonic seizures • Limbic encephalitis
CASPR2	• Limbic encephalitis • Ataxia • Neuromyotonia • Morvan syndrome
GAD	• Limbic encephalitis • Ataxia • Chronic temporal lobe epilepsy • Stiff-man syndrome

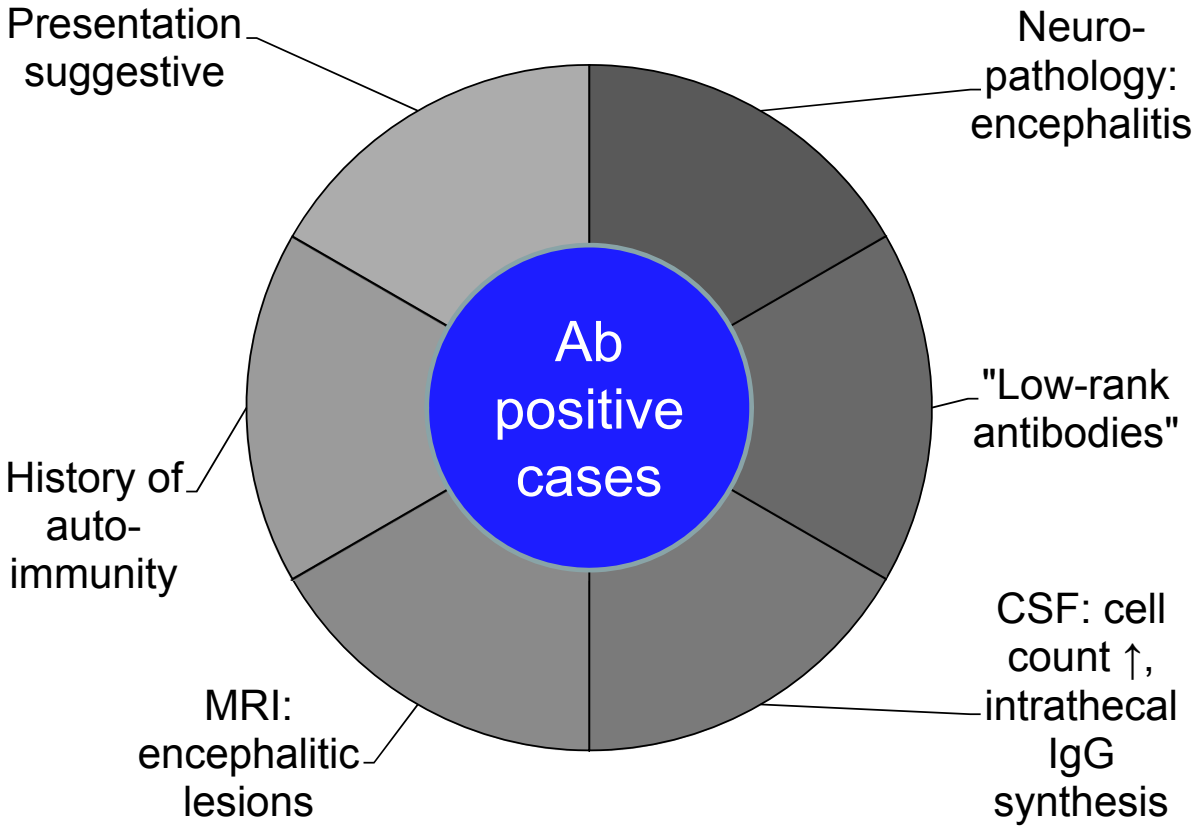
Krankenhaus **MARA**

Is it active autoimmune encephalitis?



Is it active autoimmune encephalitis?

Ab negative cases



Is it active autoimmune encephalitis?

Ab-negative but probable autoimmune encephalitis

Criterion 1	Rapid progression (< 3 mo) of - working memory deficits (short-term memory loss) - **or** altered mental status - **or** psychiatric symptoms
Criterion 2	Exclusion of the before described specific syndromes (limbic encephalitis, Bickerstaff brainstem encephalitis, ADEM)
Criterion 3	Absence of well characterised abs in serum and CSF, and ≥2 of the following: • MRI suggestive of autoimmune encephalitis • CSF: >5 cells/µl, OCB or elevated IgG index • Brain biopsy: encephalitis
Criterion 4	Exclusion of alternative causes

Graus F et al., Lancet Neurol 2016;15:391

Is it paraneoplastic?

It depends on the antibody

Antibodies against	Tumor risk	Most frequent forms
Surface antigens		
NMDAR	25%	Ovarian teratoma
LGI1	7-11%	Divers (paraneoplastic origin doubtful)
CASPR2	5-19%	Thymoma
$GABA_BR$	50%	SCLC
AMPAR	50%	SCLC
Intracellular antigens		
Hu	Very high	SCLC
Ma2		Testis, lung (non-SCLC)
CV2		SCLC, thymoma

If ab with high tumor risk and conventional tumor search is negative: consider FDG-PET

Autoimmune encephalitis

Immunotherapy?

