European Reference Network

Epilepsies (ERN EpiCARE)

European Commission

EUROPEAN REFERENCE NETWORKS

Helping patients with rare or low-prevalence complex diseases

Diagnosis, treatment and prognosis of limbic encephalitis

Subtitle

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23.04.2020

Co-founded by the EU

DIAGNOSIS OF LIMBIC ENCEPHALITIS

Dr. Tobias Baumgartner

23.04.2020

Co-founded by the EU

Diagnosis of limbic encephalitis

- Clinical presentation
- Imaging / MRI
- CSF
- EEG
- Tumor screening
- Diagnostic criteria

Clinical presentation of limbic encephalitis

Subacute onset of …

- **(refractory) epileptic seizures**
  - multimodal auras (somatosensory, abdominal, gustatory, and visual)[1]
  - change in seizure semiology
  - status epilepticus (GABAaR, GABAbR, NMDAR)
  - faciobrachial dystonic seizures
- **Psychiatric symptoms** (depression, behavioral changes, psychosis) and **cognitive deficits** (C. Helmstaedter)
- age of onset differs between the antibodies (e.g. LGI 1, CASPR 2 vs. GAD, NMDAR)

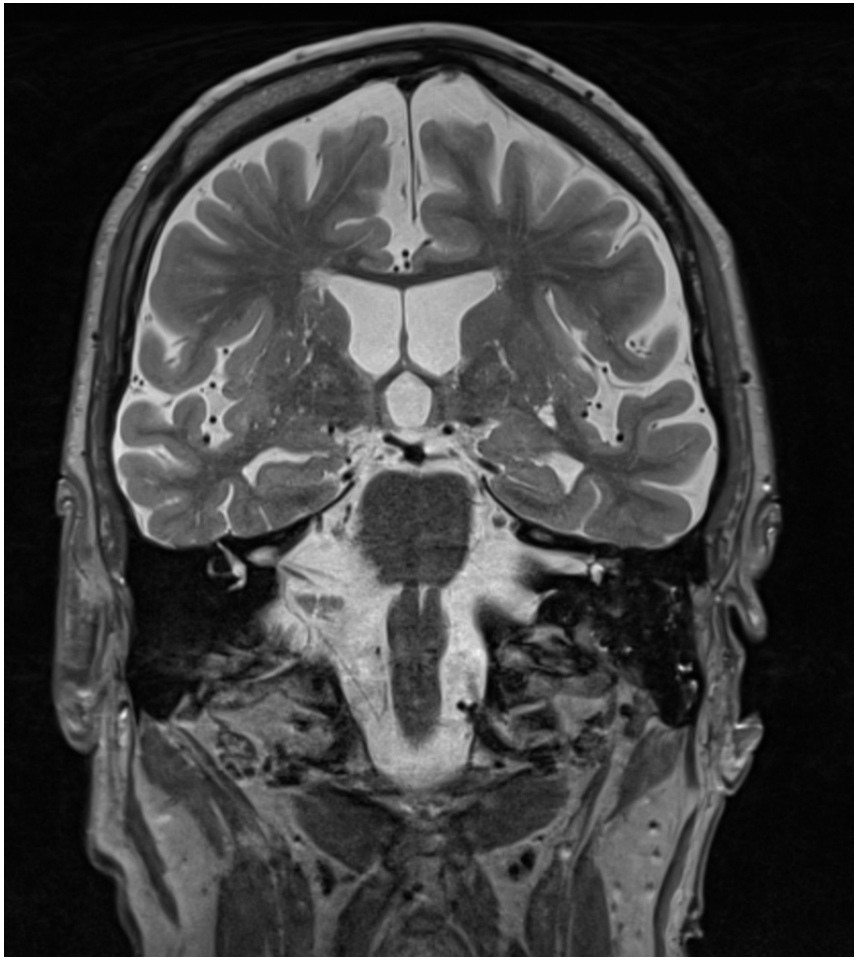
[1]Steriade et al., Seizure 2018

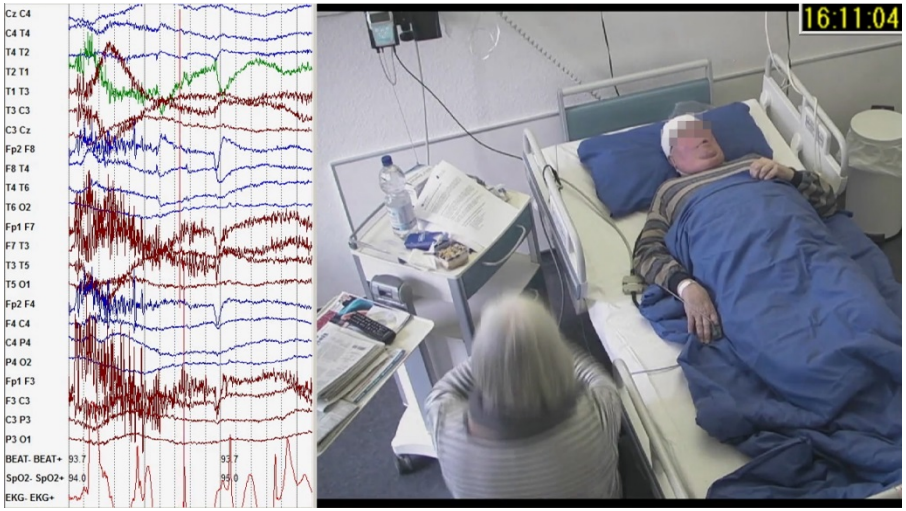
Case I

Medical history

- 74 year old patient with initial symptoms of confusion and delusions
- brief jerks (approx. 20/die) of the right and later of the left arm and face were reported after a few weeks
- recurrent falls due to the jerks occured (clavicle-, LVB 1- and rib-FX)

Case 1

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C4 T4
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Fp1 F7
F7 T3
T3 T5
T5 O1
Fp2 F4
F4 C4
C4 P4
P4 O2
Fp1 F3
F3 C3
C3 P3
P3 O1
BEAT- BEAT+ 93.7
SpO2- SpO2+ 94.0
EKG- EKG+
16:11:04

Case I

Diagnostics

- cMRI: normal (slight T2 / FLAIR signal hyperintensity of the left hippocampus)
- EEG: left temporal slowing, no epileptic activity, no recorded seizures (FBDS excluded)
- CSF: normal white blood cell count, no intrathecal IgG synthesis, no antibodies detected
- Serum: LGI-1 antibodies (1:1000)
- FDG-PET: hypermetabolism in basal ganglia and thalamus bilaterally

Initial Tretament:

- Methylprednisolone pulse therapy (5x1000 mg/die) followed by immunadsorption

[1]Probasco et al., Neurol Neuroimmunol Neuroinflamm 2017;
[2]Na et al., Epilepsia 2019

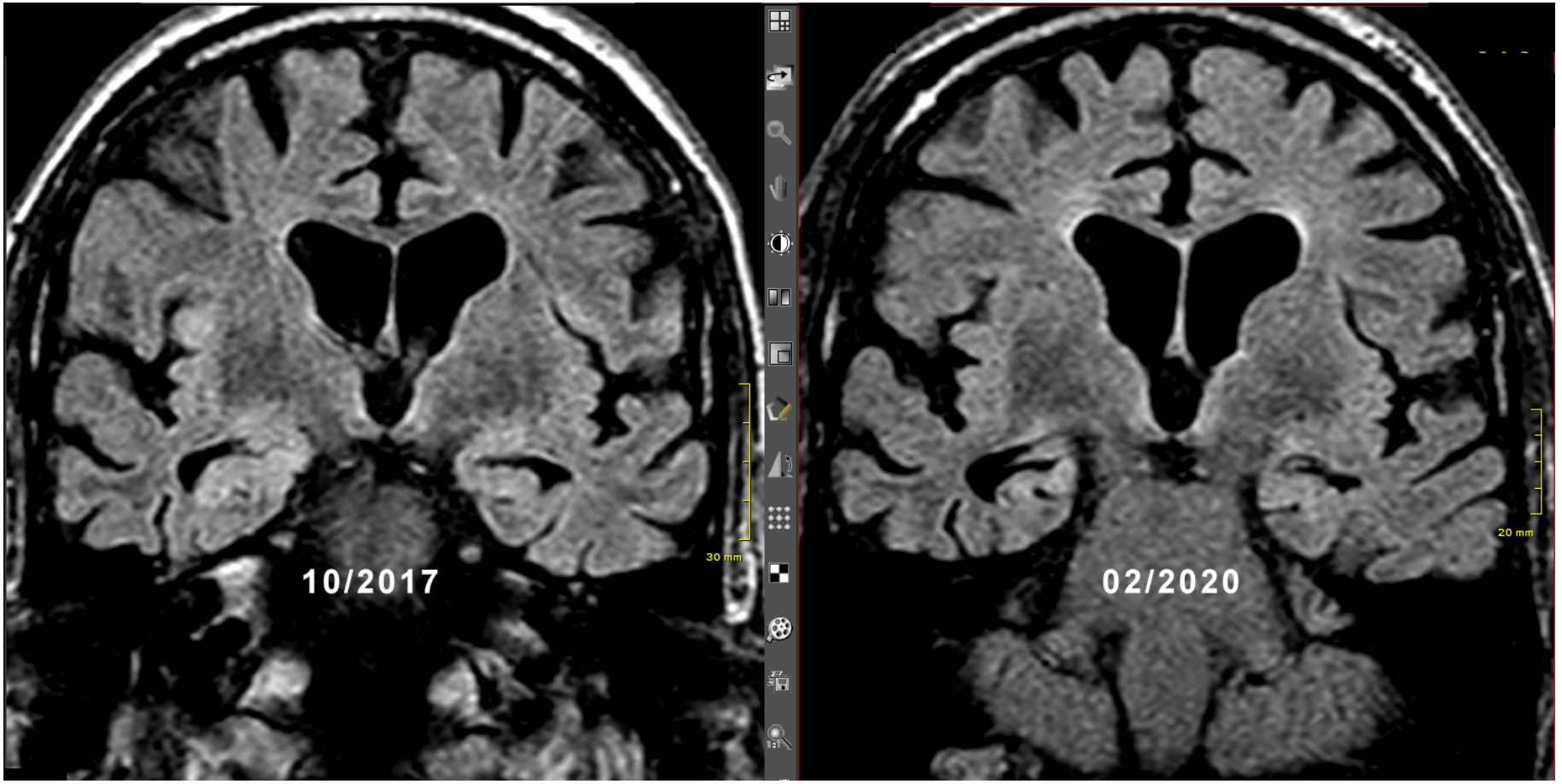
IMAGING

MRI	FDG-PET
enlargement and T2 / FLAIR hyperintensity of mesial temporal lobe structures (uni- or bilateral)	altered mesiotemporal metabolism (mostly hypermetabolism)
development of mesial temporal sclerosis in LGI-1, CASPR2, GAD, AMPAR, GABAbR during the course of the disease	more often abnormal than initial EEG, MRI, and CSF in AE[1]
typically unremarkable in the initial stage of FBDS in LGI-1 patients	hypermetabolism of basal ganglia in LGI-1 patients

differential diagnoses of mesiotemporal alterations
amygdala enlargement in patients presenting with frequent seizures may be explained by seizure-induced change[2]
Gliomas, herpes simplex virus encephalitis

