ENCEPHALITIS CONFERENCE

Encephalitis 2021

TUESDAY
7TH DECEMBER 2021
09.00 - 18.00

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Poster Booklet

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After finishing a degree in biomedical sciences in 2007, Daniëlle Bastiaansen studied medicine at the Erasmus University in Rotterdam (2007-2013). She had a big interest in neurology and started working as a resident in a teaching hospital in Dordrecht. In 2015, she returned to the Erasmus University Medical Center to resume her residency training to become a neurologist. In 2016, she started a PhD to study autoimmune and paraneoplastic encephalitis, supervised by Prof Dr P.A.E. Sillevis Smitt and Dr M.J. Titulaer.

She currently combines her PhD with the residency program in neurology.

Autoimmune encephalitis and dementia syndromes

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Introduction & Aims

Autoimmune encephalitis (AIE) is a severe but treatable disorder. Diagnosis can be challenging since it is known that patients can present with less notable encephalitis signs. Usually, it is multi-symptomatic with a subacute onset of symptoms. A slower progression with only cognitive decline is also known.

- How often does AIE resemble dementia and what are the red flags for AIE.
- What is the prevalence of neuronal antibodies in neurodegenerative dementia syndromes.

Methods

Nationwide observational cohort study in anti-NMDAR, anti-LGI1, anti-CASPR2, or anti-GABABR encephalitis. Patients were included when 3 criteria were met: age ≥45 year, fulfillment of dementia criteria, and no prominent seizures at beginning of the disease course.
Patients with various dementia syndromes were retrospectively included from established cohort at two large Dutch academic memory clinics and screened for neuronal antibodies.

Conclusions and implications

A **small, but clinically relevant** proportion of dementia have neuronal antibodies.
Clinicians should have a low threshold for neuronal antibody-testing, in particular in patients with atypical clinical dementia signs.

Autoimmune encephalitis **can** resemble dementia and its accompanied by les notable '-itis' signs.
Dementia biomarkers can be abnormal in AIE.

Red-fags AIE:

1. Rapidly progressive cognitive decline / subacute deterioration
2. (Subtle) seizures
3. Abnormal ancillary tests atypical for neurodegeneration (lack of atrophy, pleocytosis)
4. myoclonus
5. history of autoimmune disorders

Results

Study 1.
We identified 290 patients with anti-LGI1, anti-NMDAR, anti-$GABA_BR$, or anti-CASPR2 encephalitis. 175 patients (60%) were ≥45 years of age, of whom 67 patients (38%) fulfilled dementia criteria (**Figure 1**). Patients with anti-CASPR2 encephalitis were excluded from analysis due to small numbers.

Dementia was suspected by the treating physician in half of the patients and there was a rapidly progressive dementia in 48 patients (76%) (**Table 1**). Later in disease course 40 patients (64%) developed seizures. In 17 patients (27%) subtle seizures had been overlooked (16 LGI1).

Ancillary testing by CSF, EEG or MRI was normal in half of the patients (**Table 1**). No abnormalities on brain MRI nor CSF pleocytosis were seen in 25%. In 44 patients (65%) CSF biomarkers for dementia were tested. **Figure 2** shows that markers were often abnormal (27/44; 61%), including patterns resembling Creutzfeldt-Jakob disease. 5/8 positive 14-3-3 samples were analysed for RT-QuIC (Real-Time Quaking Induced Conversion): all negative.

Figure 1. Patient inclusion – study 1

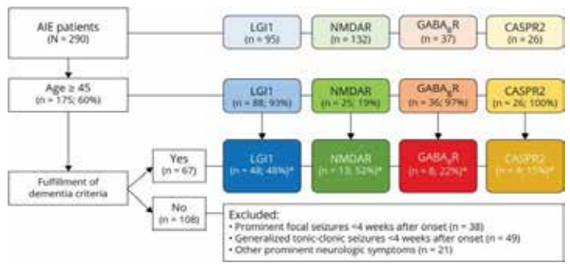
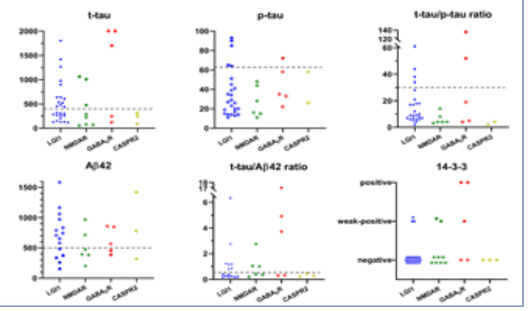