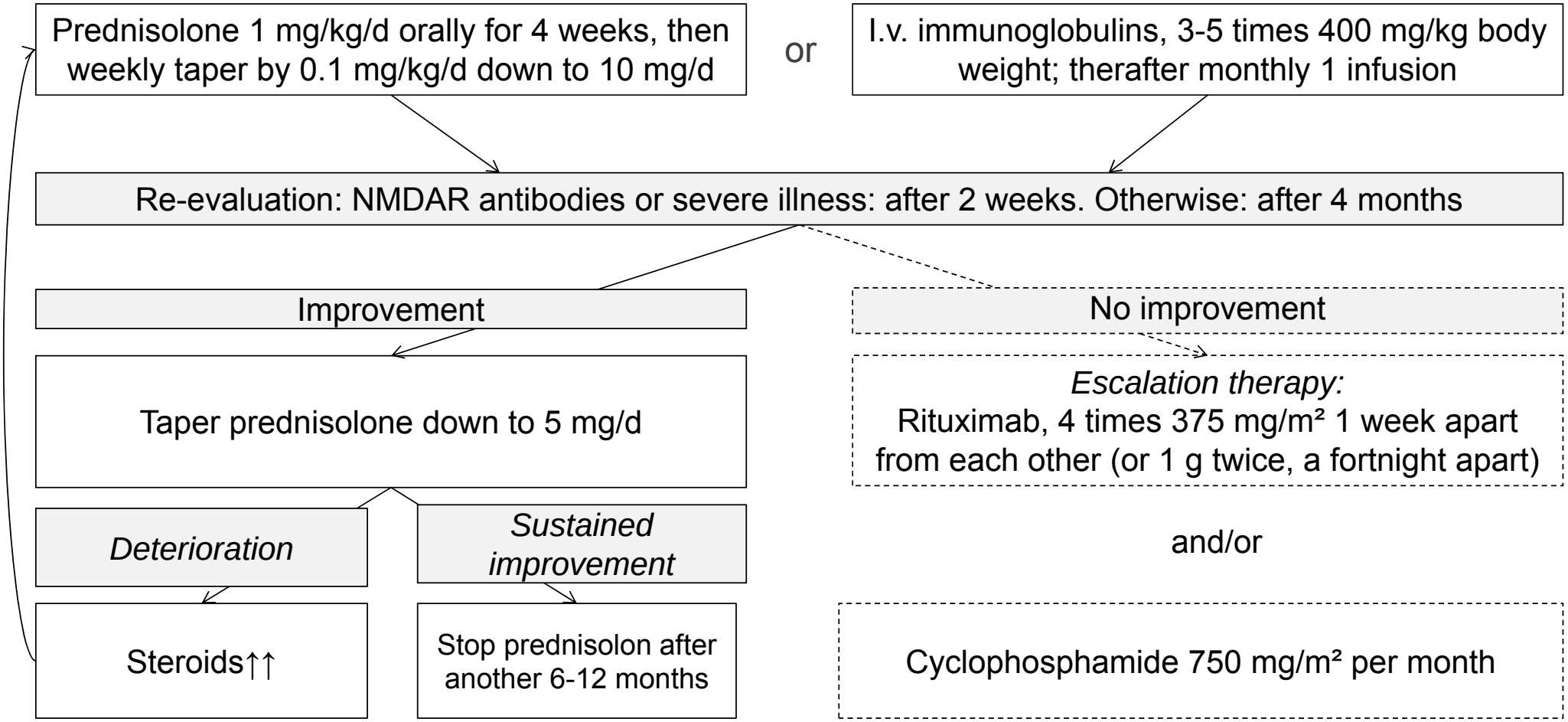
Immunotherapy
1st line/2nd line therapies

First line	
Corticosteroids	
Apheresis	
I.v. immunoglobulins	
Second line (if first line did not work within 10 days)	
Rituximab	4 x 375 mg/m² i.v., weekly administration
Cyclophosphamide	750 mg/m² i.v. per month (for months)

Dalmau J *et al.*, Lancet Neurol 2011;10:63

Immunotherapy

Our approach



Based on Dalmau J *et al.,* Lancet Neurol 2011;10:63 and Irani SR et al., JAMA Neurol 2014;71:896

Krankenhaus **MARA**

Autoimmune encephalitis

How to supervise immuno-tx and when to stop it

How to supervise immuno-tx and when to stop it

No clear recommendations possible

Some data and suggestions

- Basis of decisions: clinical presentation
- Minimum treatment duration: 6-12 months
- Titers may be supportive:
  - CSF titers for anti-NMDARE
  - Serum titers for anti-LGI1 and anti-CASPR2 encephalitis

Encephalitis	Relapse rates
Anti-NMDAR	24%
Anti-LGI1	27-35%
Anti-CASPR2	25%

Gabilondo I et al., Neurology 2011;77:996; Ariño H et al., Neurology 2016;87:759; van Sonderen A et al., Neurology 2016;87:1449; van Sonderen A et al., Neurology 2016;87:521

Krankenhaus **MARA**

Autoimmune encephalitis

Summary

Autoimmune encephalitis

Summary of the five questions

- **Whom to test?** Three strategies:
  1. Unusual combination of symptoms (Dr. Najjar, Susannah Cahalan)
  2. Checklist (Dr. Dubey)
  3. Starting from syndrome (Dr. Graus)
- **Which tests, which material?**
  - Use Ab panels
  - Send CSF-serum pairs
- **Is it active autoimmune encephalitis?** Be critical.
  - Is the antibody “high-rank”?
  - Is the antibody congruent with the syndrome?
  - Do age and gender fit?
- **Immunotherapy?**
  - Yes, if it is active autoimmune encephalitis! 1st line, 2nd line therapy.
  - Careful, if it is a grey case
- **How to monitor therapy? When to stop?**
  - Clinical course decisive, ab titers may help