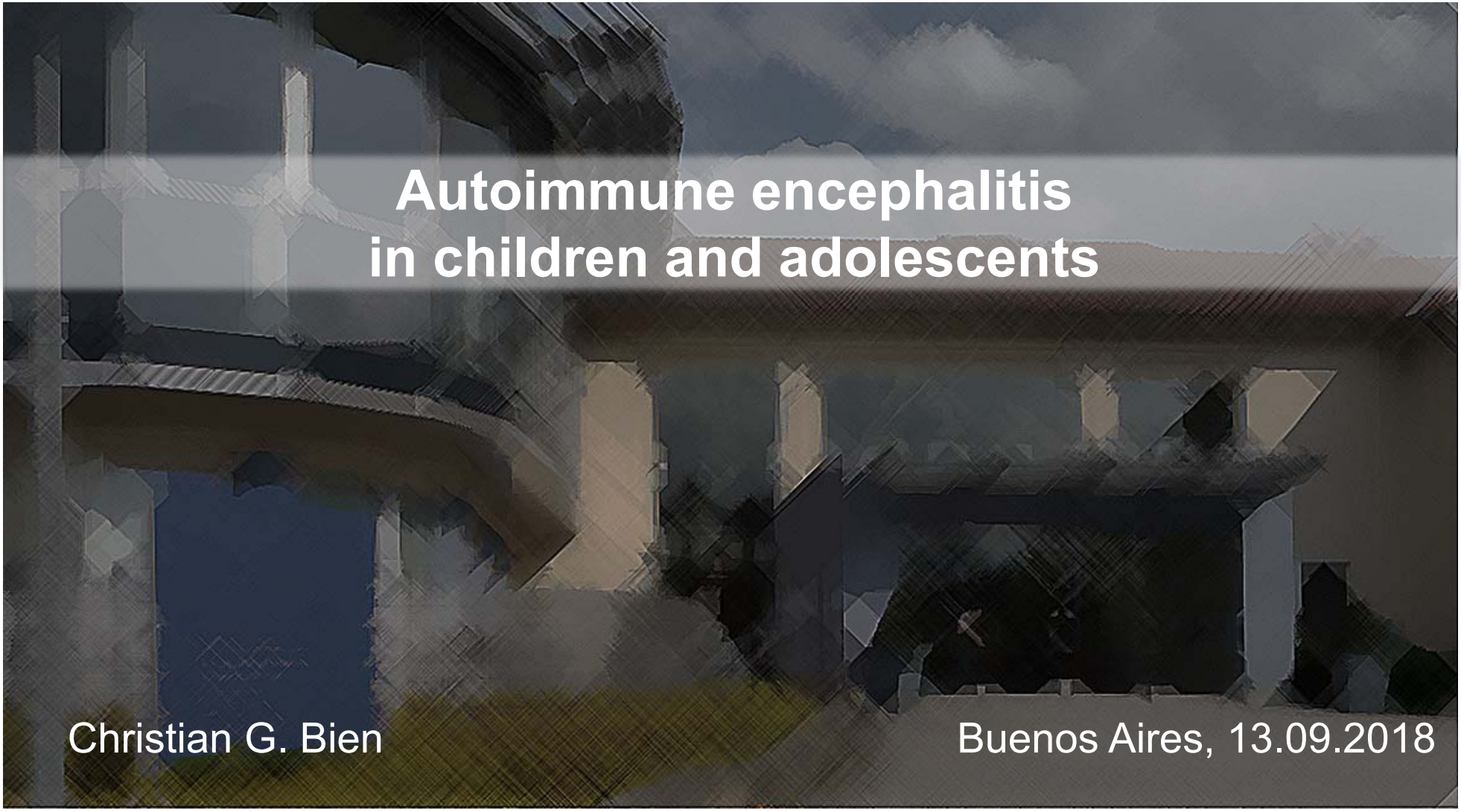
Krankenhaus **MARA**

Krankenhaus **MARA**

labor krone

Bethel



Autoimmune encephalitis in children and adolescents

Christian G. Bien

Buenos Aires, 13.09.2018

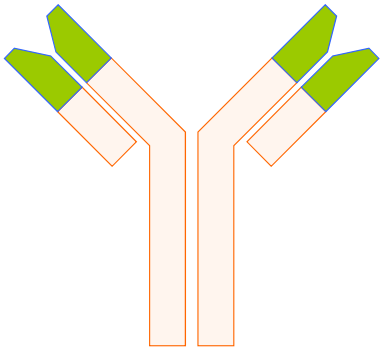
Krankenhaus **MARA**

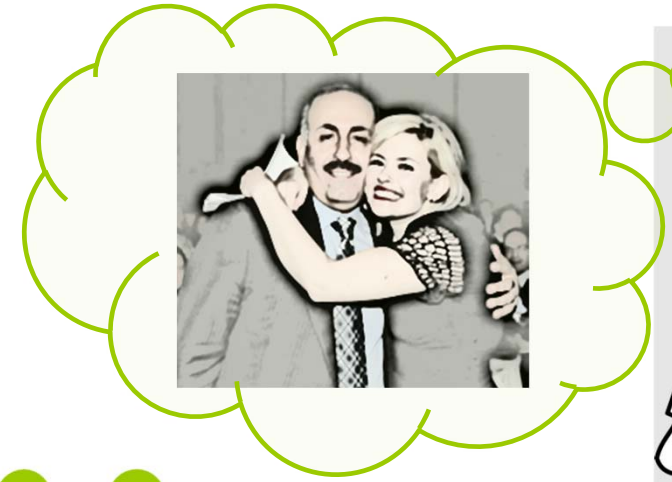
Autoimmune encephalitis in children and adolescents

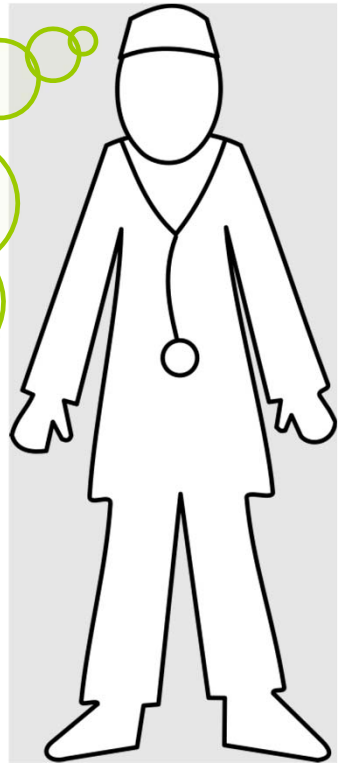
The situation of the neuropediatrician

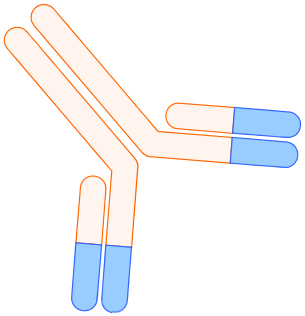
Adult neurology: Great success of autoimmune encephalitides!

…and in Neuropediatrics









Krankenhaus **MARA**

Autoimmune encephalitis in children and adolescents

Order of my talk

1	Rasmussen encephalitis - including etiology and pathogenesis -
	With discussion/training section: one case – is this Rasmussen encephalitis?
2	Pediatric encephalitides with antibodies - including etiology and pathogenesis -
3	Summary

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Autoimmune encephalitis in children and adolescents

My background

Epilepsy Center Bethel, Bielefeld

- Large pediatric section (0-17 y)
- 1200 pediatric in-patients per year (40% of all)
- Presurgical/surgical and conservative sections

www.mara.de

Laboratory Krone, Bad Salzuflen

Antibody diagnostics

Approximately 500 pediatric patients per year tested

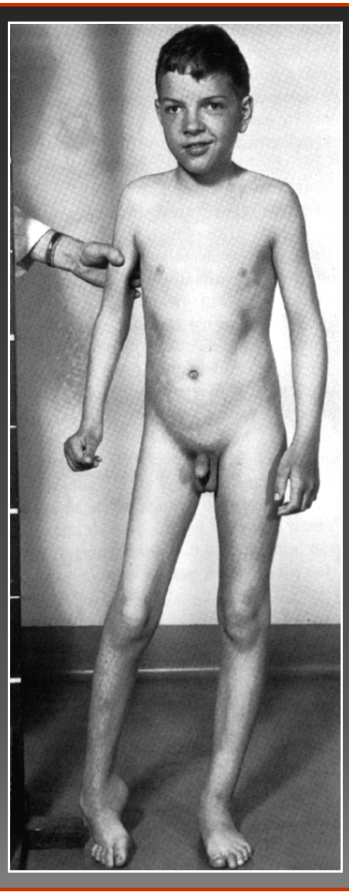
www.laborkrone.de

Autoimmune encephalitis in children and adolescents

Rasmussen encephalitis

Rasmussen encephalitis

Intro



- Rare disorder, mainly of children: 85% < 10 years
- Disease onset usually at age 6
- Pharmacoresistant epileptic seizures, unilateral Epilepsia partialis continua
- Progressive cerebral hemiatrophy
- Progressive unilateral deficit
- Histology: chronic encephalitis

T. B. Rasmussen (1910-2002)

Rasmussen encephalitis

Key messages

- Rasmussen encephalitis can be diagnosed safely
- Rasmussen encephalitis is a destructive disease mediated by cytotoxic T cells
- The only effective therapy is hemispherectomy

Rasmussen encephalitis

Aims

To make you familiar with

- the diagnostic criteria to make appropriate diagnoses
- the destructive process underlies Rasmussen encephalitis
- a suggested treatment algorithm

Rasmussen encephalitis

Potential objections

- The diagnosis of this difficult case always requires an expert. The pathogenesis remains enigmatic and Rasmussen encephalitis is untreatable.
- Diagnosis can be challenging. Fortunately, useful criteria exist – right, sometimes, only the disease course will tell. Etiology is still open but pathogenesis haes ben studied. There are treatment options.

Rasmussen encephalitis

Order of this section

- Definition
- Disease course incl. MRI and EEG
  - Case discussion: Is this Rasmussen encephalitis?
- Pathogenesis
- Treatment