[1]Probasco et al., Neurol Neuroimmunol Neuroinflamm 2017;
[2]Na et al., Epilepsia 2019

MRI

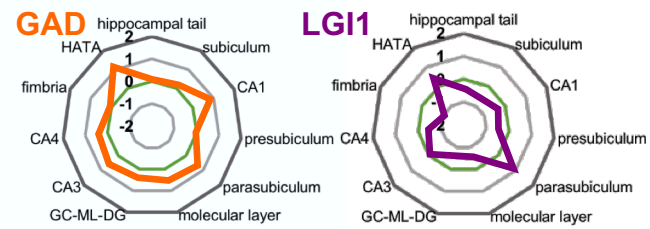


MRI in the course of LGI 1 encephalitis

Imaging of Limbic Encephalitis

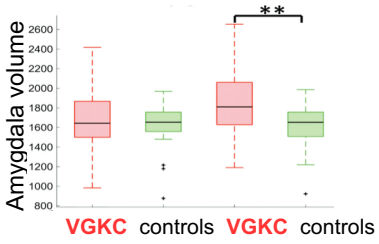
gray matter imaging

Volumetric analysis
Hippocampal subfield volumes show serospecific pattern



Hippocampal subfield volumes / *z*-scores

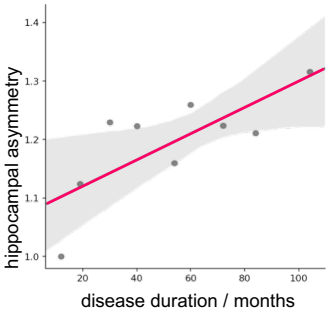
Amygdala enlargement predicts EEG lateralization



EEG unaffected ↔ **EEG affected**

Shape analysis
Increasing shape asymmetry with disease duration

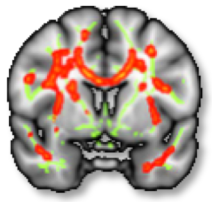
CASPR2
shapeDNA



white matter imaging

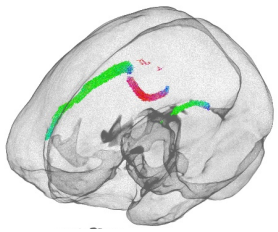
Diffusion imaging
Widespread FA reduction

GAD < controls

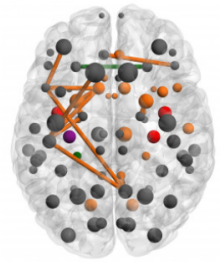


Tract-based analysis
Tract-specific reduction of fiber density and cross-section

GAD < controls

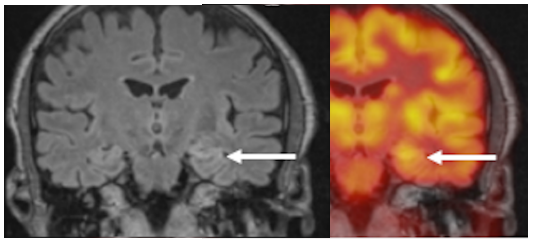


Network analysis
Serospecific alterations of global and local topology



quantitative imaging

qT2 / 18F-FDG-PET
Increased mesiotemporal qT2
Mesiotemporal 18D-FDG hypermetabolism



Wagner et al., Epilepsia, 2016
Ernst et al., AJNR, 2019
Schievelkamp et al., Clin Neuroradiol, 2019

Deuschl et al., PLoS One, 2020
Unpublished data, Translational Neuroimaging Lab, Bonn

EEG

- epileptic activity involving the temporal lobes (bilateral activity)
- lack of interictal epileptiform discharges, despite frequent ictal epileptiform events[1,2]
- change in ictal onset distribution (shifting regions or hemispheres) not uncommon[2]

- long runs of generalized rhythmic delta, with or without superimposed beta activity (extreme delta brush) in NMDA-R encephalitis[2,3]
- FBDS are preceded by an electrodecremental pattern

[1]Steriade et al., Epilepsia 2016;
[2]Steriade et al., Seizure 2018;
[3]Moiese et al., J Clin Neurophysiol 2019

CSF

- mild-to-moderate lymphocytic pleocytosis in 60–80% of patients
- elevated IgG index or oligoclonal bands in approximately 50% of patients
  - unusual in LGI 1 encephalitis
- in 15% NMDAR is only detectable in CSF[1]
- in 47 % LGI-1[2] and in 13 % CASPR2[3] are only detectable in serum

[1] Gresa-Arribas et al., Lancet Neurol 2014;
[2] Van Sonderen et al., Neurology 2016,
[3] Bien et al., Eur J Neurol 2017

TUMOR SCREENING

	antibody	risk of cancer	main types of cancer
Encephalitis with antibodies against neuronal intracellular antigens	Hu, Ma2	high	Hu: Testicular seminoma, Ma2: SCLS
	GAD 65	low	
Encephalitis with antibodies against neuronal cell-surface antigens	GABAbR, AMPAR	high	AMPAR: SCLC, thymoma, breast GABAbR: SCLC
	NMDAR	varies with age and sex	58% of women 18–45 years old have ovarian teratoma
	CASPR 2, LGI1	low	Thymoma

DIAGNOSTIC CRITERIA (GRAUS ET AL. 2016)

Possible AE

Diagnosis can be made when all three of the following criteria have been met:

1 Subacute onset (rapid progression of less than 3 months) of working memory deficits (short-term memory loss), altered mental status*, or psychiatric symptoms
2 At least one of the following:
   - New focal CNS findings
   - Seizures not explained by a previously known seizure disorder
   - CSF pleocytosis (white blood cell count of more than five cells per mm^3)
   - MRI features suggestive of encephalitis†
3 Reasonable exclusion of alternative causes (appendix)

*Altered mental status defined as decreased or altered level of consciousness, lethargy, or personality change. †Brain MRI hyperintense signal on T2-weighted fluid-attenuated inversion recovery sequences highly restricted to one or both medial temporal lobes (limbic encephalitis), or in multifocal areas involving grey matter, white matter, or both compatible with demyelination or inflammation.

Autoantibody-negativ but probable AE

Diagnosis can be made when all four of the following criteria have been met:

1 Rapid progression (less than 3 months) of working memory deficits (short-term memory loss), altered mental status, or psychiatric symptoms
2 Exclusion of well defined syndromes of autoimmune encephalitis (eg, typical limbic encephalitis, Bickerstaff's brainstem encephalitis, acute disseminated encephalomyelitis)
3 Absence of well characterised autoantibodies in serum and CSF, and at least two of the following criteria:
   - MRI abnormalities suggestive of autoimmune encephalitis*
   - CSF pleocytosis, CSF-specific oligoclonal bands or elevated CSF IgG index, or both*
   - Brain biopsy showing inflammatory infiltrates and excluding other disorders (eg, tumour)
4 Reasonable exclusion of alternative causes

*Some inherited mitochondrial and metabolic disorders can present with symmetric or asymmetric MRI abnormalities and CSF inflammatory changes resembling an acquired autoimmune disorder.[102]

Graus et al., Lancet 2016

DIAGNOSTIC CRITERIA

Definite autoimmune limbic encephalitis

Diagnosis can be made when all four* of the following criteria have been met:

1. Subacute onset (rapid progression of less than 3 months) of working memory deficits, seizures, or psychiatric symptoms suggesting involvement of the limbic system
2. Bilateral brain abnormalities on T2-weighted fluid-attenuated inversion recovery MRI highly restricted to the medial temporal lobes†
3. At least one of the following:
   - CSF pleocytosis (white blood cell count of more than five cells per mm^3)
   - EEG with epileptic or slow-wave activity involving the temporal lobes
4. Reasonable exclusion of alternative causes (appendix)

*If one of the first three criteria is not met, a diagnosis of definite limbic encephalitis can be made only with the detection of antibodies against cell-surface, synaptic, or onconeural proteins. †^{18}Fluorodeoxyglucose (^{18}F-FDG) PET can be used to fulfil this criterion. Results from studies from the past 5 years suggest that ^{18}F-FDG-PET imaging might be more sensitive than MRI to show an increase in FDG uptake in normal-appearing medial temporal lobes.[44,45]

Graus et al., Lancet 2016

Cognitive Disorders in autoimmune Encephalitis

Prof. Dr. Christoph Helmstaedter

23.04.2020

Co-founded by the EU

Diagnostic criteria for definite autoimmune limbic encephalitis

Graus et al. 2016 position paper: A clinical approach

***Panel 2:* Diagnostic criteria for definite autoimmune limbic encephalitis**

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➔ Subacute onset (rapid progression ..) of „working memory deficits" needs to be questioned

Graus et al. Lancet Neurol. 2016 Apr;15(4):391-404.