Rasmussen encephalitis

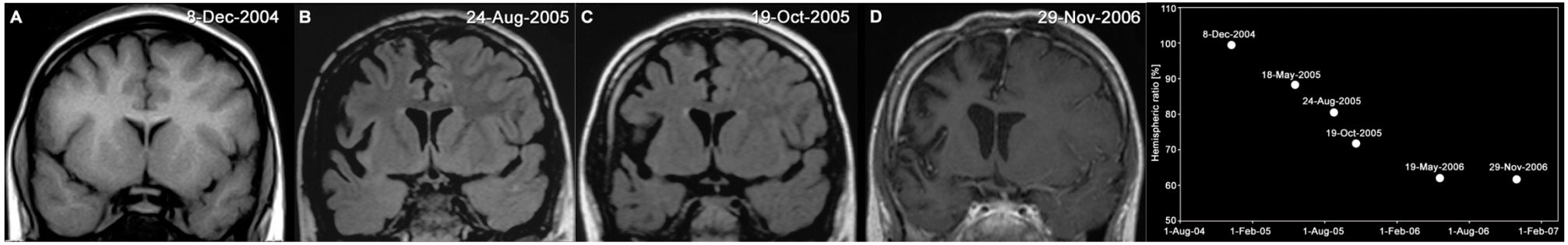
Epidemiology – Serial MRI

Incidence

2,4 cases among 10 mio. children and adolescents* per year

*≤18 y

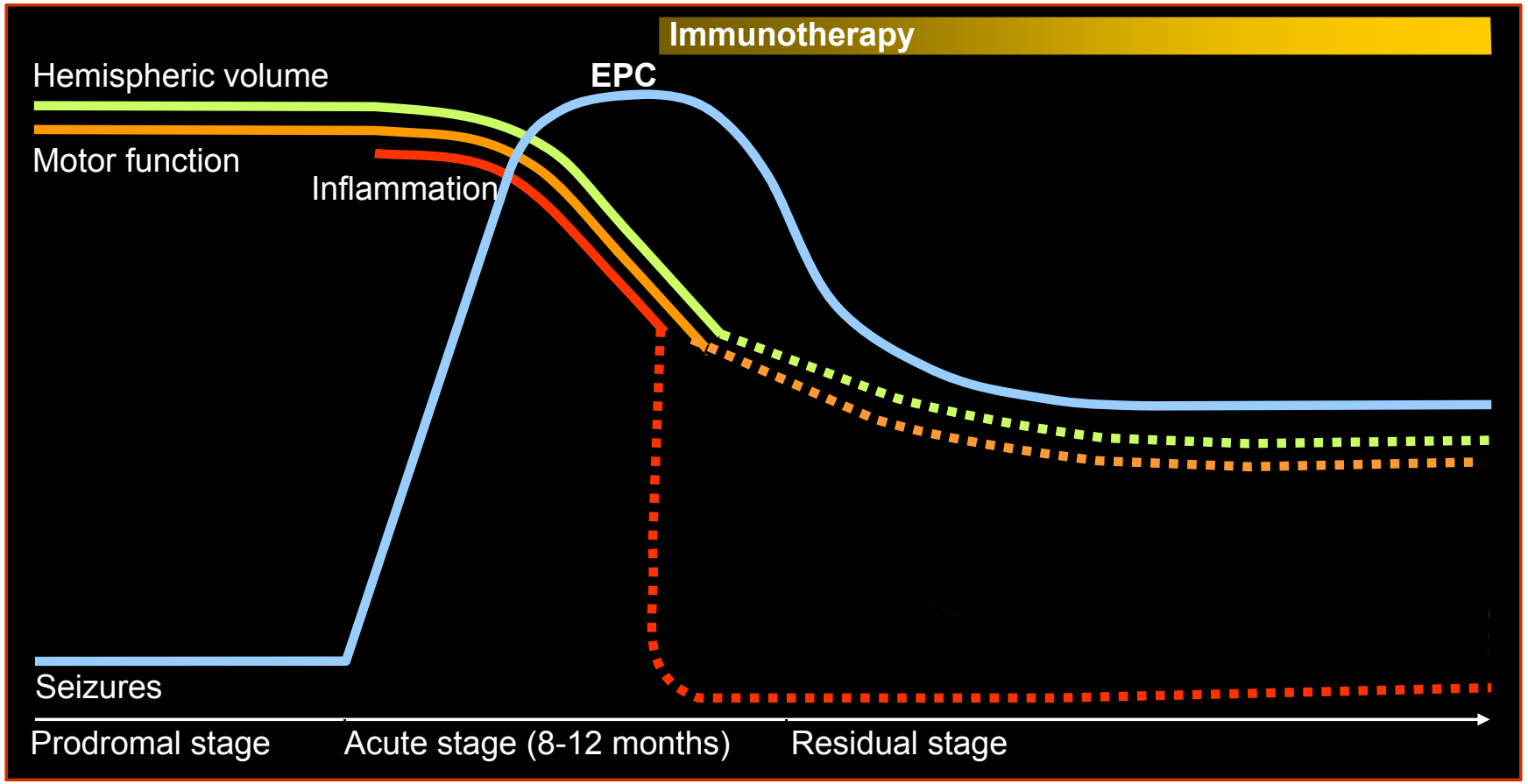
MRI course



Bien CG et al., Epilepsia 2013;54:543; Bien CG, Z Epileptol 2008;21:59

Rasmussen encephalitis

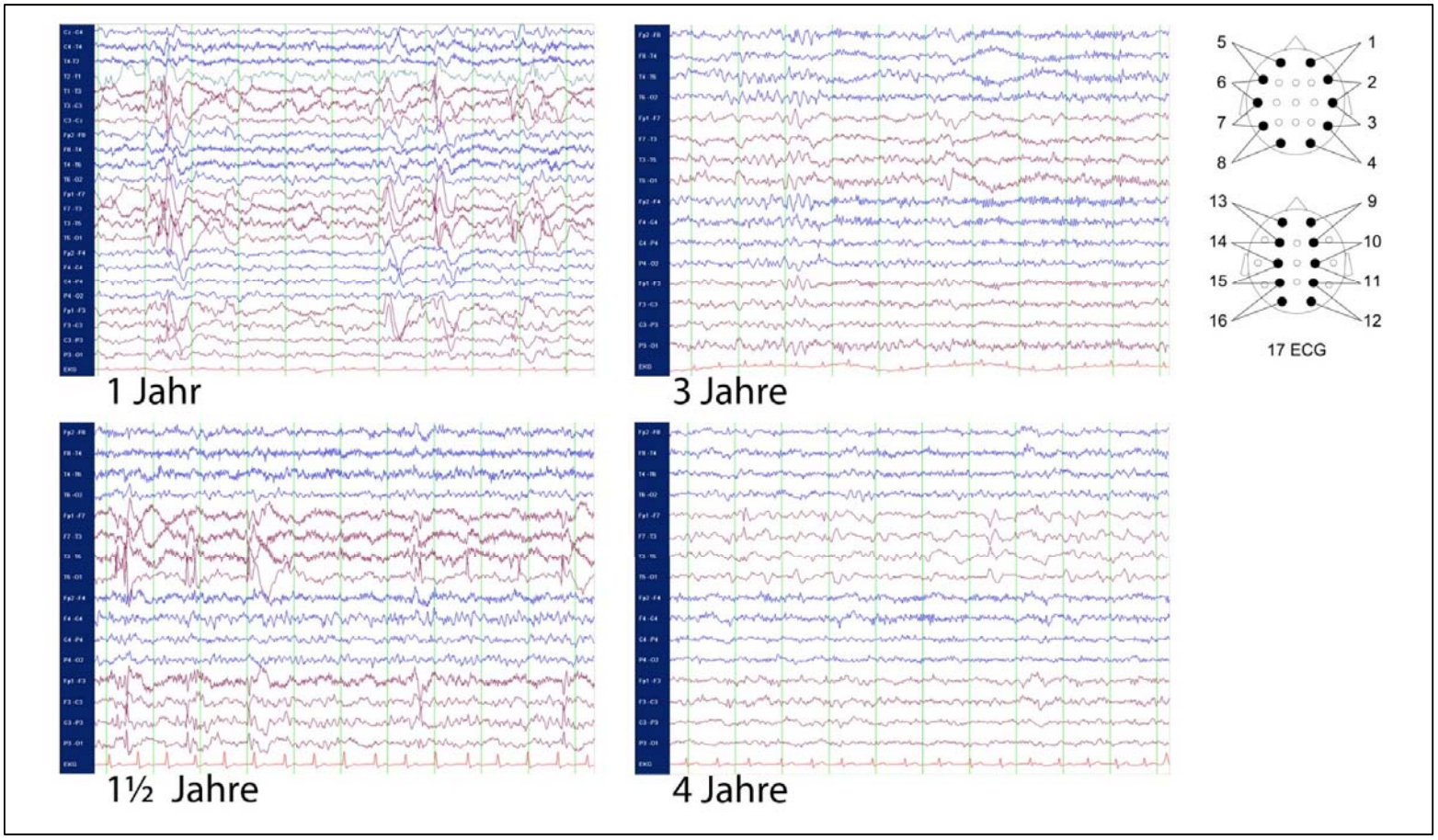
Natural course and expected effect of immuno-tx



Varadkar S et al., Lancet Neurol 2014;13:195

Rasmussen encephalitis

EEG



K., J. ♂ *09.10.1994, University of Bonn, Dept. of Epileptology

Rasmussen encephalitis

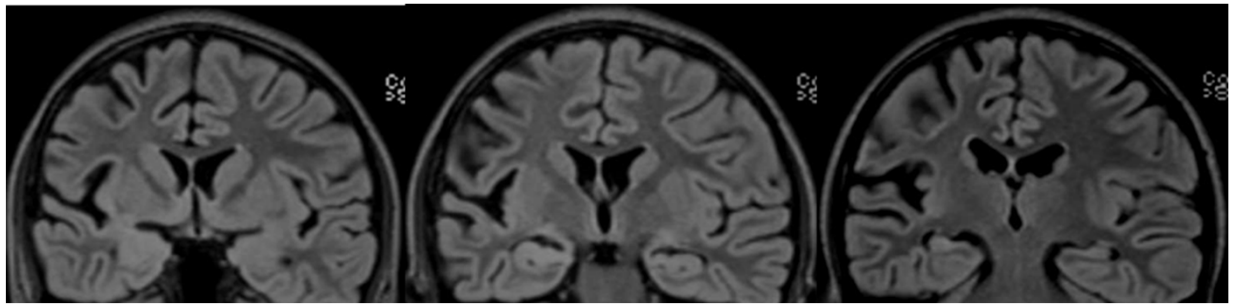
Case:

Is this Rasmussen encephalitis?

Case

R., S. ♀: disease onset at age 8

- Monomorphic focal seizures suggested of right hemisphere onset, 4-5/wk
- No neurological deficit
- EEG:
  - interictal: R hemispheric slowing. Frequent R fronto-temporal spikes
  - ictal: R temporal and frontotemporal area involvement.
- MRI:



- Seizure frequency increases, no effect of multiple drug trials
- Brain biopsy: Chronic encephalitis dominated by T cells. Astrogliosis. No microglial nodules.

Case R., S. ♀

Checking the diagnostic criteria – 1 y 9 mo into the disease

Part-A-criteria (cross-sectional): all 3 must be fulfilled

1. Clinical — Focal seizures (+/- EPC) ***and*** Unilateral cortical deficit(s)
2. EEG — Unihemispheric slowing+/- ETP ***and*** Unilateral seizure onset
3. MRI — Unihemispheric focal cortical atrophy
   and ≥1 of the following:
   (1) Grey or white matter T2/FLAIR hyperintense signal
   (2) Hyperintense signal or atrophy of the ipsilateral caudate head

Part-B-criteria (longitudinal/histopathological): 2/3 must be fulfilled

1. Clinical — Epilepsia partialis continua ***or*** Progressive unilateral cortical deficit(s)
2. MRI — Progressive* unihemispheric focal cortical atrophy
3. Histopathology — T cell dominated encephalitis, activated microglial cells, reactive astrogliosis

Case R., S. ♀, now age 15

8 yrs after disease onset, still 4 szs per day

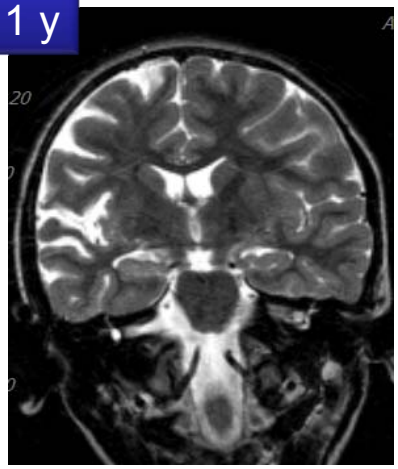
Clinically:

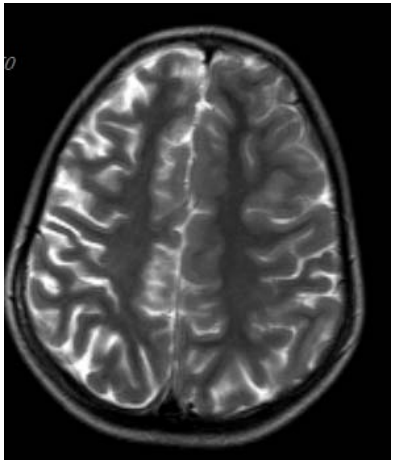
Progressive
R sided
hemiparesis.

But still partly useful
hand motricity.

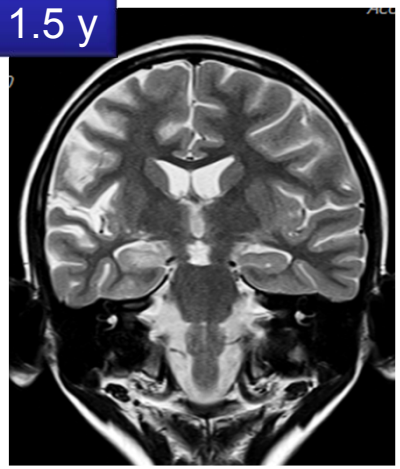
No aphasia.

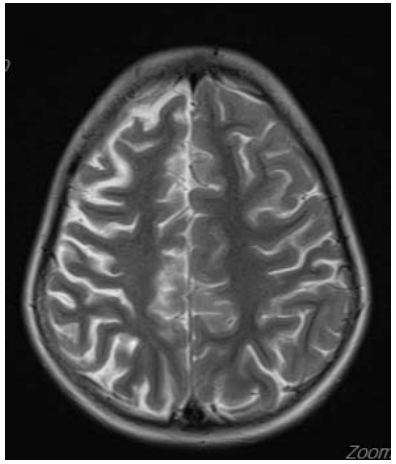
+ 1 y



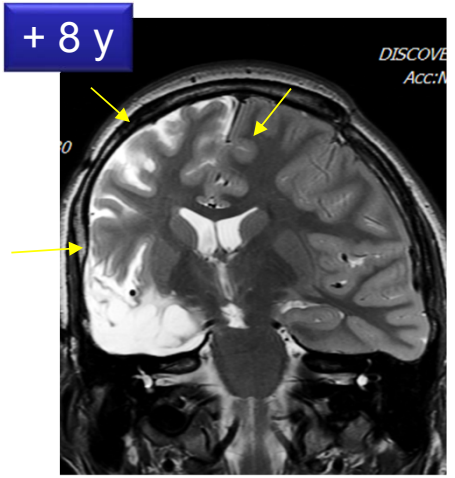


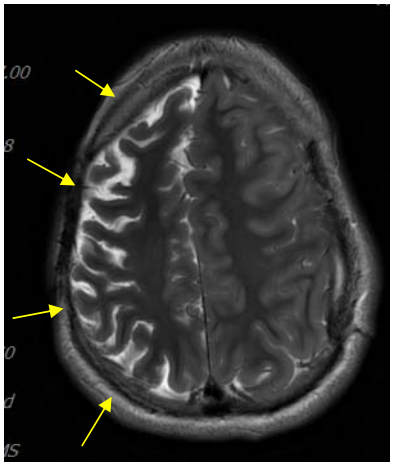
+ 1.5 y





+ 8 y





Case R., S. ♀

Checking the diagnostic criteria – 8 y after onset

Part-A-criteria (cross-sectional): all 3 must be fulfilled

1. Clinical — Focal seizures (+/- EPC) ***and*** Unilaterale cortical deficit(s)
2. EEG — Unihemispheric slowing+/- ETP ***and*** Unilateral seizure onset
3. MRI — Unihemispheric focal cortical atrophy
   and ≥1 of the following:
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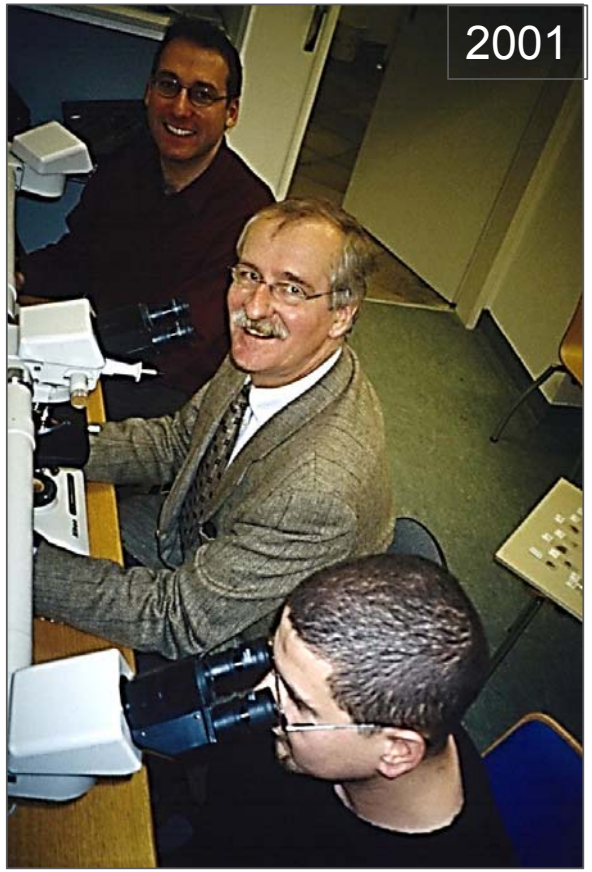
   (2) Hyperintense signal or atrophy of the ipsilateral caudate head

Part-B-criteria (longitudinal/histopathological): 2/3 must be fulfilled

1. Clinical — Epilepsia partialis continua ***or*** Progressive unilateral cortical deficit(s)
2. MRI — Progressive* unihemispheric focal cortical atrophy
3. Histopathology — T cell dominated encephalitis, activated microglial cells, reactive astrogliosis

Rasmussen encephalitis

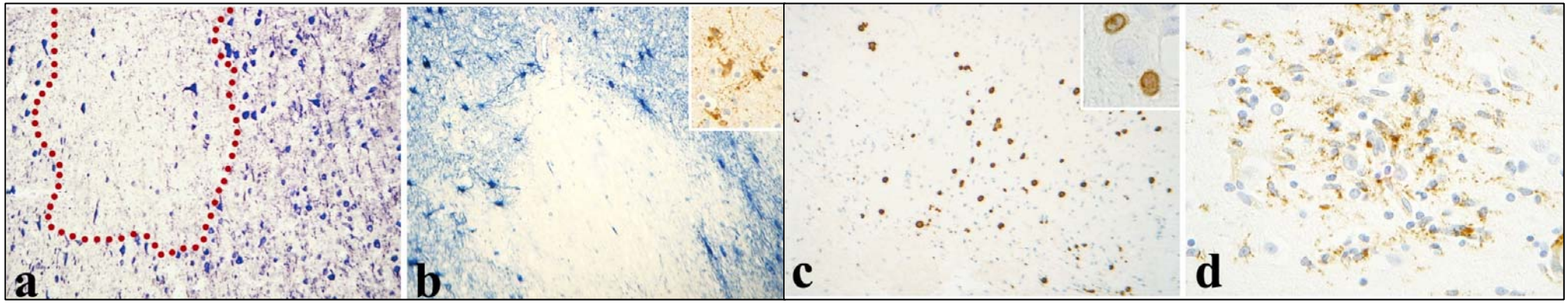
How does it all come about (pathogenesis)?



Center for Brain Research Med. Univ. Vienna
Prof. Hans Lassmann
Prof. Jan Bauer

Rasmussen encephalitis

Immunopathology



MAP2: Neurons

GFAP: Astrozytes. Detail: Apoptotic astrocytes

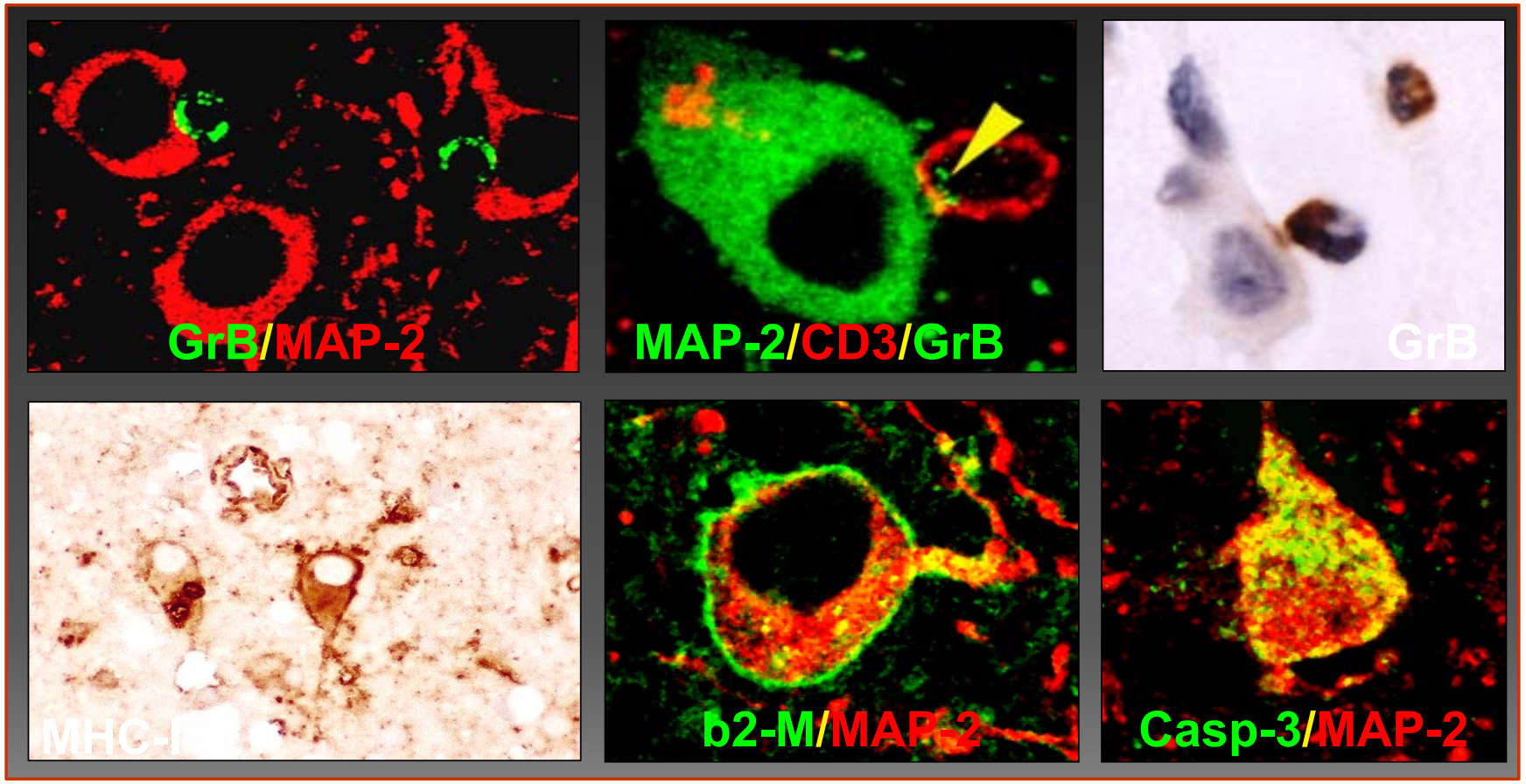
CD8: cytotoxic T-lymphozytes. Detail: Apposition to neurons

CD68: Microglial nodules

Bien CG et al., Epilepsia 2013;54:543; Bien CG J Bauer, in: Inflammatory and Autoimmune Disorders of the Nervous System in Children, Dale, RC, A Vincent, Eds. (Mac Keith Press, London, 2010).

Rasmussen encephalitis

Cytotoxic T cell attack against neurons



Bien CG et al., Ann Neurol 2002;51:311

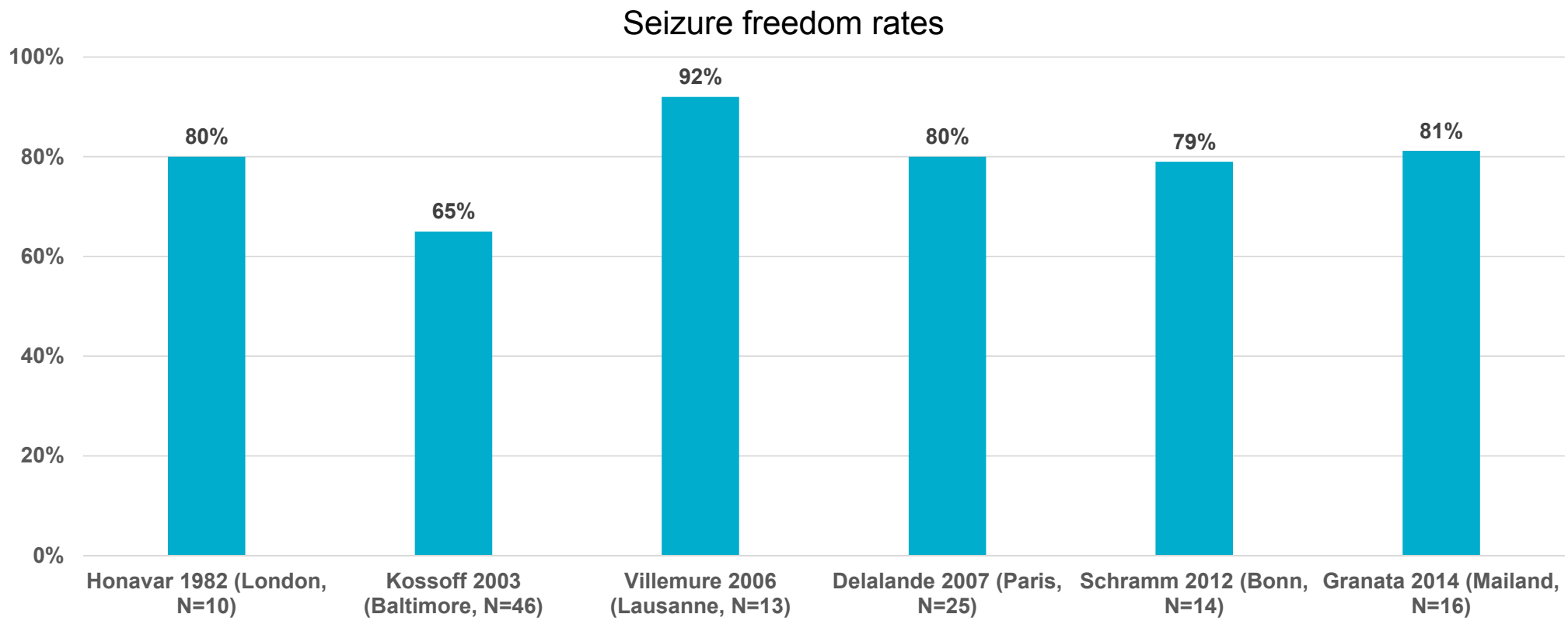
Rasmussen-Enzephalitis

Epilepsia partialis continua

M., C. ♀ 12 y. University of Bonn, Dept of Epileptology

Rasmussen encephalitis

Hemispherectomy outcome



Rasmussen encephalitis

Immunotherapy

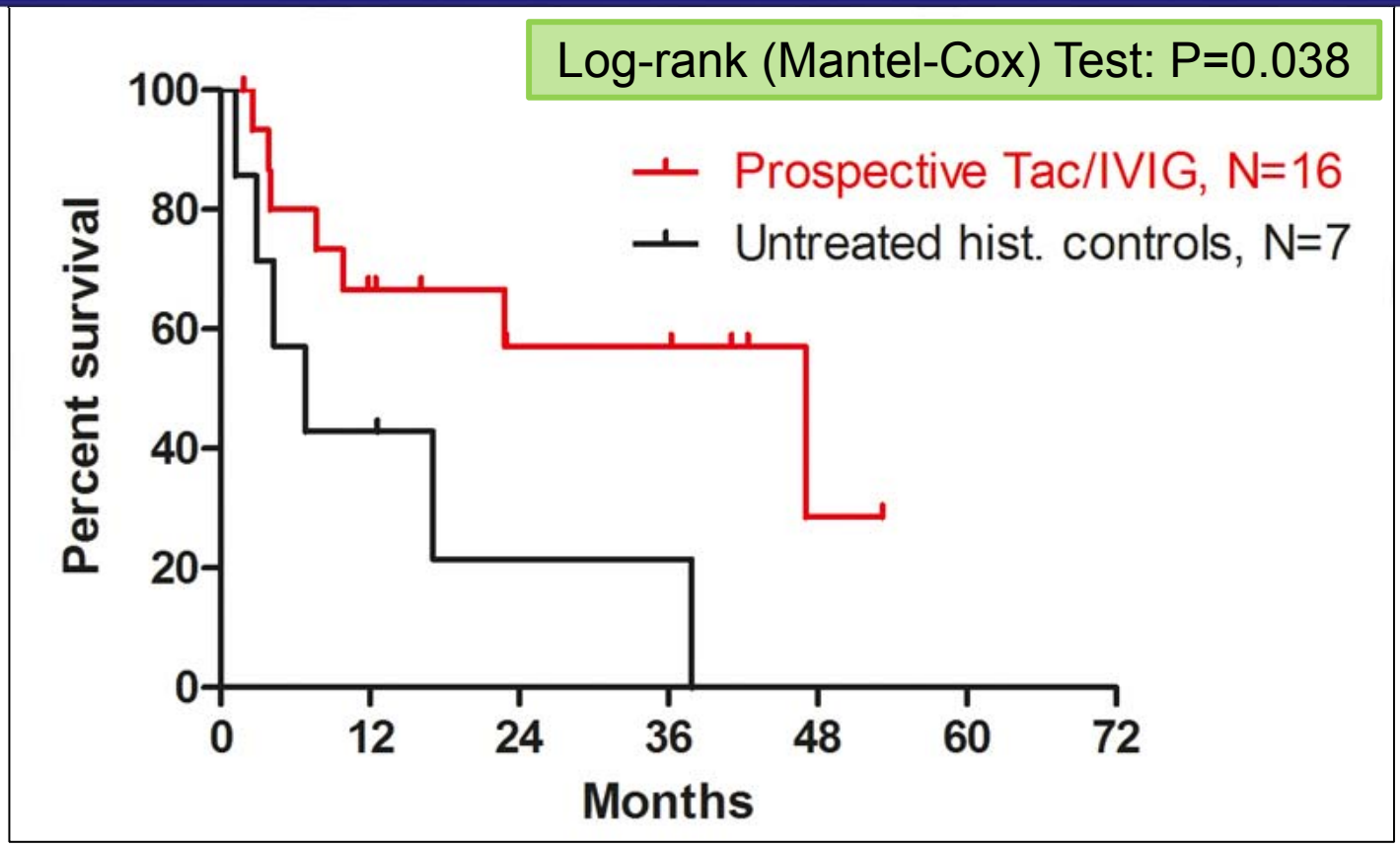
	N	Median age at disease onset (yrs)	Median duration until treatment (yrs)	Seizures	Neurological functions	Complications
IVIG	7	11,5	3	↓ - ↓↓	↑	-
Steroids	18	~5	~3	↓ - ↓↓	partly ↑	++
IVIG + Steroids	19	5.5	~3	temp ↓↓	partly ↑	++
Cyclophosphamide	1	15	14	temp ↓	temp ↑	-
Intraventricular IFN-α	2	3,7	1,2	↓↓	↑/=	+
Plasmapheresis/ IgG-Immunoadsorption	6	~7	~4	partly, temp ↓	partly, temp ↑	+/++
Ganciclovir	4	6,5	1,8	partly, temp ↓	partly, temp ↑	-
Zidovudine (AZT)	1	14	4	temp ↓ ↓	=	+

Bien CG et al., Expert.Opin.Investig.Drugs 2002;11:981

Rasmussen encephalitis

Prospektive: Tacrolimus vs. IVIG (N=16); hist. controls (N=7)