AUTOIMMUNE ENCEPHALITIS

Autoimmune-dementia (encephalopathy) (see Flanagan et al. 2010/11/16)[1,2,3]

- primary symptoms = altered cognition + auto-immunological etiology
  - acute: progressive cognitive decline with/without delir
  - subclinical: chronic fluctuating symptoms with variable course, memory almost always affected (evolve over 1 to 6 weeks)

LE in epilepsy: Seizures + subacute/acute neurobehavioral symptoms

- spectrum of behavior:
  - emotional lability, irritabiliy, anxiety, depression ➔ delirant and psychotic states
- spectrum of cognition:
  - episodic anterograde as well as retrograde memory impairment, dysexecutive symptoms ➔ amnestic episodes (syndrome), dementia

[1] Flanagan et al. Mayo Clin Proc. 2010;85(10):881-897
[2] Flanagan et al. Semin. Neurol. 2011;31(2):144-157
[3] Flanagan et al. Handbook of Clinical Neurology 2016:133:247-267

Neuropsychological evaluation

1. learning phase [2000 ff no systematic evaluation ➔ invalid & missing data]:

- confrontation with acute and dynamic states + various treatments, which called for frequent testing in short intervals for monitoring disease & treatment success
- mixed use of computerized [NeurocogFX]* and standard tests, which in part were not sufficiently sensitive for this condition

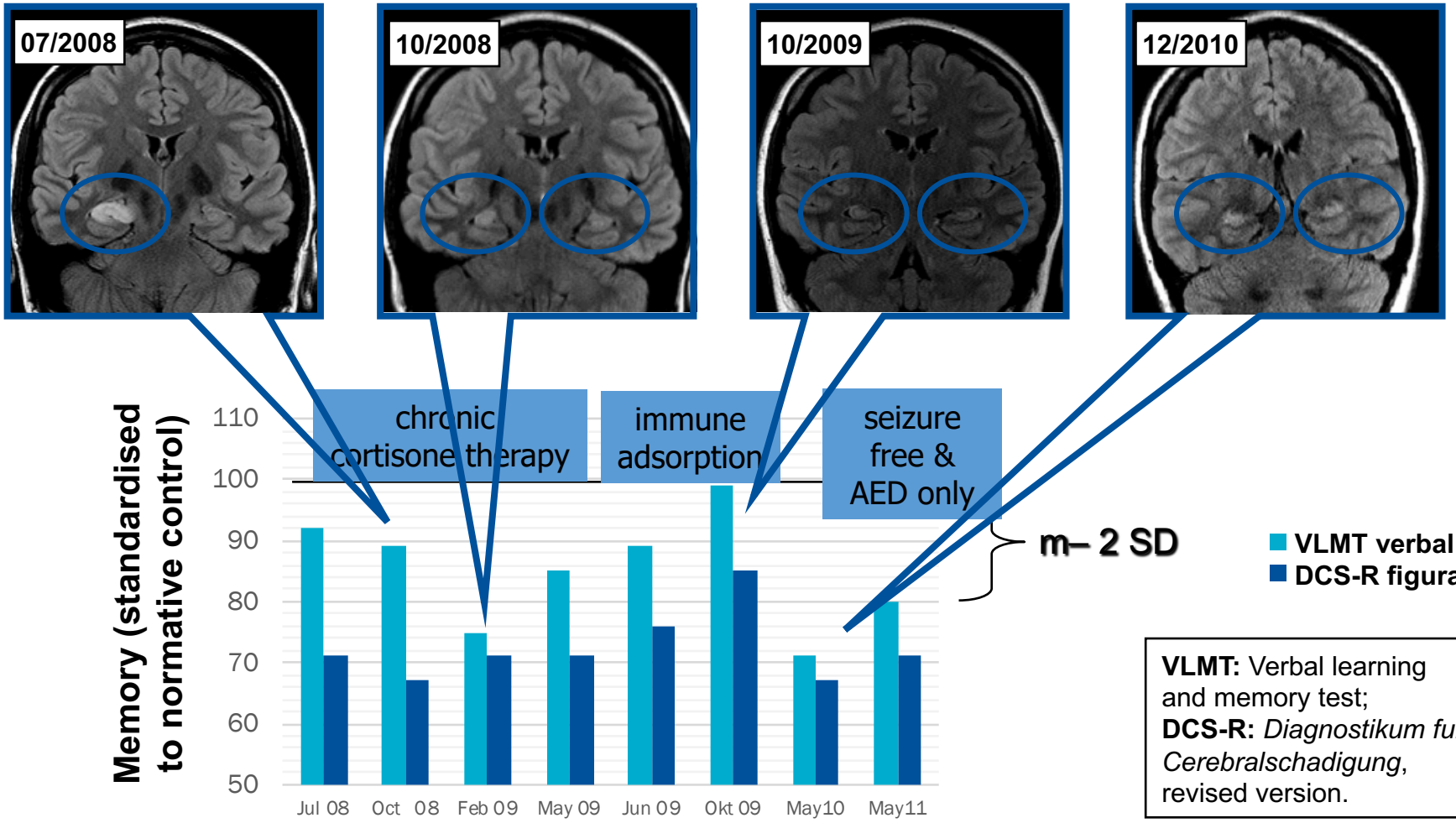
2. more systematic evaluation [since ~2010]:

- tests sensitive for temporal/frontal fcts. [**RAVLT/VLMT; DCS-R; EpiTrack 45 min.**]
- Screening of depression, anxiety etc. [**BDI, SAS, extended AEP**]
- baseline (no acute states), long intervals, with sufficient distance to medical interventions (negative effect of immune therapy on memory?)

RAVLT Rey Auditory Verbal Learning Test, VLMT Verbaler Lern- und Merkfähigkeitstest, DCS-R Diagnosticum für Cerebralschädigung- revidiert, EpiTrack screening tool focusing on frontal lobe functions, BDI Beck Depression Inventory, SAS Zung Anxiety Scale, AEP Adverse Event Profile

* https://www.ncbi.nlm.nih.gov/pubmed/?term=Neurocog+FX

MONITORING LE: FROM UNILATERAL INFLAMMATION TO BILATERAL SCLEROSIS



VLMT: Verbal learning and memory test;
DCS-R: *Diagnostikum fur Cerebralschadigung*, revised version.

*GAD (Glutamic Acid Decarboxylase) antibody positive limbic encepahlitis
Malter et al. Ann Neurol 2010;67:470-8.

CLINICAL COURSES

6/72 were voltage-gated potassium channel **(VGKC)**–complex antibody-positive

- methylprednisolone,
- immunoglobulin
- corticosteroids

Improvement

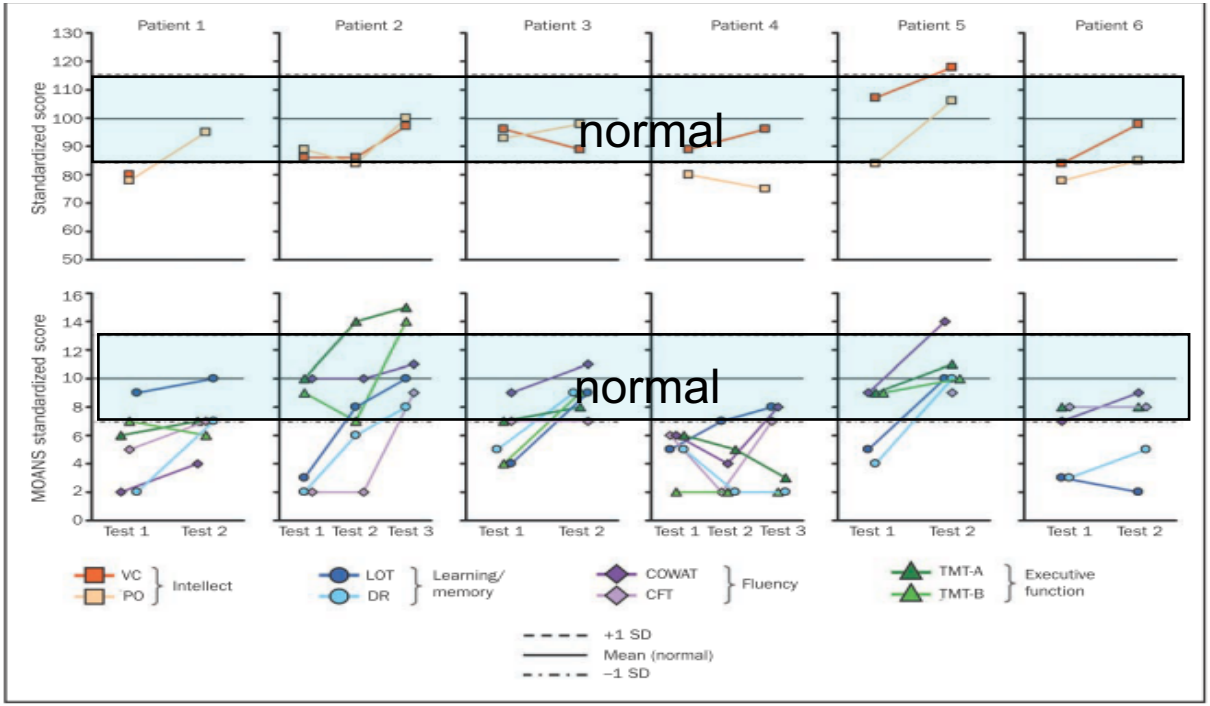
- IQ
- Memory
- Verbal fluency
- Executive fct.

(in part early response)

ORIGINAL ARTICLE

Autoimmune Dementia:
Clinical Course and Predictors of Immunotherapy Response

EOIN P. FLANAGAN, MBBCH; ANDREW MCKEON, MBBCH; VANDA A. LENNON, MD, PHD; BRADLEY F. BOEVE, MD; MAX R. TRENERRY, PHD; K. MENG TAN, MD; DANIEL A. DRUBACH, MD; KEITH A. JOSEPHS, MD; JEFFREY W. BRITTON, MD; JAYAWANT N. MANDREKAR, PHD; VAL LOWE, MD; JOSEPH E. PARISI, MD; AND SEAN J. PITTOCK, MD



Flanagan et al. Mayo Clin Proc. 2010;85(10):881-897

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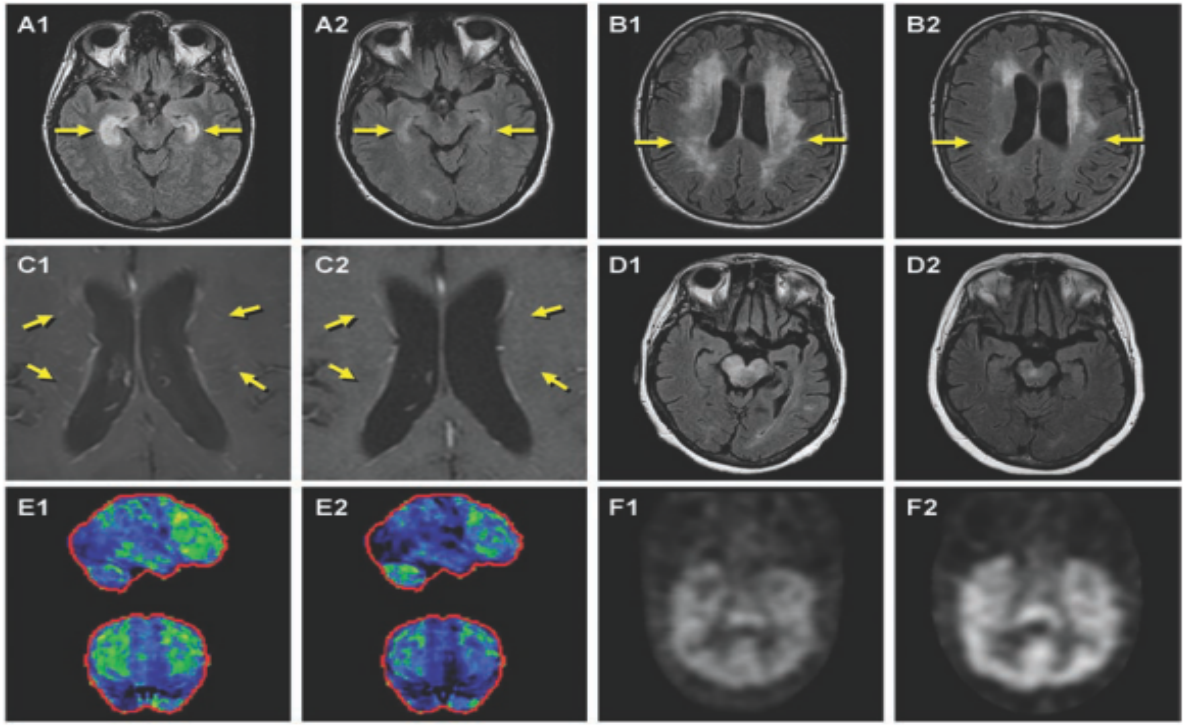