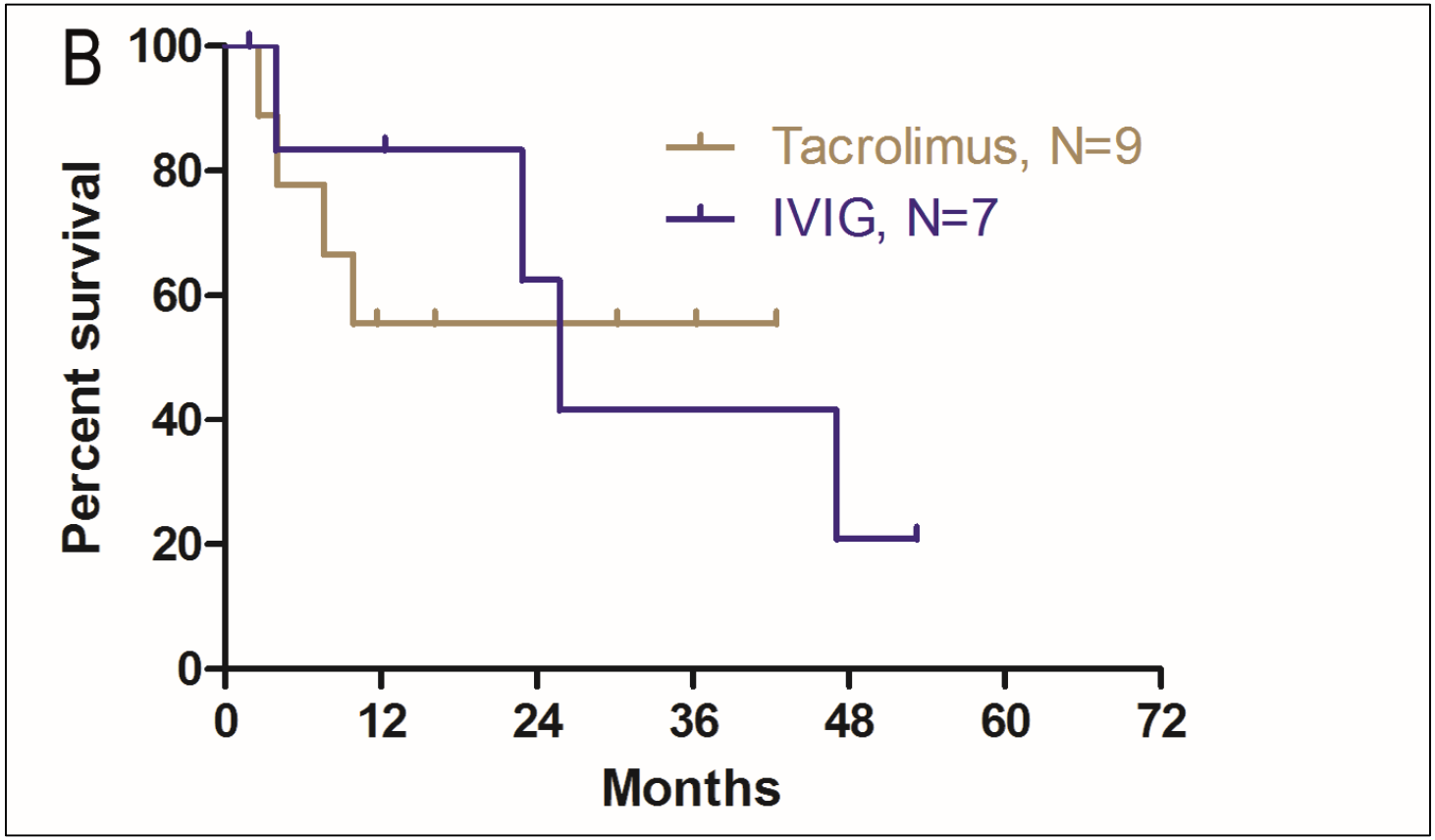
Endpoint: predefined loss in motricity



Bien CG et al., Epilepsia 2013;54:543

Rasmussen-Enzephalitis

Prospektive Studie Tacrolimus (N=9) und IVIG (N=7)

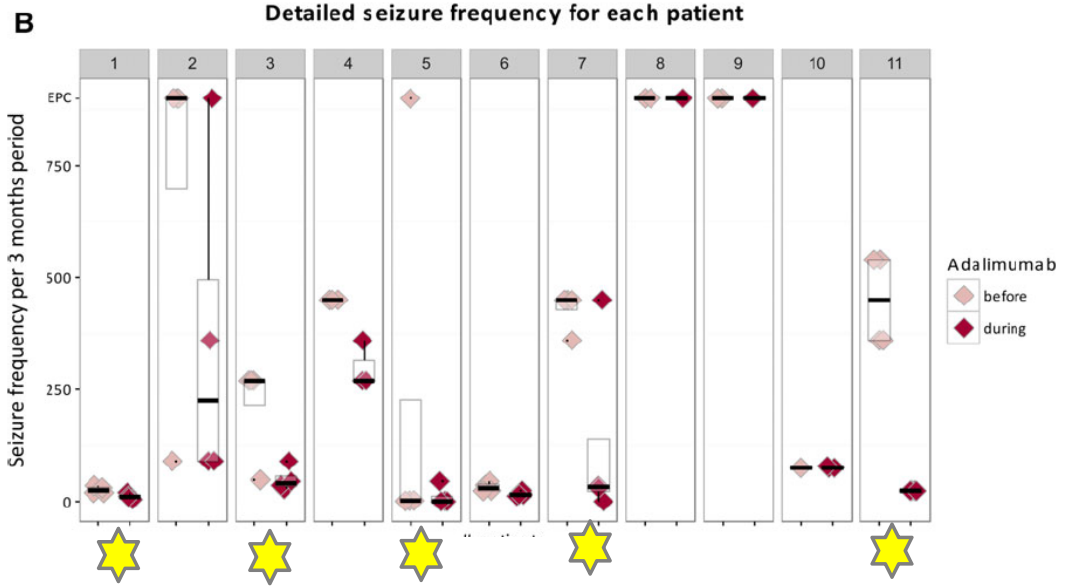


Bien CG et al., Epilepsia 2013;54:543

Rasmussen encephalitis

Adalimumab (anti-TNFα)

- 11 patients open uncontrolled study: every 14 d: 24 mg/m² (max 40 mg)
- Disease onset: median 6,5 y (1.5-37 y)
- Disease duration: median 31 months (1 mo up to 16 y)
- Sz reduction in 5/11: all had slow disease progression

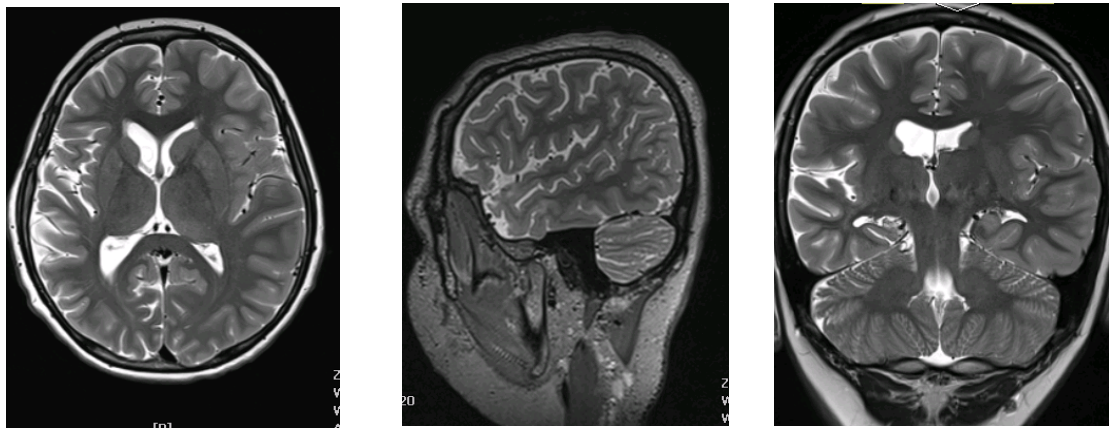


Lagarde S et al., Epilepsia 2016;57:956

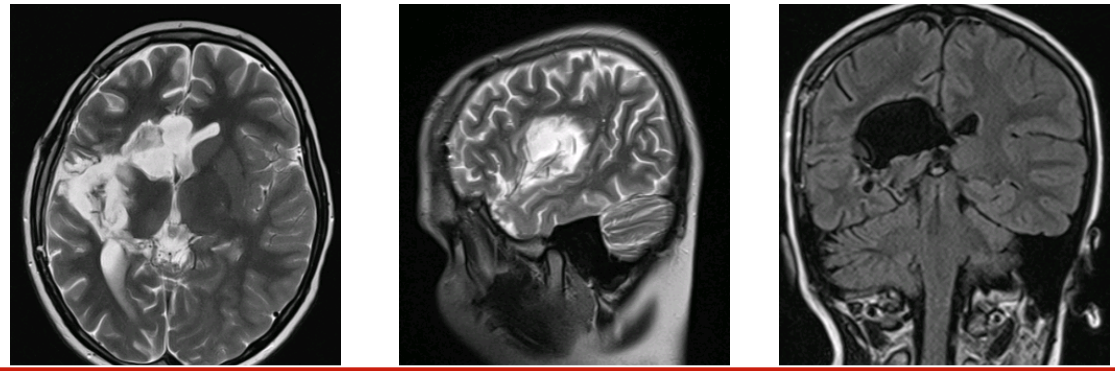
Rasmussen encephalitis

Bethel: modified periinsular hemispherotomy

Patient O., N. ♂, RE right hem,
manifestation age 5
Preoperative MRI
5 y after onset



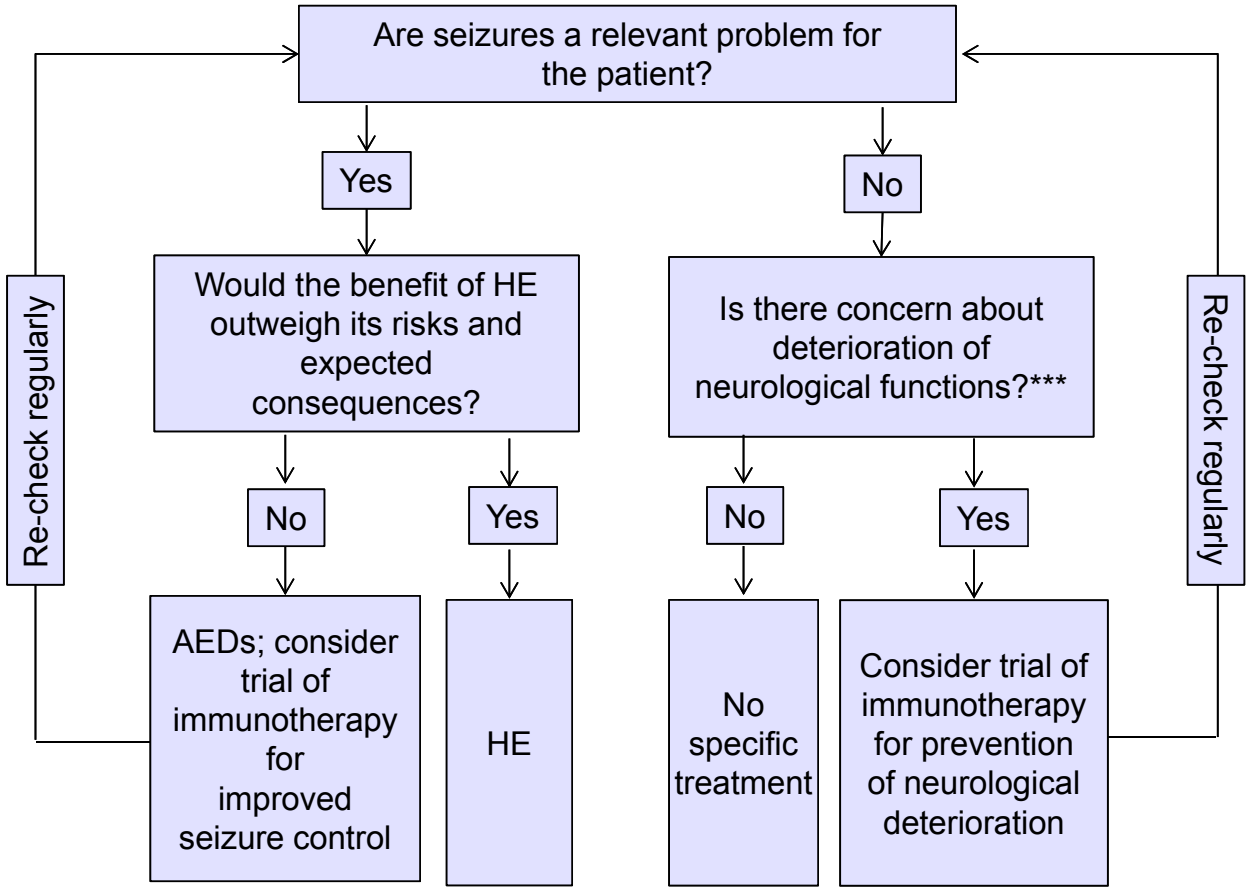
MRI 1 mo after surgery



2 y follow-up: Engel IA. No AED. No complication

Rasmussen encephalitis

Pathway treatment decisions



Varadkar S, Bien CG et al., Lancet Neurol 2014;13:195

Rasmussen encephalitis

Summary

- Very good outcome of hemispherectomy/hemispherotomy (HE)
- No lasting effect of immunotherapies
- Patients with left-sided disease often atypically dominant*
- In patients with severe epilepsies, deterioration of motor functions as a consequence of HE may be justified.

*Bulteau C et al., Epilepsy Behav 2015;53:51

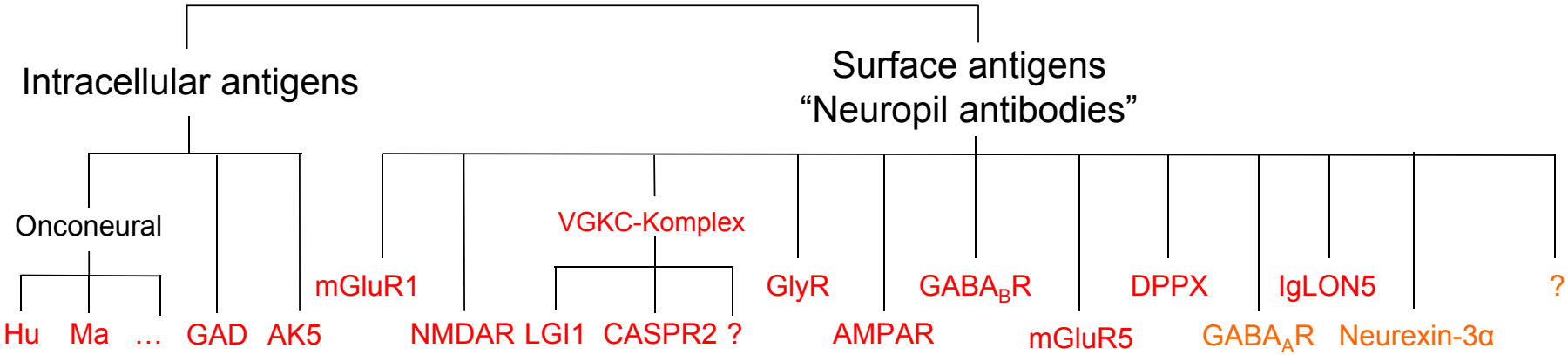
Krankenhaus **MARA**

Autoimmune encephalitis in children and adolescents

Pediatric antibody associated autoimmune encephalitides

Autoimmune encephalitides

Antigens of IgG antibodies



Publication	1980/90er	1990	2007	2000	2007	2010	2010	2008	2009	2010	2011	2012	2014	2014	2016
Published Patients	>400	70	12	4	>700	160	120	100	35	75	4	27	35	8	5
Tumors	>90%	<10%	0%	100%	40%	10%?	<20%	10%	50%	50%	66%	0%	0%	0%	0%

Modified from: Bien CG et al., Immunvermittelte Erkrankungen der grauen ZNS-Substanz sowie Neurosarkoidose, in: Leitlinien für Diagnostik und Therapie in der Neurologie, 5. Aufl., hrsg. v. Diener, HC & Weimar C, Thieme: Stuttgart/New York, 2012, S. 476-487.

Krankenhaus **MARA**

Antibody diagnostics

Laboratory Krone, Bad Salzuflen

www.mara.de

www.laborkrone.de

Antibody associated encephalitides

Key messages

- The frequent auto-antibodies and autoimmune encephalitide can also be found in the pediatric population.
- The relative frequency is not much smaller than in the adult population.
- The most relevant pediatric antibody: anti-NMDA receptor. Very well treatable.

Experience with antibody testing

Patients

- **Samples** from the routine diagnostic service: The Mara and external senders
- **Period:** 1st Dec, 2011 - 31st Dec, 2015 (4 y 1 mo)
- **Patients:** N=10927
- **Materials:** Serum only: 44.0%, CSF only: 4.8%, CSF-serum pairs: 51.2%, all tested with cell based assays (biochips, Euroimmun/Lübeck)
- **Selection:** In cases with multiple samples, the first one was included
- **Additional tests** (not all patients): onconeural antibodies (immunoblot, Ravo, Freiburg, Germany), mouse brain IIF, VGKC complex ab (RIA, RSR Cardiff)

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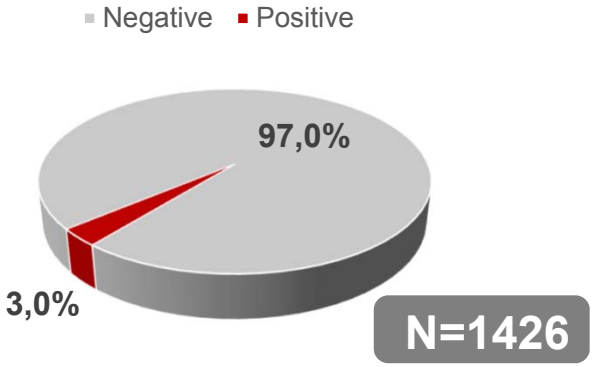
Experience with antibody testing

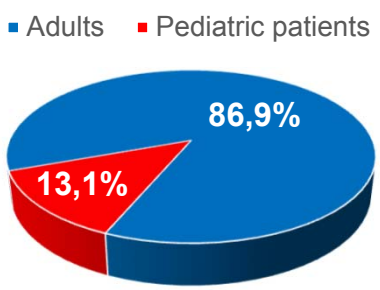
Patients with IgG antibodies 2011-2015 (4 y 1 mo)

Pediatric patients



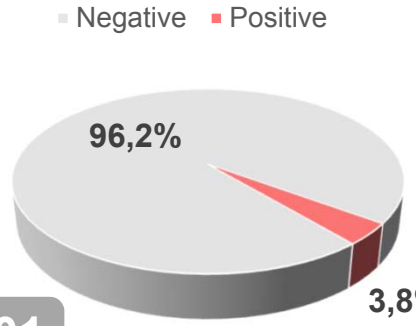
N=1426

Patients tested



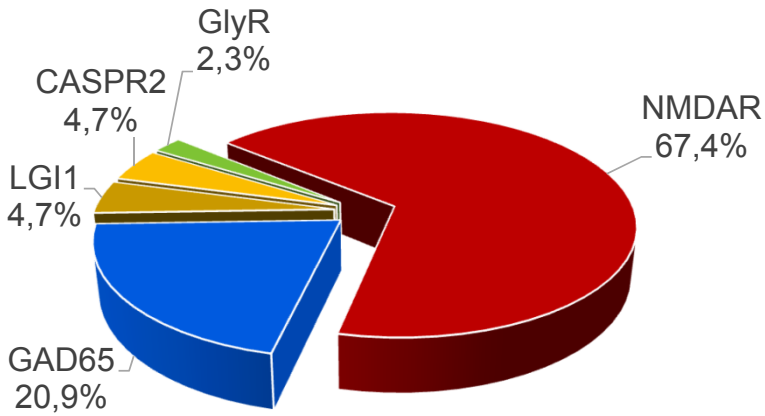
N=10927

Adult patients

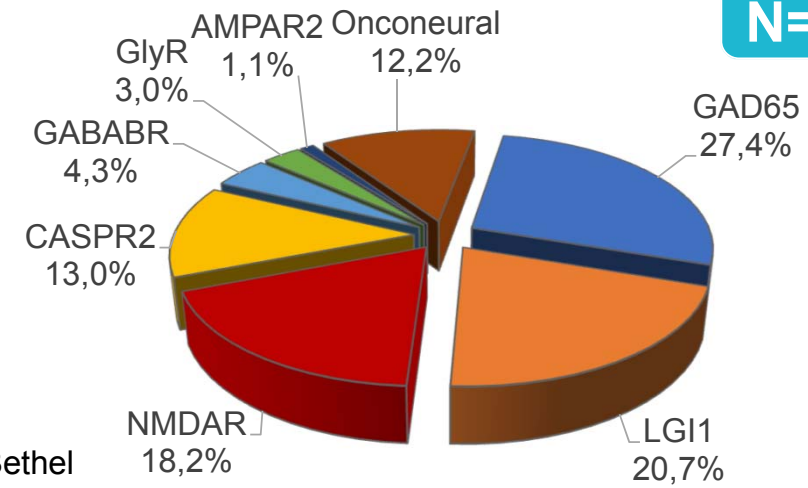


N=9501

N=43



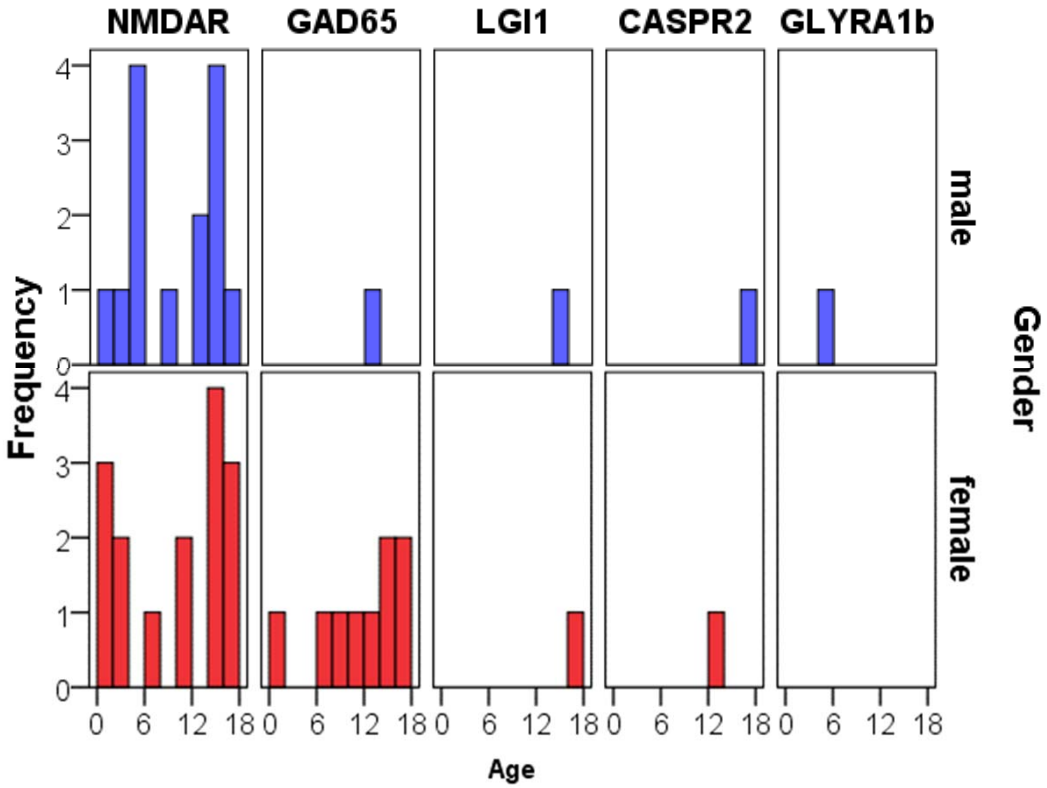
N=359



Preliminary results Antibody Lab Bethel

Experience with antibody testing

Age and gender distribution



Autoimmune encephalitis

NMDAR antibodies

NMDAR antibodies

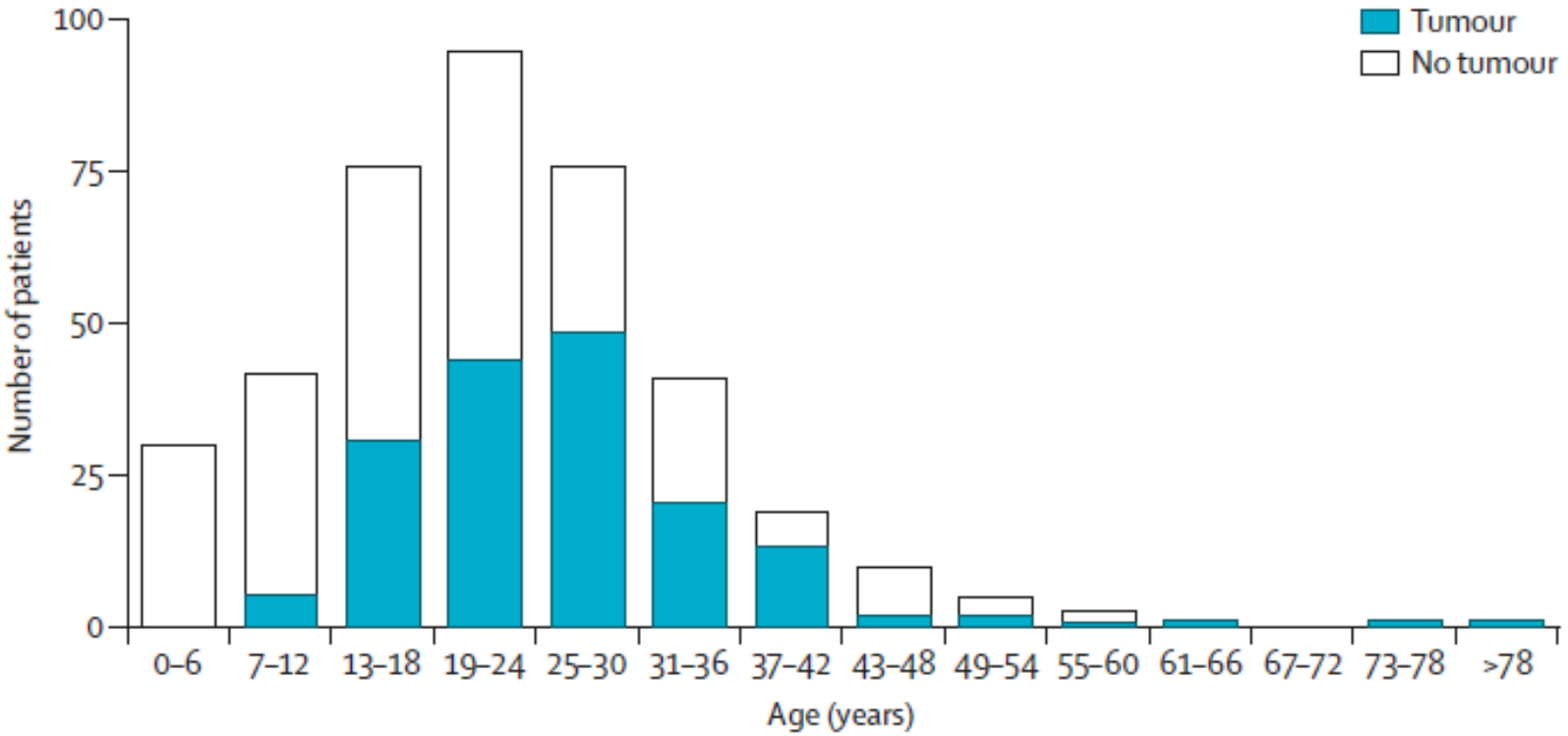
Epidemiology

- ≤ 18y: 1 out of 1 mio persons per year*
- 80% of patients are female
- Paraneoplastic in ≈25% (ovarian teratoma)