As for quantitative imaging and monitoring of LE via MRI

see

Wagner J et al.
Epilepsia 2012
Epilepsia 2013
JNNP 2015
Epilepsia 2015
Epilepsia 2016

Flanagan et al. Mayo Clin Proc. 2010;85(10):881-897

LIMBIC ENCEPHALITIS: LONG TERM FOLLOW-UP

N= 43 at T1; N= 34 at follow-up T2: median 3 years

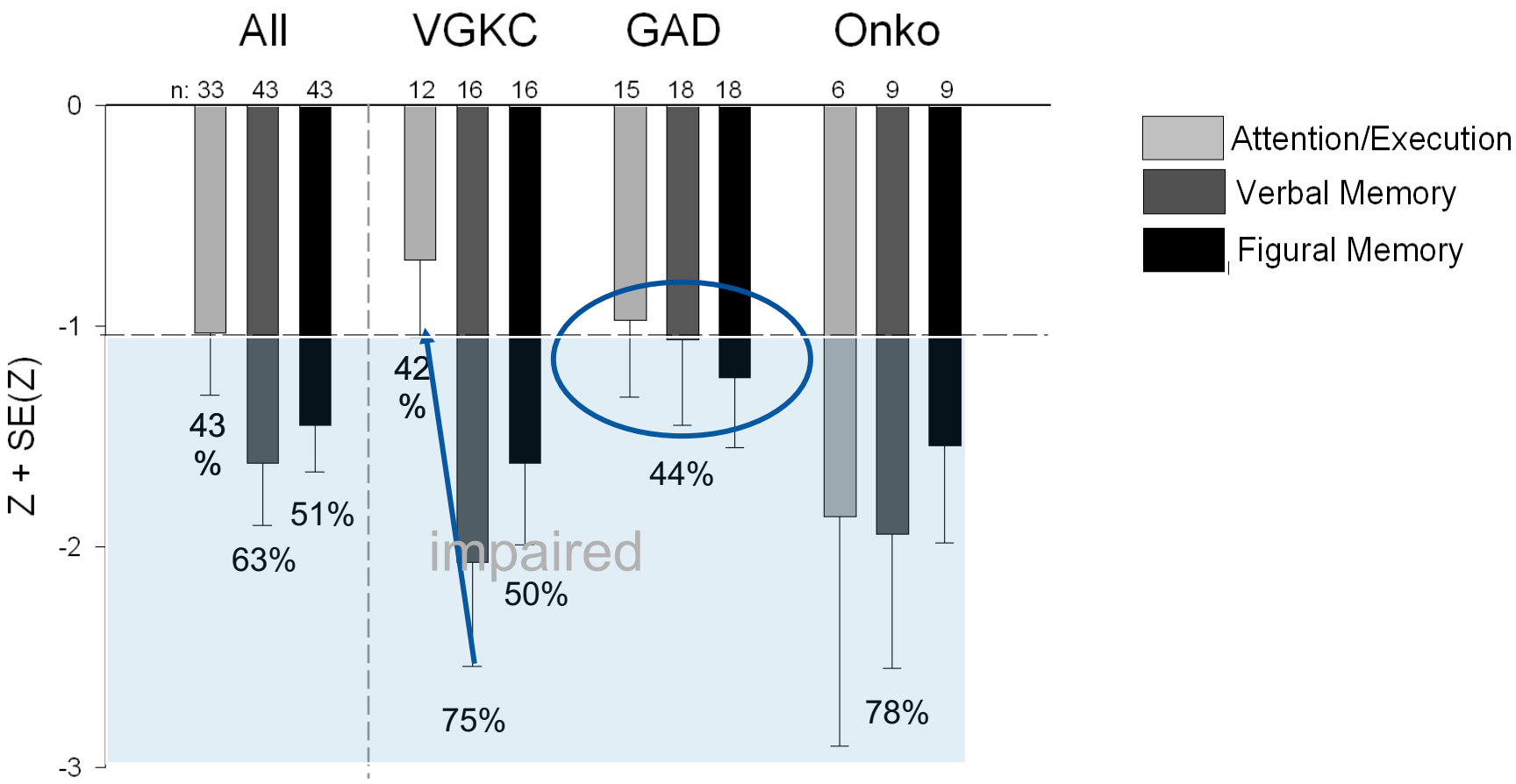
	VGKC [16]	GAD [18]	ONCO [9]	Sign.
Sex (f) %	43%	67%	67%	n.s.
Age (yrs.) m/SD	**54/15**	**31/11**	43/14	0.00
Duration (yrs.) m/SD	**2/6**	**5/7**	**1/1**	n.s.
Education (>10y.)	63%	72%	78%	n.s.
MRI (bilateral) %	**43%**	**22%**	38%	n.s.
	VGKC [16]	**GAD [13]**	**ONCO [5]**	**Sign.**
Follow-Up (yrs.) m/SD	3/2	3/1	3/2	n.s.
Treatment	**1**	**various 1-7***	1	0.00
MRI (AHS/~/↑) %	44/31/**25**	30/**70**/0	0/60/**40**	n.s.
Seizure free >6 mon.	**81%**	**0%**	20%	0.00

* 1 steroidal pulse, 2 chronic steroidal, 3 immune adsorption, 4 plasmapherese, 5 liquorpherese, 6 endoxan (cyclophosphamid), 7 tysabri (natalitsumab)

Frisch et al. Eur J Neurol. 2013 Sep;20(9):1297-304

Limbic Encephalitis

Impairment at baseline [T1]



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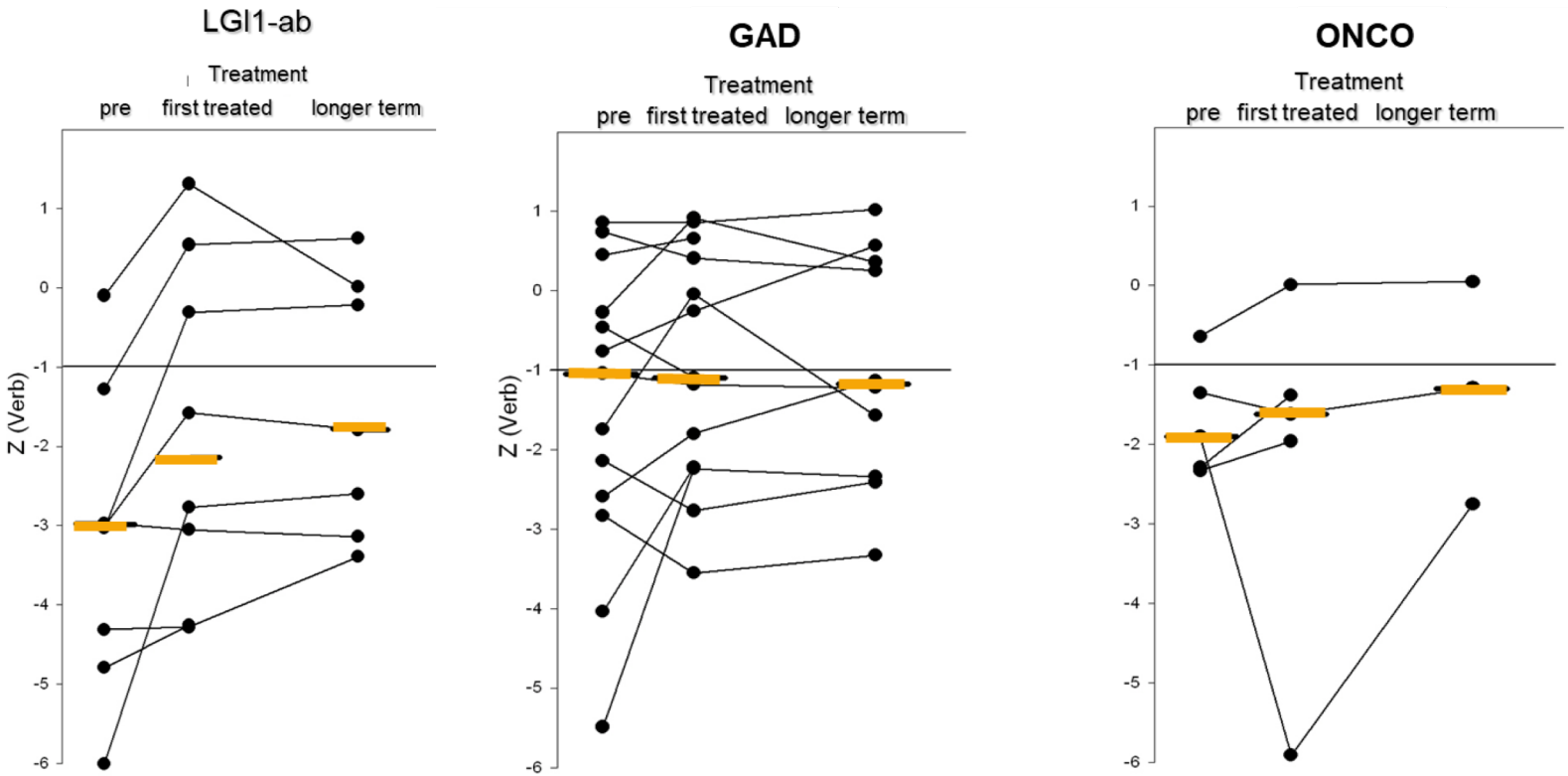
LGI1 AND CASPR2 SUBTYPES

Early response

verbal memory



LGI1 leucine-rich, glioma inactivated
CASPR2 contactin associated protein

Malter et al. J Neurol. 2014; 261/9:1695-705

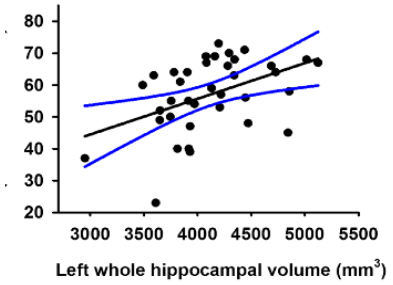
NMDAR AB+ LE

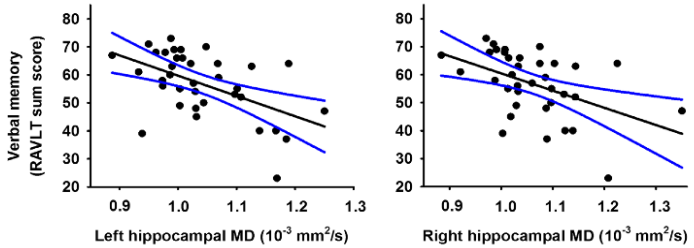
Degree of hippocampal damage related to memory performance*