Wright S et al. Arch Dis Child 2015;100:521–526

Anti-NMDAR encephalitis

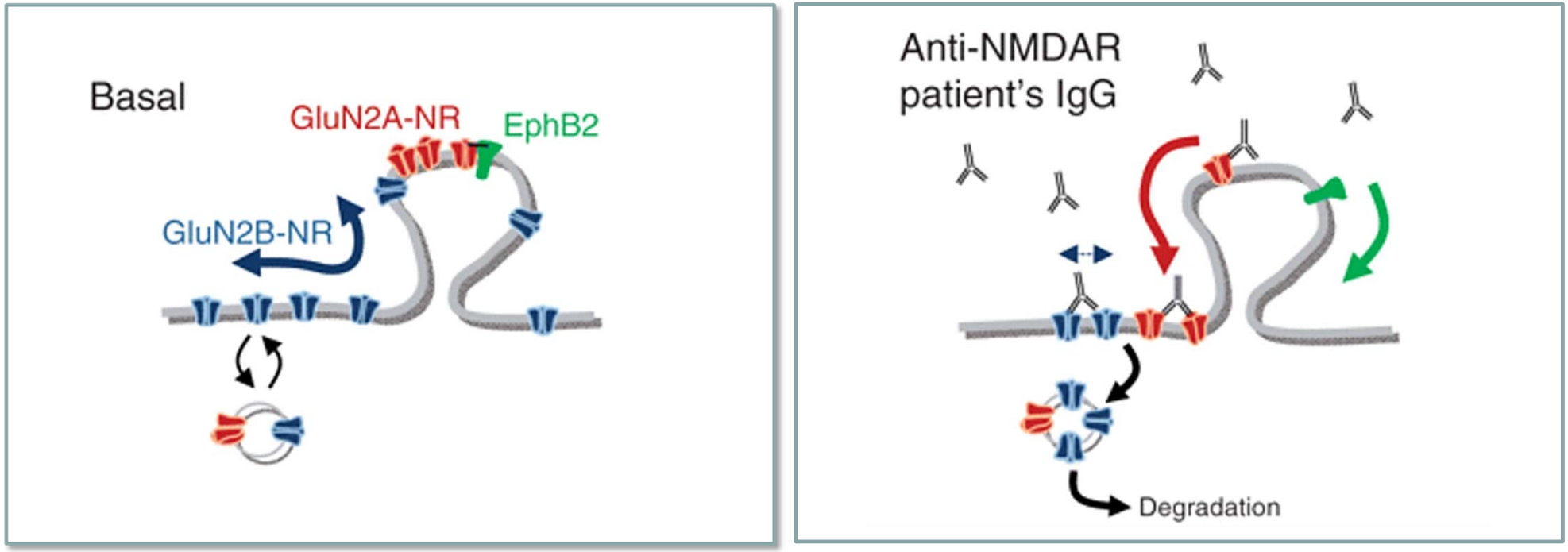
Age distribution



Dalmau, et al., Lancet Neurol 2011: 10, 63

NMDAR antibodies

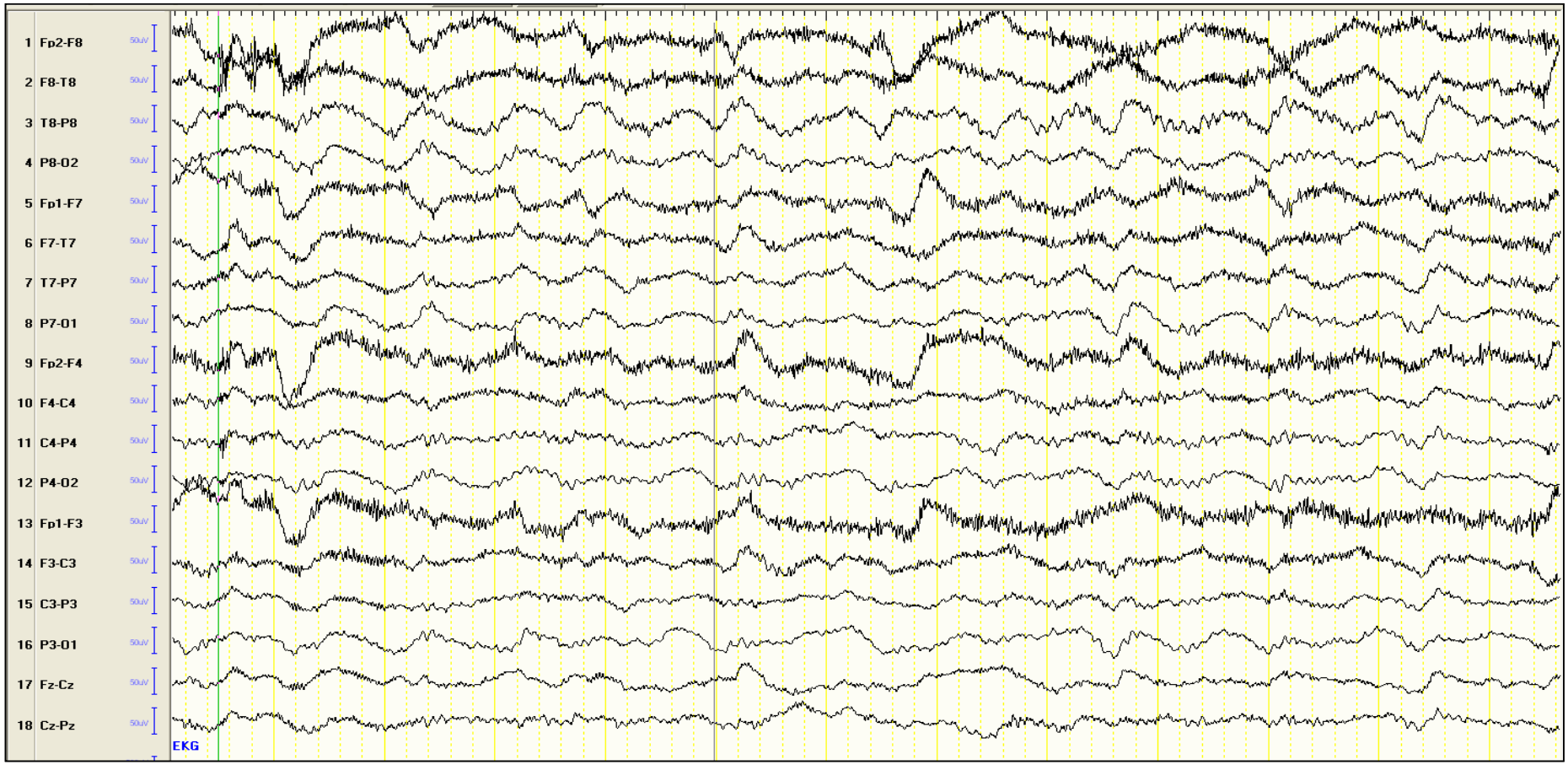
NMDAR abs lead to internalization of NMDAR



Mikasova L et al., Brain 2012;135:1606

Anti-NMDAR encephalitis

O., N. ♀ 24 y, NMDAR (NR1) antibodies: “Extreme delta brush“

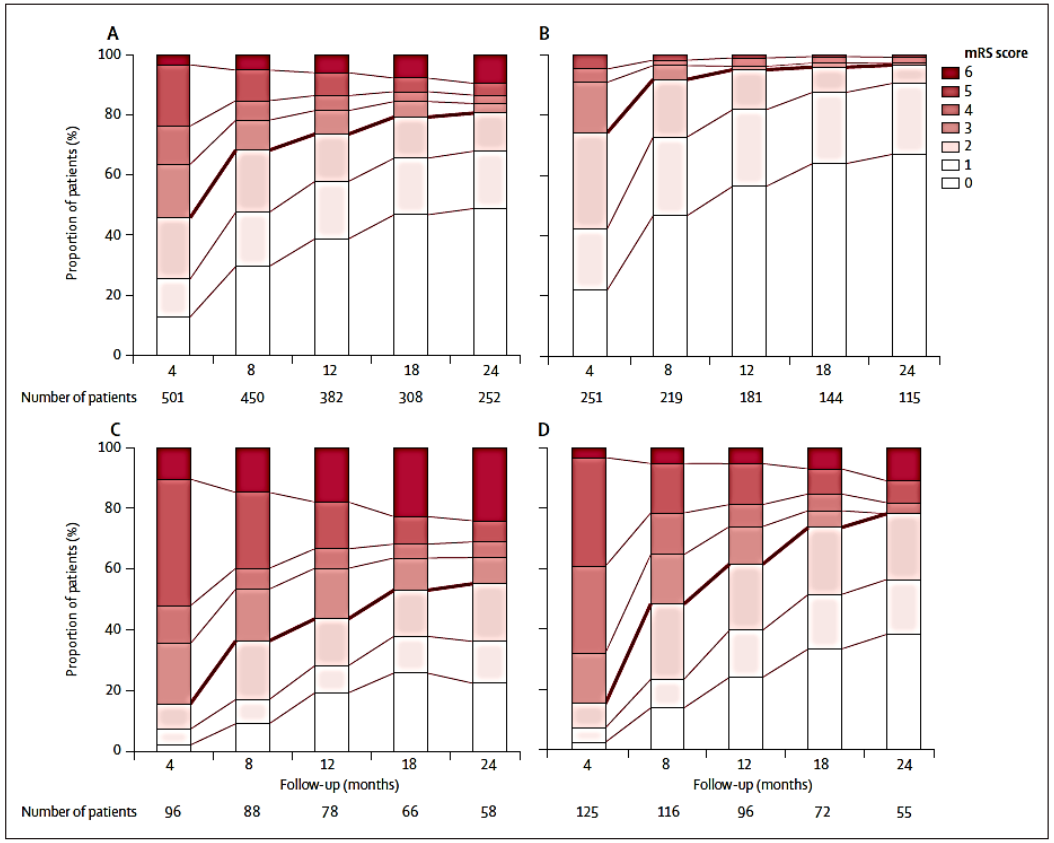


Anti-NMDAR encephalitis

Treatment-related outcome

All patients N=501

Failed 1st line therapy, no 2nd line N=96



Response to 1st line therapy N=251

Failed 1st line, received 2nd line N=125

Titulaer MJ et al., Lancet Neurol 2013;12:157

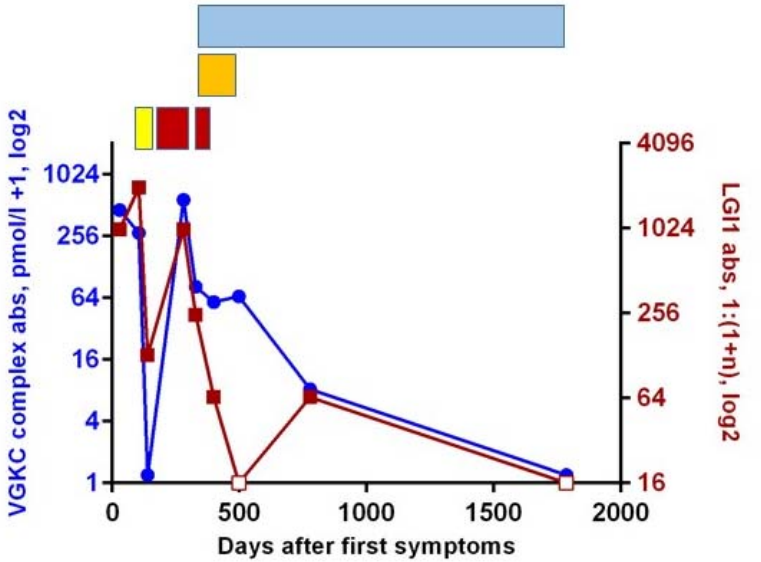
Krankenhaus **MARA**

Autoimmune encephalitides

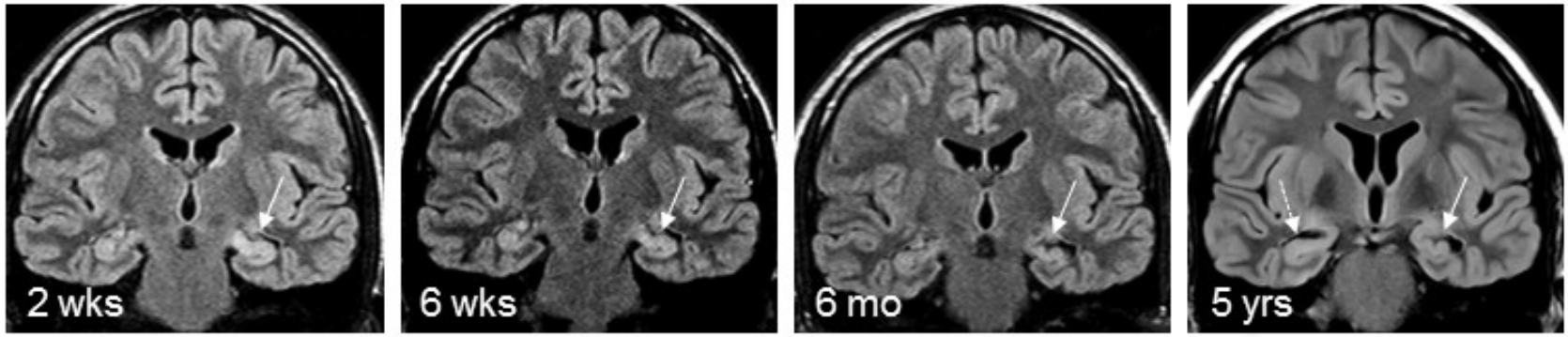
LGI1 antibodies

LGI1 antibodies

Patient K., R. ♂ 14 yrs, subacute memory loss



Yellow: methylprednisolone pulse
Red: plasma exchanges
Orange: oral prednisolone
Blue: mycophenolate mofetil



Schimmel M, Bien CG, Frühwald MC, under review

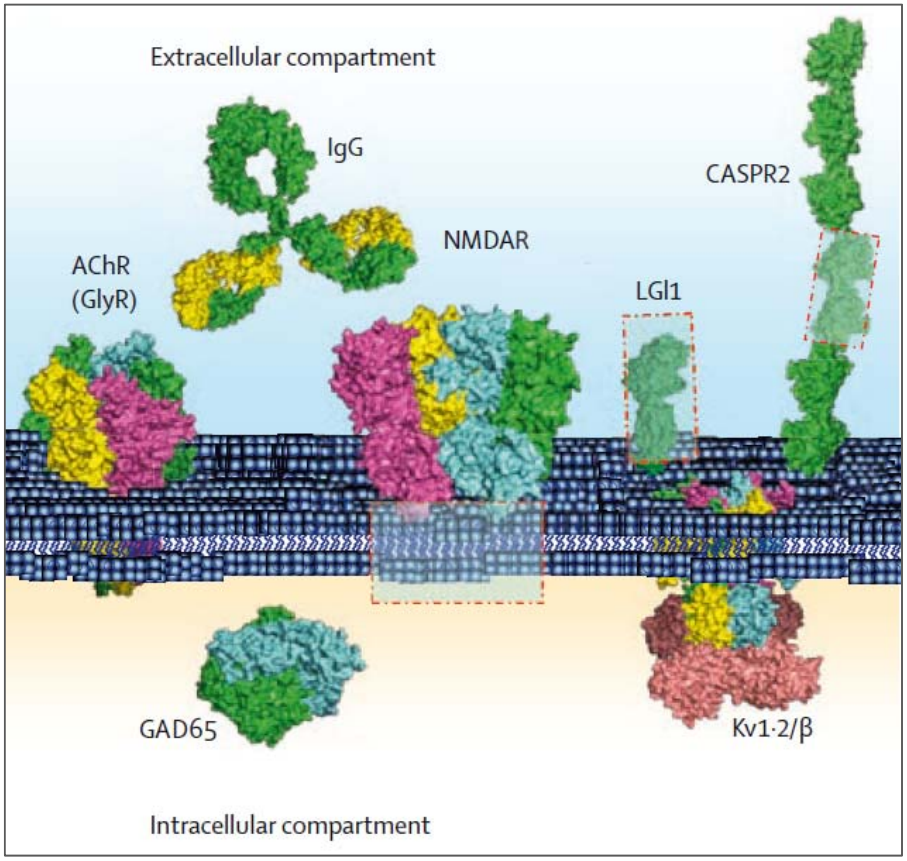
LGI1 antibodies

What is typical about this case?