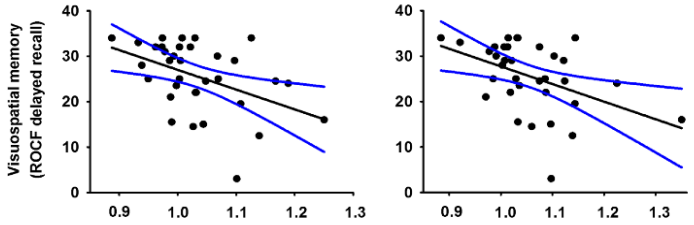
Patients (N= 40)

- Duration 120 ±18 days
- Time after onset 27± 3 mts.
- MRI/DTI subfield volumetry and diffusivity
- verbal memory AVLT
- figural memory ROCF
- seizures seen in 31/40 pts. were rapidly controlled
- correlation of memory and subfields [CA2/3, CA4/DG, subiculum]

MRI







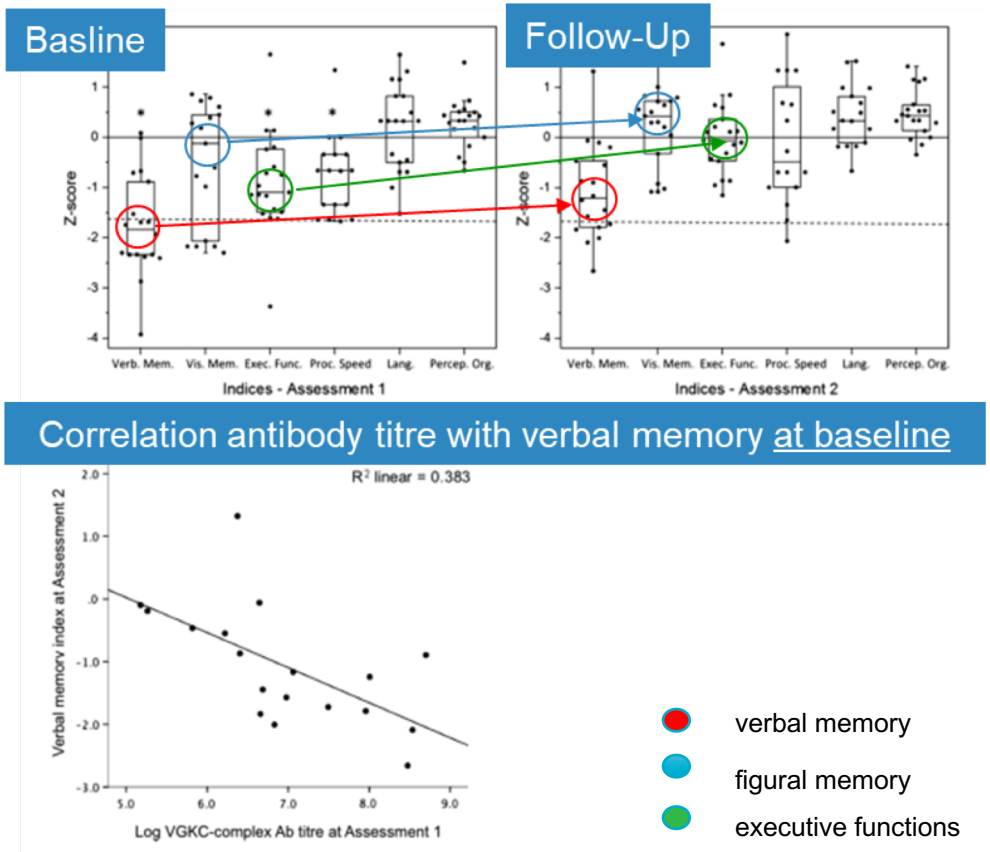
*Finke et al. Biol. Psychiatr. 2016;79:727-734
Findings in neuro-oncological LE patients: Hansen et al. Epilepsy Behav. 2016 Dec;65:18-24
For classic mTLE see: Witt et al. Hippocampus 2014; 24:446-54; and J Neurol. 2015;262:2214-24

VGKC AB+ LE

Persisting deficits & memory related to antibody load

19 patients with VGKC ab+

- follow-up: 3-44 months
- dependent measures:
  - memory: WMS III
  - executive and other fcts.: WAIS III
- some improvement in cognition but with residual deficits (probably less sensitive tests)
- at baseline correlation of antibodies with verbal memory! (and follow-up?)



Butler CR, et al. J Neurol Neurosurg Psychiatry 2014;85: 387-391

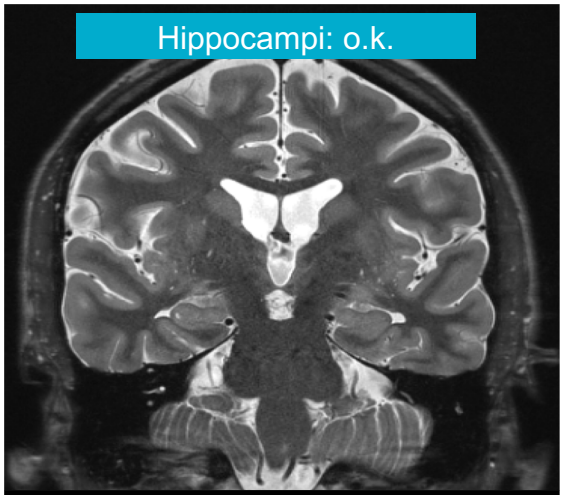
Retrograde Amnesia: Specificity and Curiosity in LE

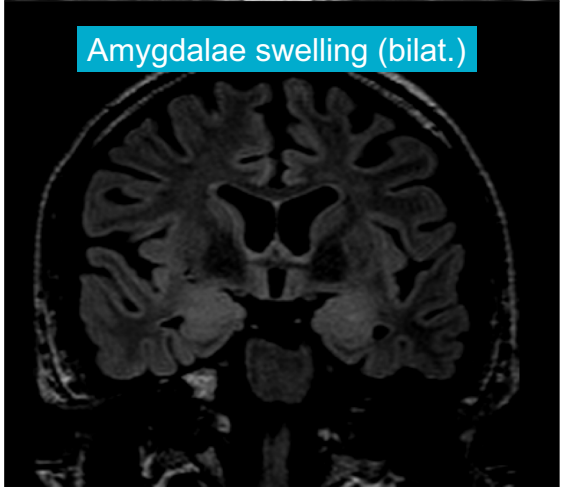
Heavy memory complaints, often no or mild impairment in standard memory tests, and retrograde insular memory loss of events, not following a gradient

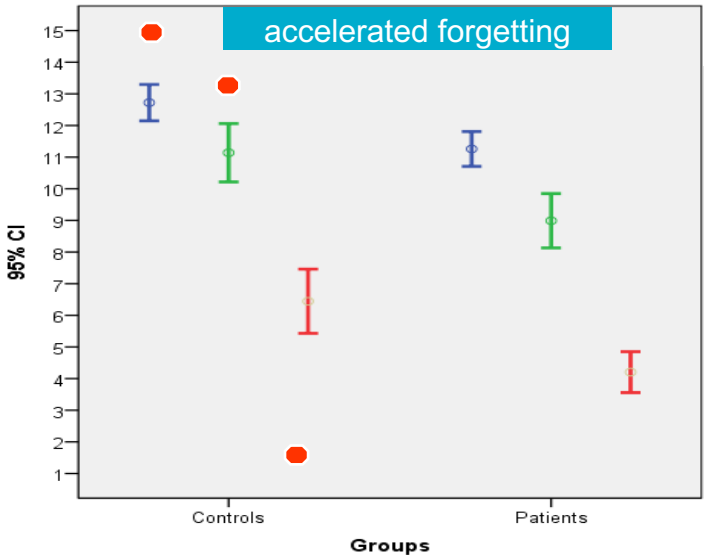
First author	Year	Subtype	Key finding
Kapur	1999	HSV	Pat 1: marked anterograde and limited retrograde deficits (cortex more important than hippocampus)
Bak	2001	ab- PNLE	Pat 1: biographical deficits (recent life, recovery, but memory loss spanning 3 months); Pat 2: severe retrograde memory loss
Hirayama	2003	anti Hu	Retrograde episodic memory loss (< 2 yrs)
Chan	2007	VGKC	3 patients with retrograde amnesia for public events (> 20 yrs); no gradient; 2/3 with subjective improvement after immunotherapy
Kataoka	2008	HSV	Persistent retrograde amnesia (10 yrs)
Kartsounis	2011	VGKC	Impaired retrograde memory (recent life events) with subsequent improvement; remaining tendency to confabulate

PNLE = paraneoplastic LE;
HSV Herpes Simplex

LE: Single Case Report
(retrograde amnesia + accelerated long term forgetting)



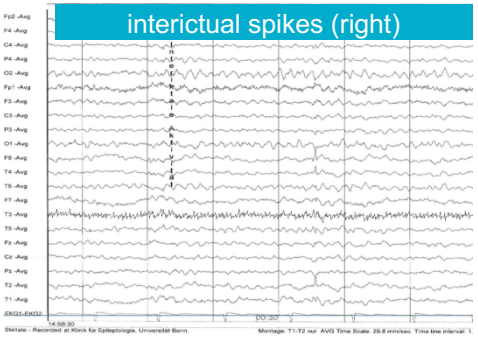


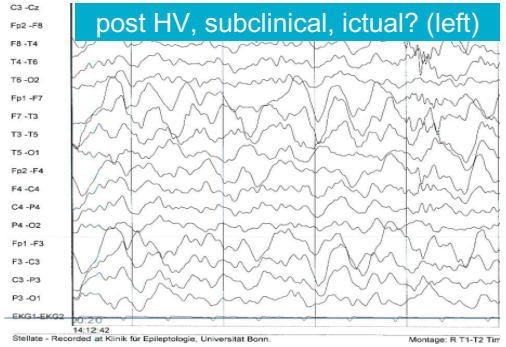


learning

retrieval ½ hour

retrieval 1 week



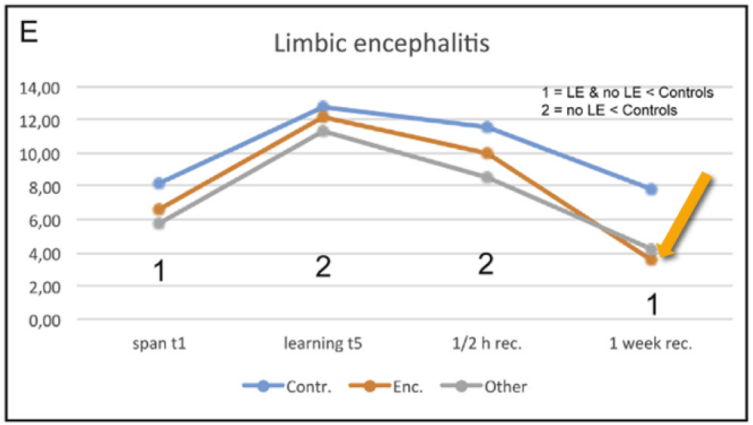


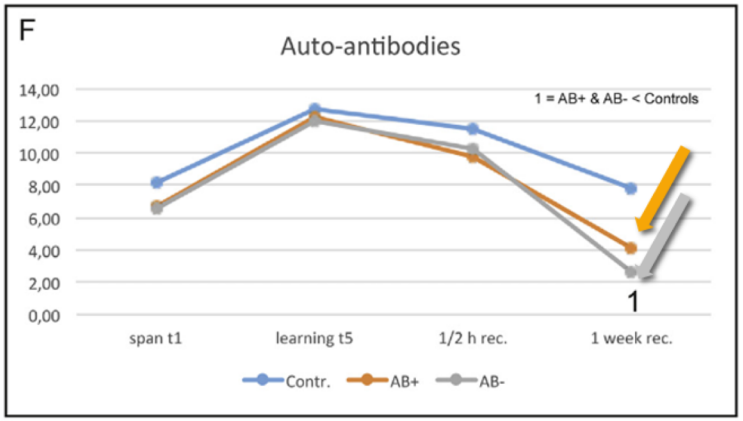
GAD65 ab+ & later development of left temp. seizures

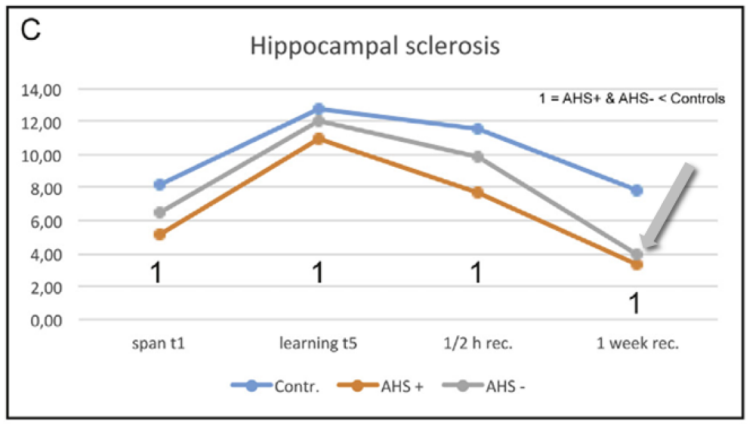
Witt et al. Front Neurol 2015; 9(6):130

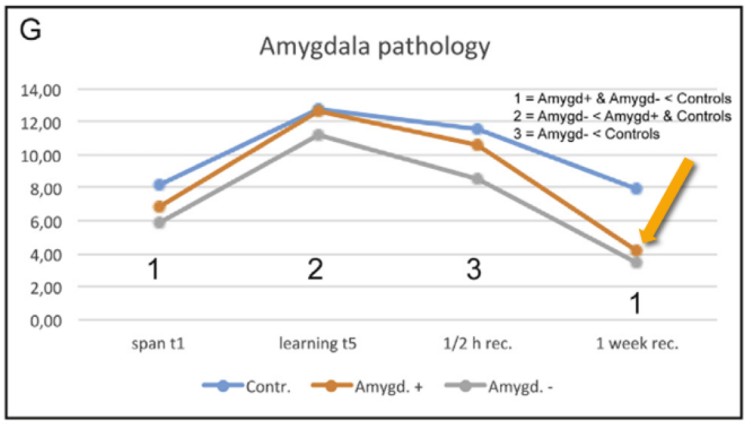
ACCELERATED LONG TERM FORGETTING (ALF) SPECIFIC FOR LE?

ALF an initial symptom and precursor of hippocampal damage?









ALF more likely when ….

- LE
- AB neg/pos
- no sclerosis
- Amydgala affected

Helmstaedter et al. Cortex. 2019 Jan;110:58-68.

SUMMARY

- LE characterized by acute vs. chronic subacute neurobehavioral deficits (can mimic neuroses, depression/burn-out, (psychogenic) amnesia, dementia, psychosis)

- LE subtypes (mainly surface vs. intracellular antigens) differ in regard to deficit pattern, course (mono/multi phasic), acuity (acute, mild, subclinical), correlations of symptoms to antibodies, MRI, treatment response

- In LE seizures, cognition, as well as mood are all (co-morbid) symptoms

  ➔ requires independent and multilevel diagnostics and monitoring of antibodies, MRI, seizures, cognition, mood/behavior

  ➔ neuropsychology serves as a useful disease parameter for monitoring disease and treatment

- Challenges……
  - Disease dynamics: when in the course of the disease is the patient assessed? (sampling bias)
  - Which tests are sensitive at different stages of the disease?
  - Difficult to objectify neuropsychiatric symptoms (i.e. retrograde amnesia? emotional instability)
  - Correlates of amygdala pathology (swelling)? (emotion, arousal, emotional lability)
  - Symptoms related to inflammation vs. structural damage? (lack of biomarkers)

https://www.ncbi.nlm.nih.gov/pubmed/?term=Helmstaedter+encephalitis

Limbic encephalitis – neuropatholgical and serological diagnostics

Prof. Dr. Albert Becker

23.04.2020

Co-founded by the EU

LE-RELEVANT ANTIGENS - OVERVIEW

Antigens	Clinical Presentation	Tumor
Surface Antigens		
NMDAR	severe encephalitis, autonomic dysfunction	ovarian teratoma
LGI1	LE, FBDS	rare
CASPR	Morvan`s Syndrome, LE	rare
AMPAR	LE, psychosis	Thymoma, SCLC
$GABA_bR$	LE, severe seizures	SCLC
Intracellular Antigens		
Hu	Encephalomyelitis, sensory neuropathy, cereb. degeneration	SCLC, prostate cancer
Ma2/Ta	LE, brain-stem encephalitis	testicular cancer
Amphiphysin	Stiff-person syndrome, LE	SCLC, breast cancer
CV2	Encephalomyelitis, sensory neuropathy, cereb. degeneration	SCLC, thymoma
GAD65	LE, chronic TLE, Stiff-person syndrome, cereb. ataxia	rare

Neuropathological approach & potential obstacles

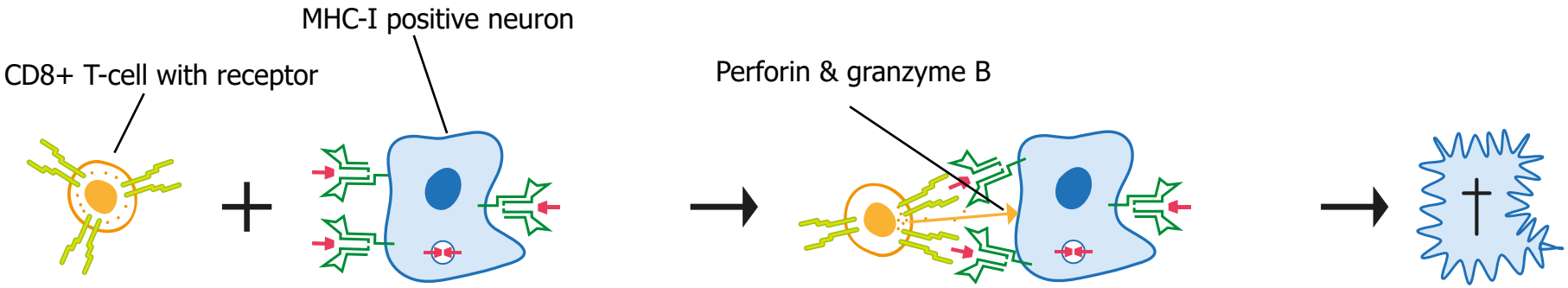
- Cytology und histology using standard- / special stainings
- Immunohistochemistry
- Frequently minute biopsy tissue samples → representative?
- Conservation state of the tissue samples → quality assessment

Spectrum and neuropathological hallmarks

- Antibodies (ABs) against glutamate decarboxylase 65 (GAD65-AB).
- Paraneoplastic onconeuronal ABs (e.g. anti-Hu, anti-Ma, anti-Yo).
- Neuropathology of GAD65-AB encephalitis → predominant cytotoxic T-cell reaction.
- Neuropathology of onconeuronal ABs → multiple Granzyme B positive lymphocytes in the close vicinity of neurons; often more extensive T-lympocytes compared to GAD65-AB.

reviewed in: Bauer & Bien, Handb Clin Neurol. 2016

Pathogenetic concept – T-cell mediated cell death in onconeuronal/GAD65 AB-positive brain tissue



modified from Bien and Bauer, 2013

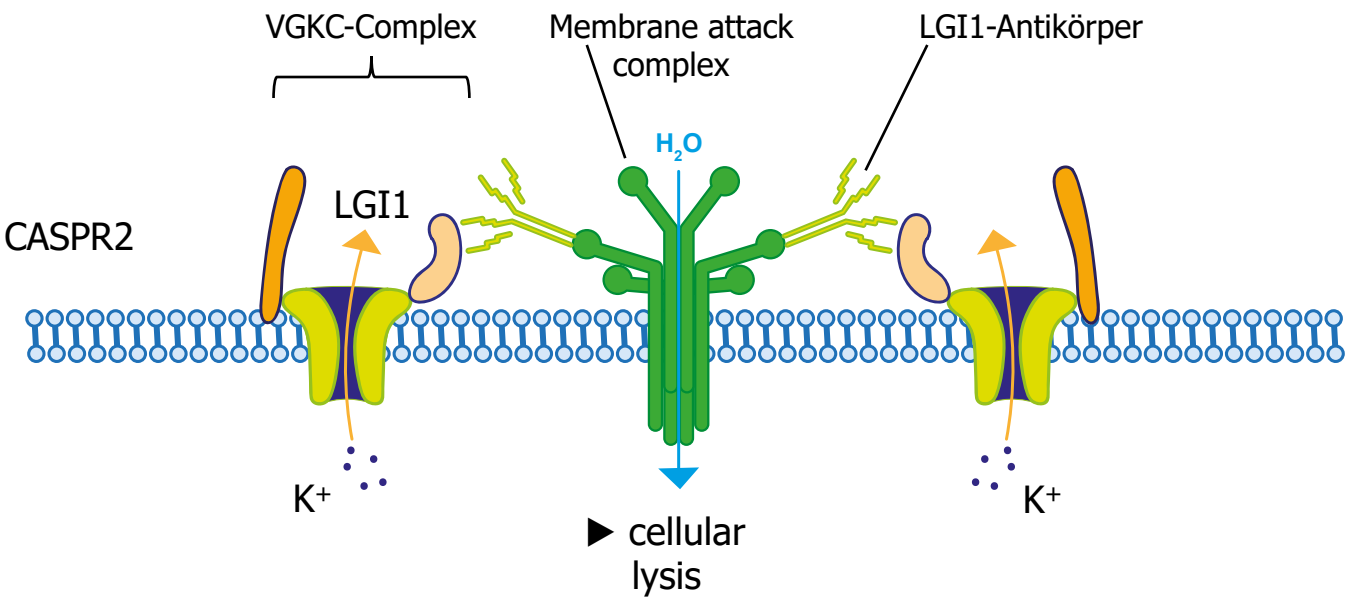
Encephalitis with ABs against neuronal surface targets with robust complement activation