- Prominent memory problems
- Good response to immunotherapy
- Antibodies go down
- Hippocampal sclerosis
- Remaining memory deficits

LGI1 antibodies

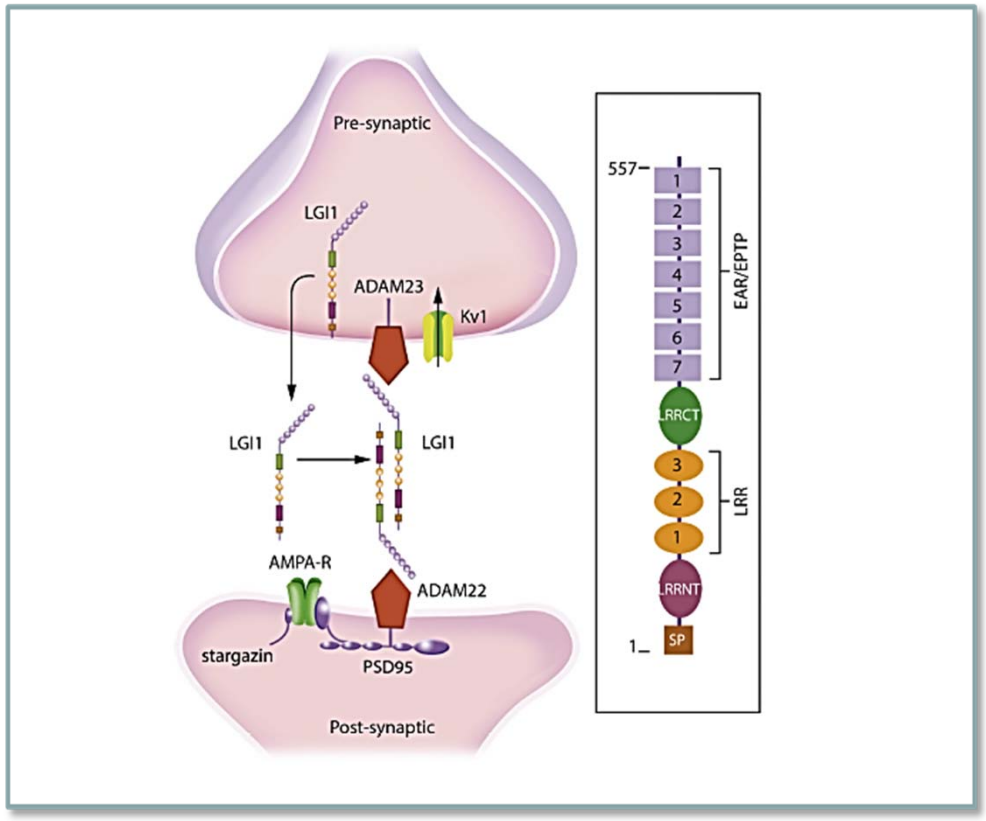
Soluble, secreted element of the potassium channel complex

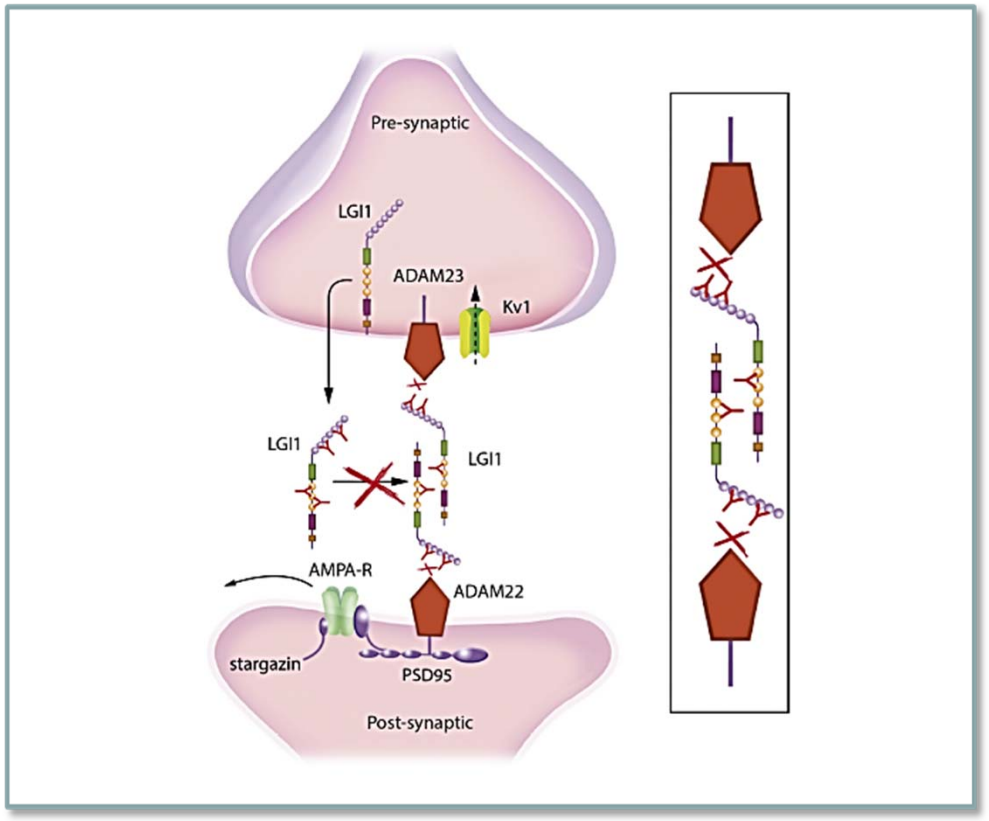


Vincent A et al., Lancet Neurol 2011;10:759

LGI1 antibodies

LGI1 abs disrupt transsynaptic protein complexes



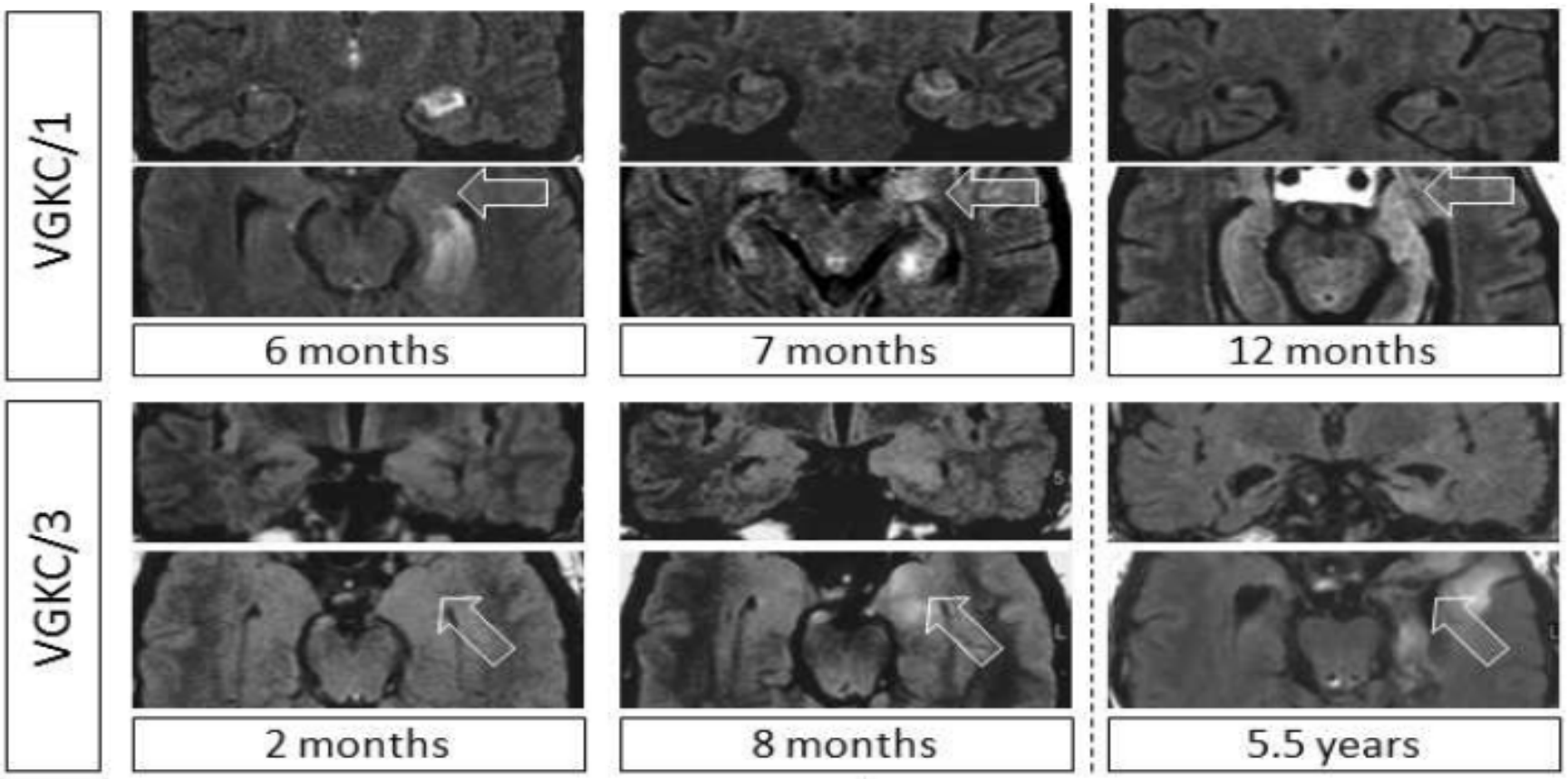


Loss of AMPARs: Does this explain seizures?

Dalmau J et al., Physiological reviews 2017;97:839, based on Ohkawa T et al., J Neurosci 2013;33:18161

VGKC complex/LGI1 antibodies

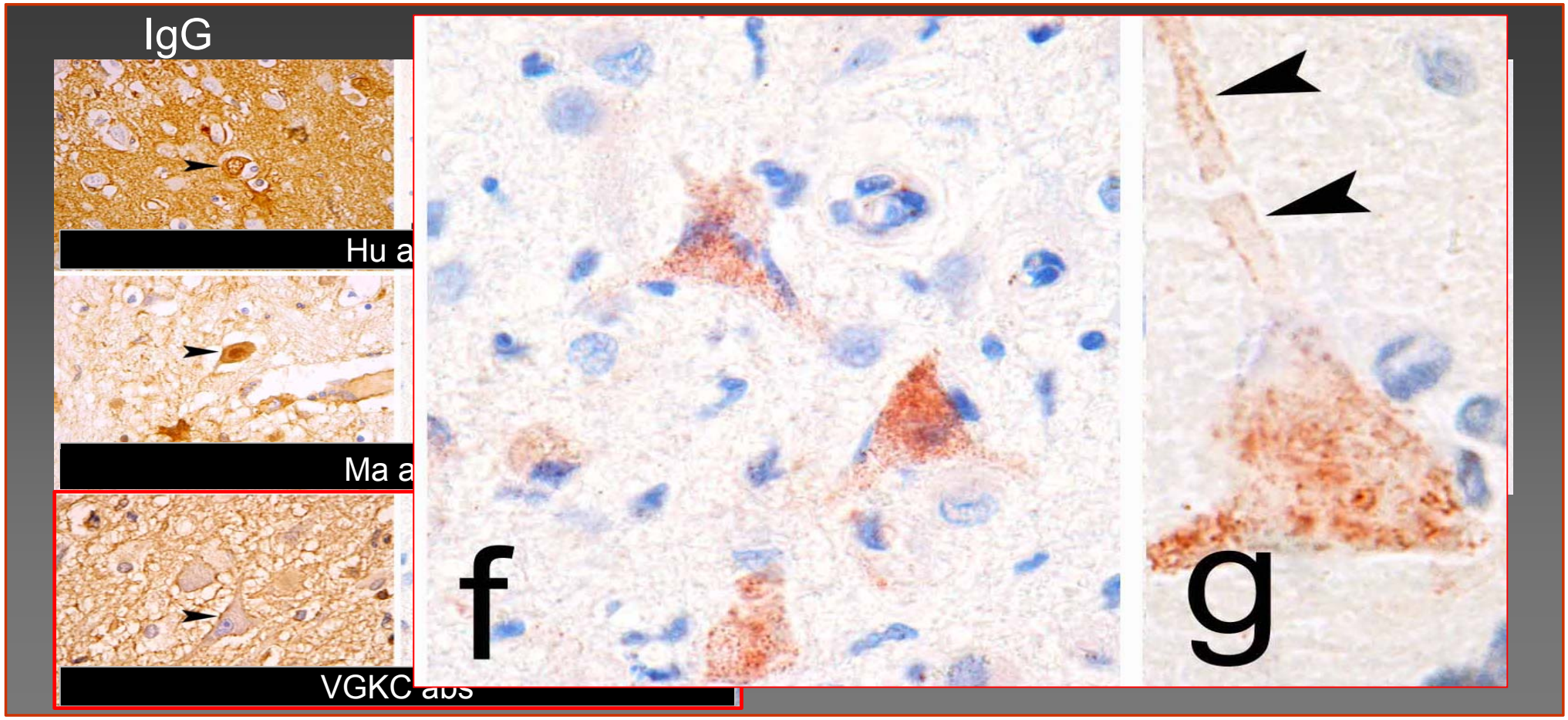
Hippocampal atrophy



Bien CG et al., Brain 2012;135:1622; case 1: LGI1 ab+; case 3: LGI1/CASPR2 ab status unknown

VGKC-Komplex-Antikörper

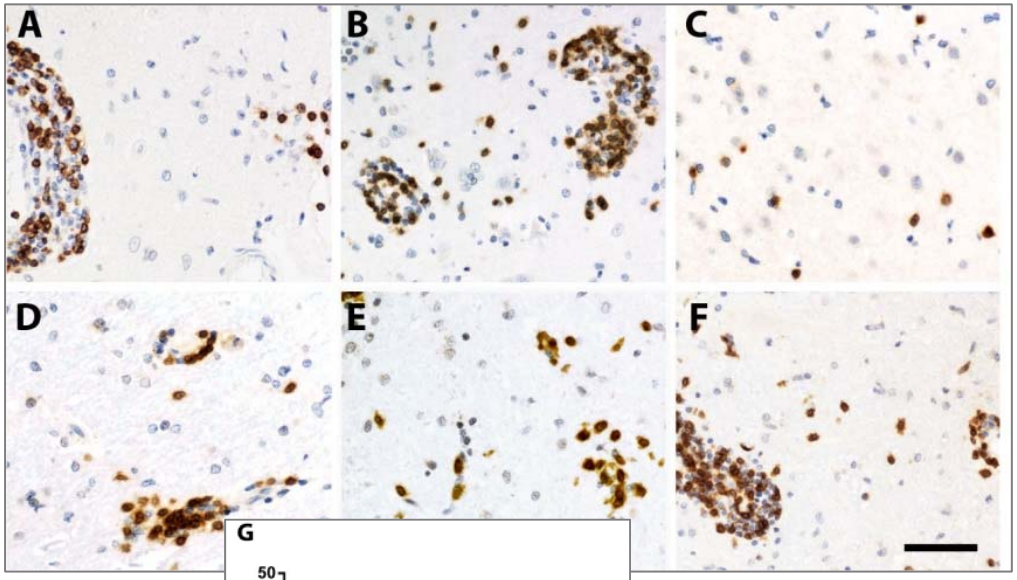
IgG und Komplement (C9neo)

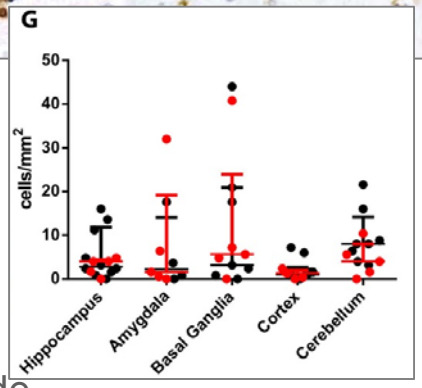


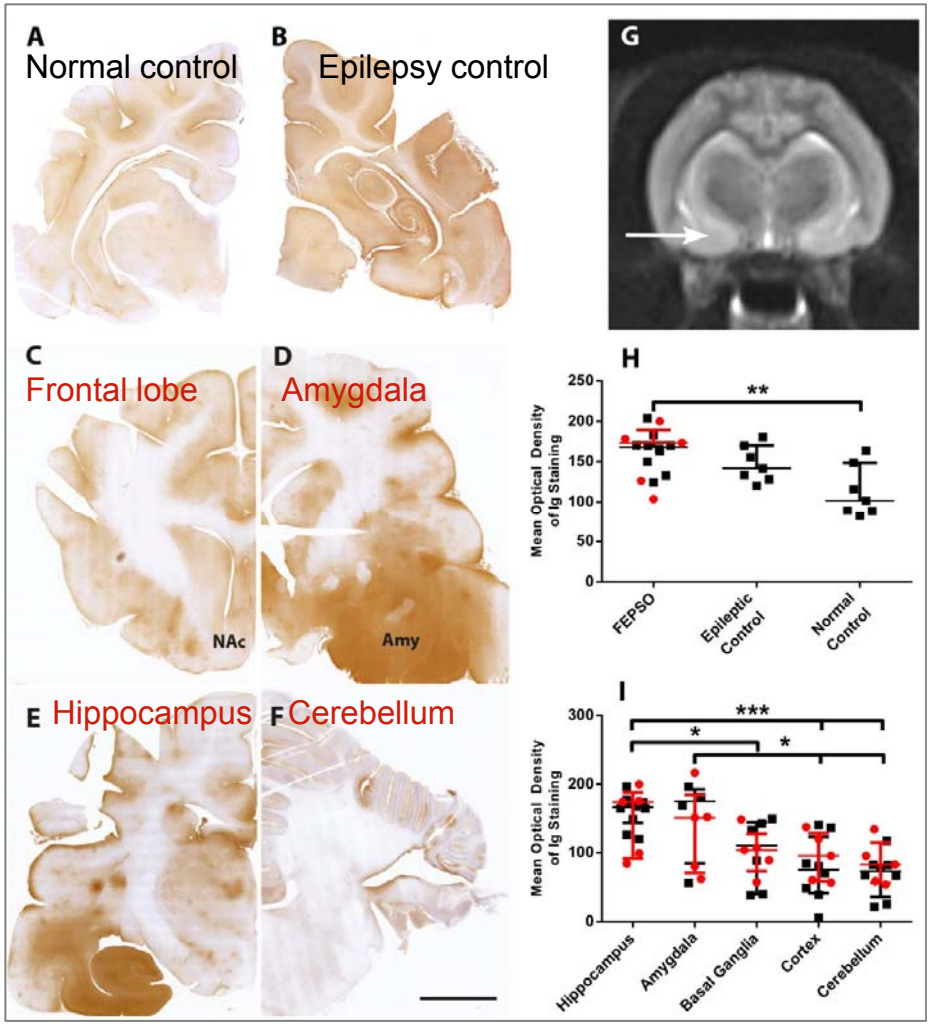
Bien CG et al., Brain 2012;135:1622; g=VGKC/1, LGI1-Ak-positiv

Encephalitis and blood brain barrier

Spontaneous cat model, LGI1 abs



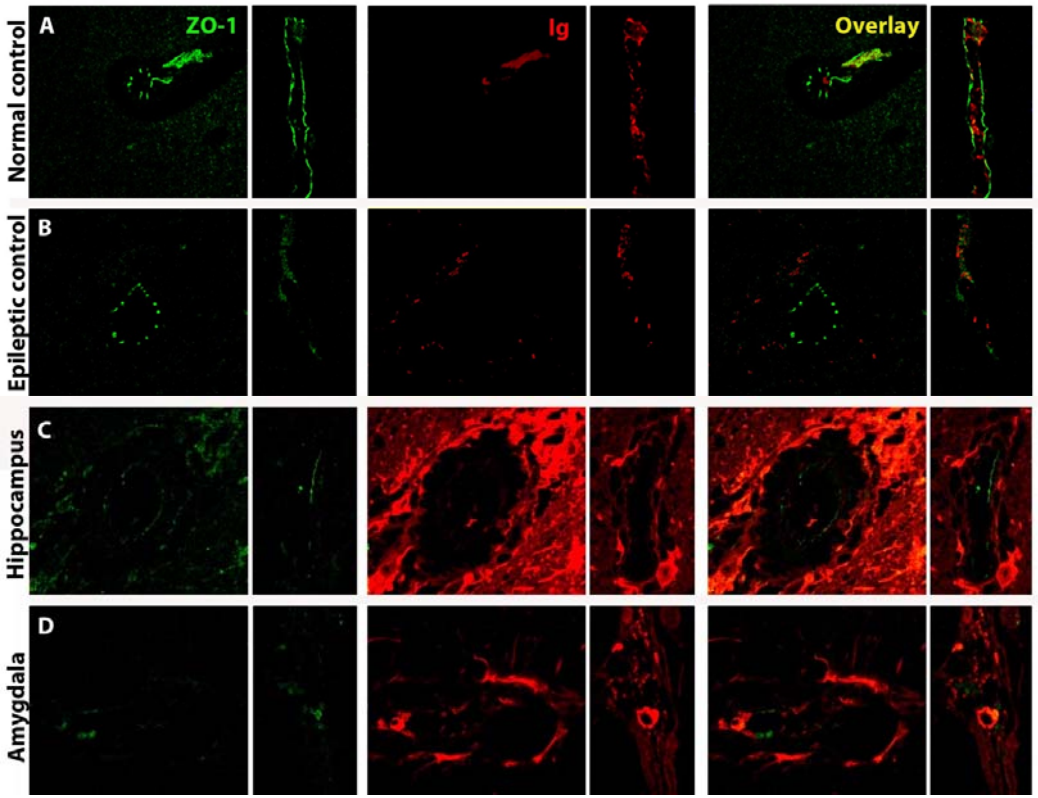


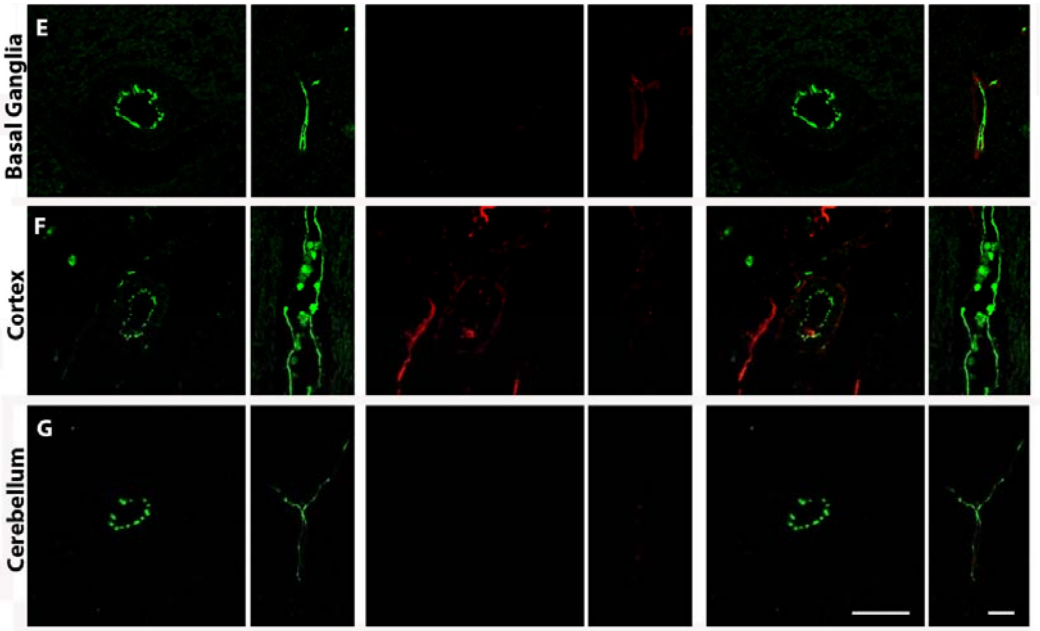


Tröscher AR et al., Front Immunol 2017;8:article 1364

Bluthirnschranke bei Anti-LGI1-Enzephalitis

Spontanes Katzenmodell: löchrige Tight junctions

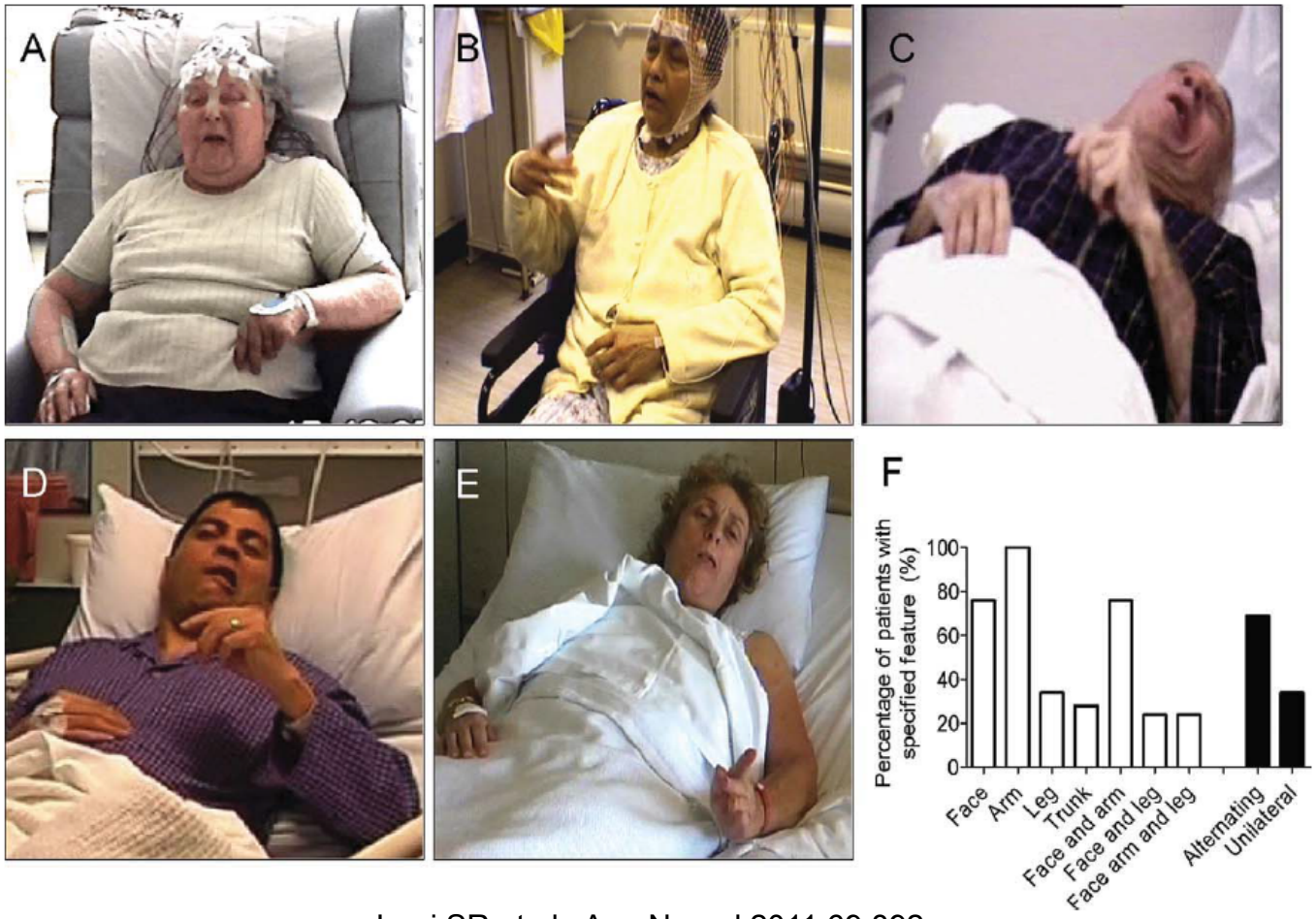




Tröscher AR et al., Front Immunol 2017;8:article 1364

LGI1-Antikörper

Faciobrachiale dystone Anfälle



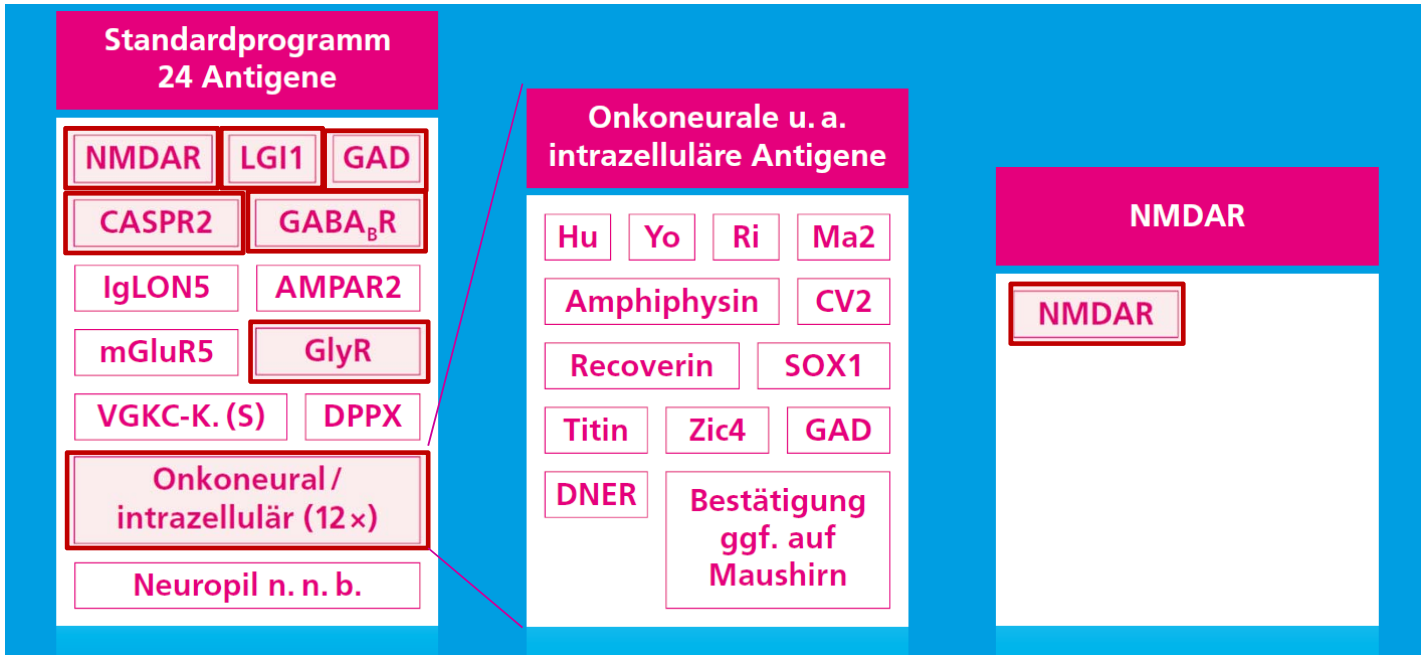
Irani SR et al., Ann Neurol 2011;69:892

Autoimmune encephalitis in children and adolescents

Summary

Future perspectives

Antibody panel diagnostics



Brochure „Diagnostics of autoimmune encephalitides“, Laboratory Krone

Krankenhaus **MARA**

Autoimmune encephalitis in children and adolescents

Not so fruitful ↔ Promising

Routine testing in "standard syndromes" (epilepsies, psychoses …)	Testing in patients with longstanding disorders	Serum only or CSF only tests*	Testing of single antibodies*	Testing only if standard CSF is abnormal
Testing of patients with <u>complex</u> neuro-psychiatric disorders	Subacute onset conditions	Testing Serum-CSF-pairs	Application of antigen panels	Immuno-therapy!

*Exception: NMDAR antibodies in patients with typical syndrome

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Antibody research laboratory

30 km apart: Bad Salzuflen

cgbien@laborkrone.de

Antibody diagnostic laboratory