Spectrum and neuropathological hallmarks

- Autoimmune encephalitis with antibodies against voltage-gated potassium channel complex, VGKC.
- Frequent target structure LGI1 (leucine-rich glioma-inactivated 1) as well as less frequent CASPR2 (contactin associated protein 2).
- Less well studied → ABs against α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid-(AMPA)-receptor and ABs against γ-aminobutyric acid (GABA)-receptor.
- Neuropathology of VGKC-ABs → T-lymphocyte mediated neuronal damage, only few Granzyme-B positive lymphocytes in touch with neurons, immunoreactive for C9neo.

Bien et al., Brain 2012; Körtvelyessy et al., Neurology 2015

Pathogenetic concept – LGI1-AB induced cell death



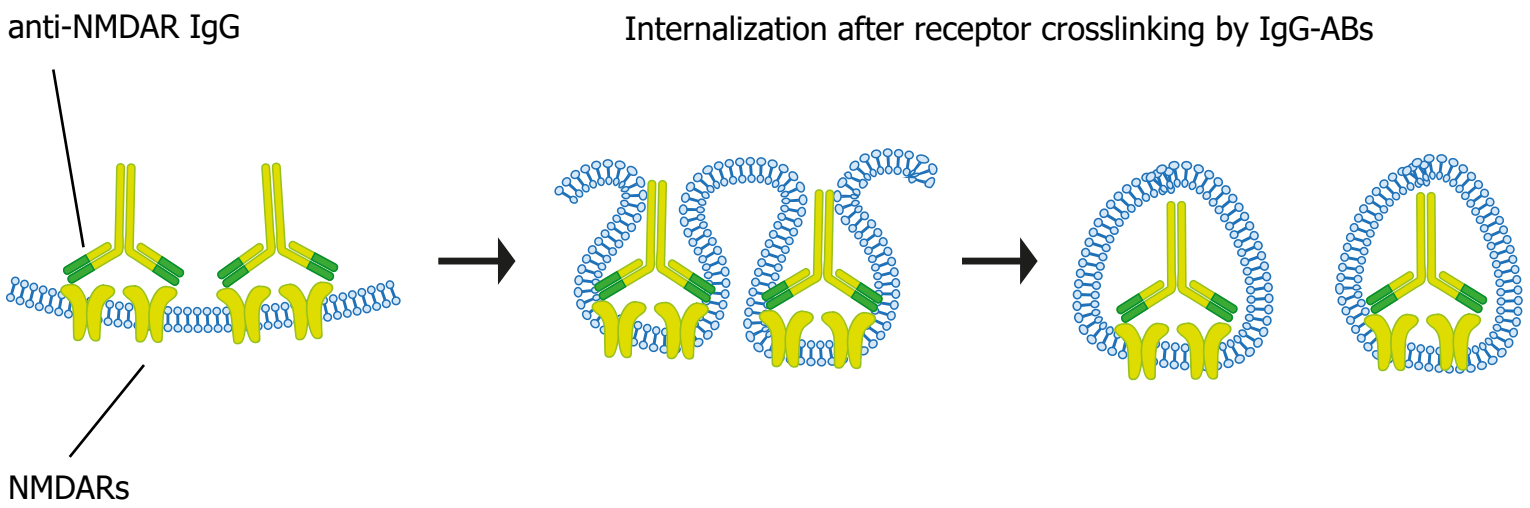
modified from Bien and Bauer, 2013

Neuropathological hallmarks

- Encephalitis mit ABs against surface targets lacking substantial activation of complement.
- Neuropathology → minor immune cell infiltrates than in encephalitic disorders with intracellular antigens.
- B-lymphocyte predominant perivascular arrangements, intraparenchymally mostly T-lymphocytes (CD8/CD3 < compared to onconeuronal ABs); plasma cells can occur in perivascular, intraparenchymal location and Virch.-Robin-spaces.

Bien et al., Brain 2012; Martinez-Hernandez et al., Neurology 2011

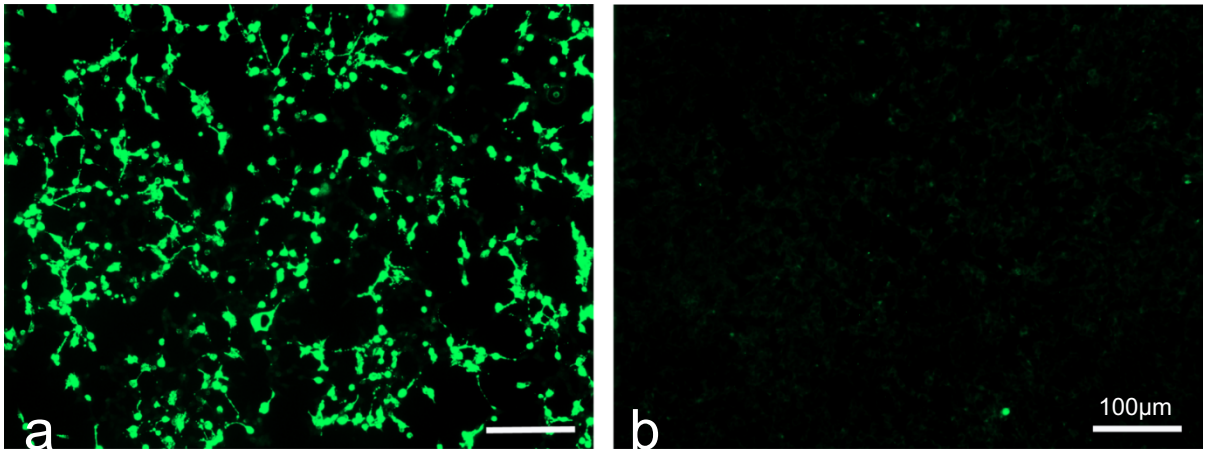
Pathogenetic concept – NMDAR-AB mediated cross linking and internalization of NMDA receptors



modified from Bien and Bauer, 2013

AB DIAGNOSTICS – GENERAL APPROACH

Specific ABs	so far unknown ABs
• Cell-based-Assays: transfected HEK-cells • Immunoblots: purified protein	• Immunohistochemistry: brain slices • Western blots: brain lysates

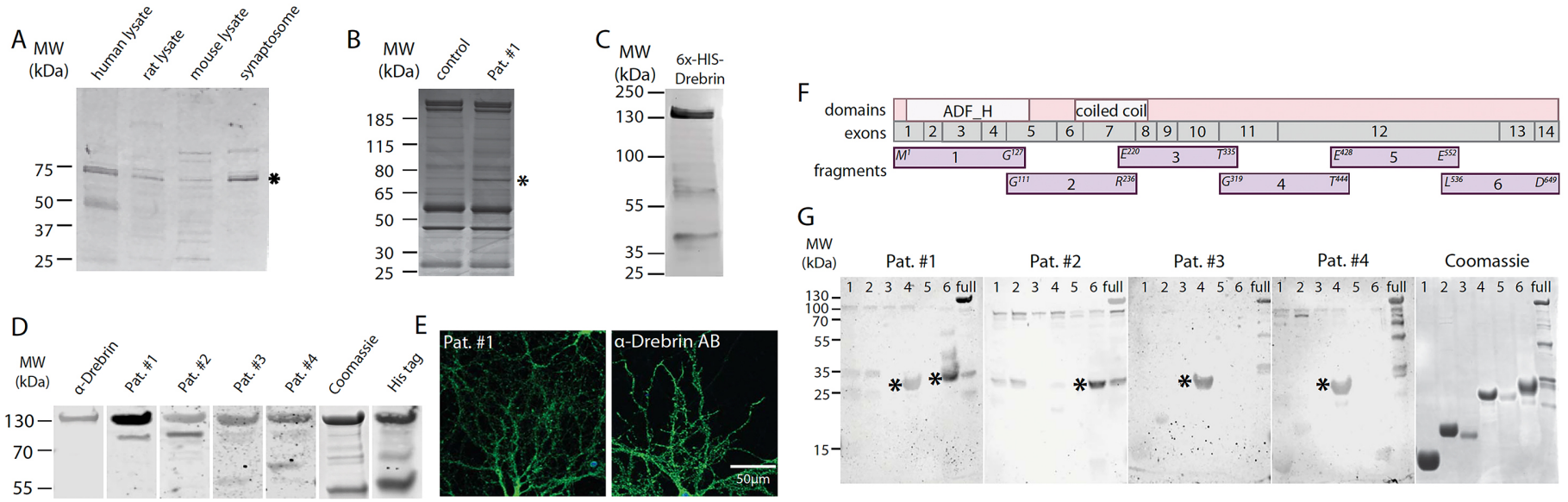


Characterization of autoantibody spectrum in a consecutive series of patients suspicious for LE

Overview

- A series of 830 patients with epileptic seizures and suspicious for LE.
- 1515 samples of serum and CSF analyzed for well known autoantibodies and so far unknown autoantibodies.
- In 15.05% of those patients → previously reported Auto-ABs (anti-Amphiphysin, CV2, PNMA2 (Ma2/Ta), Ri, Yo, Hu, Recoverin, SOX1, Titin, Zic4, GAD and Tr (DNER), anti-NMDA, CASPR-, LGI1-, GABAa-, GABAb-, AMPAR- and GAD65).
- More than 20% of patients considered as seronegative by any test for specific antibodies → additional immunoblot bands or binding pattern on mouse / simiiforme brain sections potentially suggesting novel autoantibodies.

IDENTIFICATION OF A NOVEL LE-AUTOANTIBODY AS ANTI-DREBRIN AB AND TARGET EPITOPE MAPPING



Pitsch et al., Ann Neurol in press

TREATMENT OF LIMBIC ENCEPHALITIS

Prof. Dr. Rainer Surges

23.04.2020

Co-founded by the EU

Treatment of limbic encephalitis

- Treatment goals (and follow-up evaluation)
- Treatment modalities
- Treatment criteria and algorithms (who, when, how long)

When is treatment successful (follow-up evaluation) ?

- Cessation of inflammation (biomarkers)
  - Reduced / normalized antibody levels or CSF signs (?)
  - Normalized MRI findings (reduction of enlarged volumes)?
  - EEG (regional slowings, epileptiform potentials)
- Improved seizure frequency
- Recovery of memory deficits
- Improved mood (?)

TREATMENT MODALITIES

- Immunosuppression
  - Cortisone, plasmapheresis, IVIGs, rituximab, cyclophosphamide, azathioprine, mycophenolate mofetil
- Seizure control
  - Anti-seizure drugs
  - Epilepsy surgery
  - Neuromodulatory devices (?)
- Tumor resection (if paraneoplastic)

Current treatment algorithm in Bonn

Disease duration	<12 months		>12 months
Disease severity	High	Moderate	Low
Antibody type	High predictive value		Unknown / low predictive value

Recommendation for immunosuppression

PREDICTIVE VALUE OF ANTIBODIES

	Antibodies	Improvement with immunotherapy
Specific and predictive	**NMDA-R in CSF**	+
	LGi1	+
	CASPR2	+
	AMPA-R	+/-
	$GABA_B$	+/-
	DPPX	+/-
Specific or predictive	**Onconeural**	-
	GAD65	-
	GlyR in CSF or >1:50 i.S.	+
	Neurexin-3α	+/-
	$GABA_A$	+/-
	No antibodies	+/-

Bien CG, Holtkamp M. Epilepsy Curr 2017;17:134-41.

When to initiate immunosuppression - typical constellations (examples)

Current treatment algorithm in Bonn

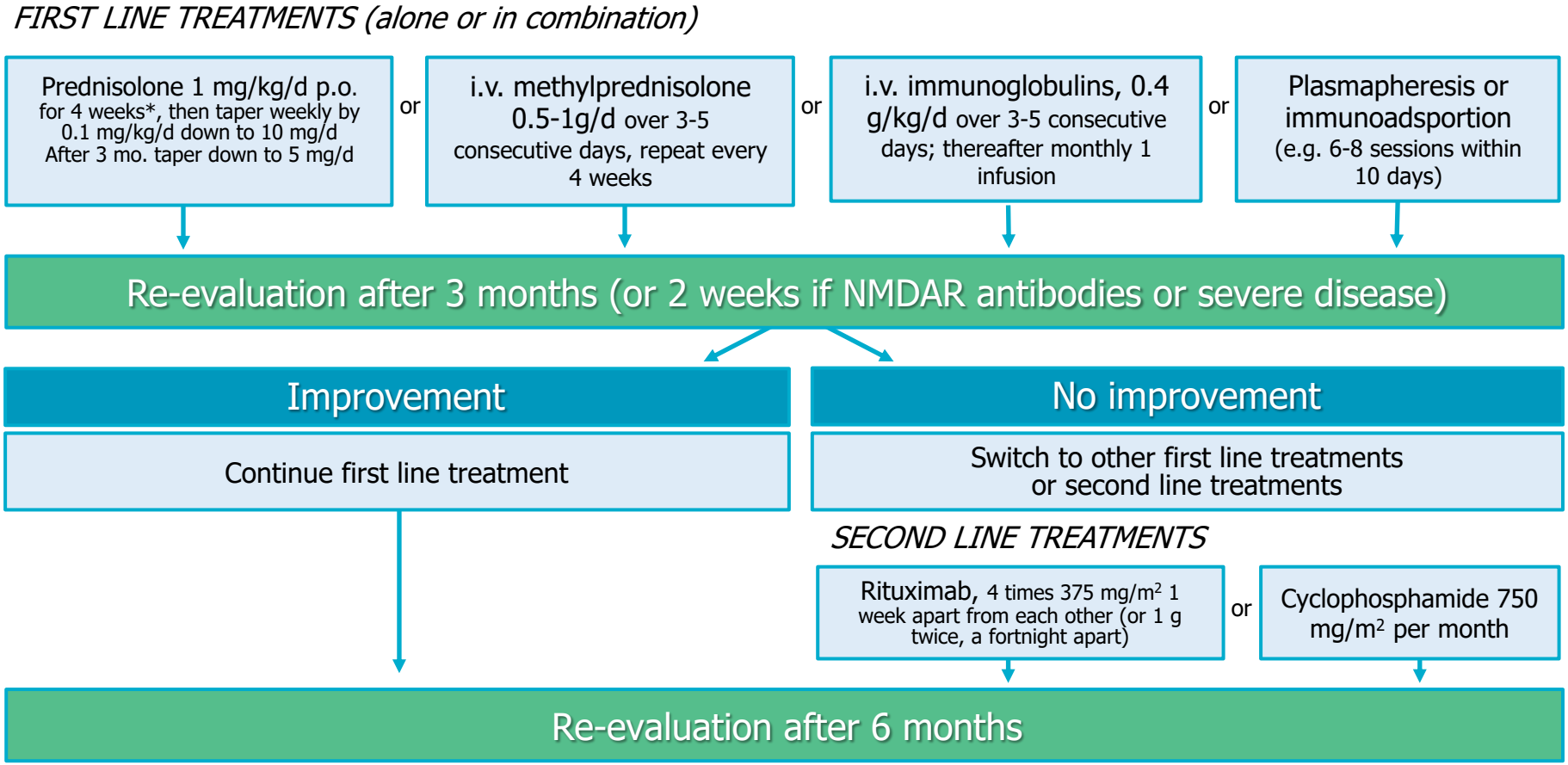
General neurology departments

Specialized epilepsy centers

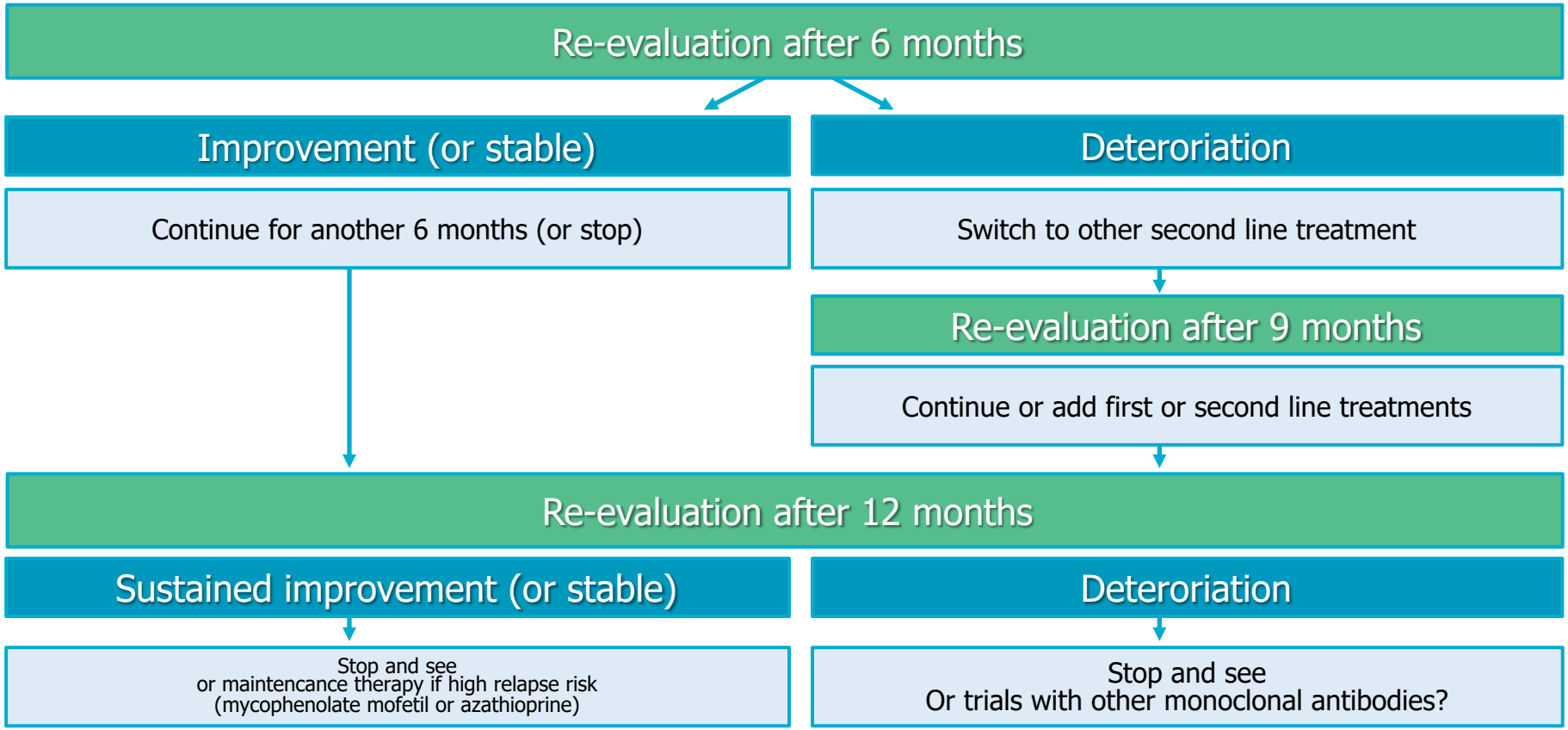
Full picture of LE Severe disease LGi1/CAspr2 antibodies Disease duration <6 mo.	All features of LE Significant memory deficits No antibodies Disease duration <18 mo.	All features of LE Low severity No antibodies Disease duration >12 mo.
		All features of LE Low severity High titre of GAD65 ab Disease duration >12 mo.

Recommendation for immunosuppression

WHICH IMMUNOSUPPRESSIVE THERAPY - TREATMENT ALGORITHM (BONN)



Which immunosuppressive therapy - treatment algorithm (Bonn)



6, 12 and 24 months (inpatient)

- Clinical assessment
- Brain MRI
- Cognitive testing
- Video-EEG monitoring over 2-3 days
- Antibodies in serum (or CSF if NMDAR)

Seizure control

- FBDS do not (or only partially) respond to anti-seizure drugs
- Selection according to guidelines for focal epilepsies

- Epilepsy surgery may be considered if longer disease duration and predominant/leading seizure generator (reported cases yielded mixed outcomes)

- Neuromodulatory devices may be used earlier (no case series to date)

THANK YOU

European Reference Networks

Epi CARE

European Reference Network for rare or low prevalence complex diseases

Network Epilepsies (ERN EpiCARE)

the EU