Table 1. Patient and cognitive characteristics

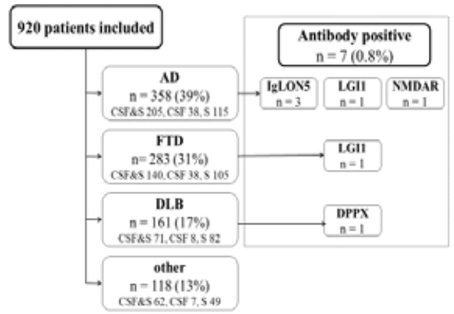
	LGI1 (n=42)	NMDAR (n=13)	$GABA_BR$ (n=8)	p-value
Sex, male	29 (69%)	4 (31%)	4 (50%)	0.047
Age at onset in years, median [IQR]	66 (59-72)	61 (57-68)	73 (58-76)	0.11
Cognitive decline presenting symptom	30 (71%)	11 (85%)	7 (88%)	0.55
Rapidly progressive dementia	32 (76%)	11 (85%)	4 (50%)	0.24
Dementia suspected by treating physician	21 (50%)	7 (54%)	5 (63%)	0.87
Seizures during disease course	32 (76%)	3 (23%)	25 (63%)	***0.002***
Median days onset to prominent seizures	117 (42-181)	221 (34-409)	52 (38-85)	0.44
Subtle seizures early in disease course	16 (38%)	0	1 (13%)	***0.011***
CSF abnormal	13 (31%)	9 (69%)	4 (50%)	0.047
MRI mesiotemporal hyperintensities	66 (59-72)	61 (57-68)	73 (58-76)	0.11

Figure 2.



Study 2.
920 patients were included and in total 1398 samples were tested (477 both CSF and serum). Neuronal antibodies were detected in 7 patients (0.8%), including anti-IgLON5 (n=3), anti-LGI1 (n=2), anti-DPPX, and anti-NMDAR (**Figure 3**).
Atypical signs for neurodegenerative disease included myoclonus (n=2), a fluctuating disease course (n=1) and epileptic seizures (n=1). No patients fulfilled the criteria for RPD, while 3 patients had subacute deterioration. Brain MRI was normal in all and CSF pleocytosis was found in one patient.
Compared to the patients without neuronal antibodies, there was no significant difference with respect to clinical characteristics or ancillary testing.

Figure 3. Patient inclusion – study 2



Reference: Bastiaansen AEM, van Steenhoven RW, de Bruijn MAAM, et al. Autoimmune Encephalitis Resembling Dementia Syndromes. Neurol Neuroimmunol Neuroinflamm. 2021;8(5):e1039. Published 2021 Aug 2.

Dr Sophie Binks

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Sophie is a neurology trainee in Oxford who completed her first year of registrar training in February 2019, and is now studying for a full-time Wellcome Trust-funded DPhil, with the goal of establishing herself as a clinician-scientist. In 2016-2017, she investigated clinical and immunogenetic aspects of antibody-mediated encephalitides as an academic clinical fellow within the Oxford Autoimmune Neurology Group of the Nuffield Department of Clinical Neurosciences, leading to a joint first author research paper outlining human leucocyte antigen associations of these conditions (Brain).

During the DPhil to date, she has published "Residual Fatigue and Cognitive Deficits in Patients After Leucine-Rich Glioma-Inactivated 1 Antibody Encephalitis" (JAMA Neurology, joint first author) and gained two small grants as lead investigator to study a translational model of autoimmune encephalitis. She had previously successfully completed an Academic Foundation Programme in neurology at Brighton and Sussex University Hospitals NHS Trust (BSUH). The principal project was: "Effect of high-dose simvastatin on cognitive, neuropsychiatric, and health-related quality-of-life measures in secondary progressive multiple sclerosis: secondary analyses from the MS-STAT randomised, placebo-controlled trial" (Lancet Neurology, joint first author). In July 2013, she graduated first in her cohort at Brighton and Sussex Medical School, achieving the prize for best performance in the overall programme, distinction in the BMBS, and honours for integrated medicine, surgery and therapeutics, as well as 18 other prizes/scholarships in years 1-4. Prior to medical school she gained a BA (Hons) 2:1 from the University of Oxford in Classics & Modern Languages (French).

Spilling your December drink – a serious matter: the 'messy carpet sign' & LGI1-antibody seizures

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Introduction

Encephalitis with antibodies to leucine-rich glioma-inactivated 1 (LGI1) is the commonest form of autoimmune encephalitis in middle-aged and older adults, particularly men.[1] Faciobrachial dystonic seizures (FBDS) represent a pathognomic seizure type in this condition, seen in up to 70% of LGI1-antibody patients.[2] These brief dystonic movements, typically affecting the face, arm, and sometimes the leg, can occur hundreds of times per day, resulting in falls, serious injuries and domestic accidents.[2,3] EEG and MRI may be unremarkable, contributing to delay in recognising these events as seizures.[4-6] Yet, FBDS are exquisitely sensitive to immunotherapies and their early treatment can prevent development of frank encephalitis and cognitive deficits.[3] We present a simple and memorable sign, the "messy carpet sign", with high specificity and positive predictive value (PPV) to help identify FBDS.

Patients

In the index patient, a 61-year-old man, violent and frequent FBDS at disease nadir resulted in spillage of many cups of tea, necessitating the cleaning or replacement of carpets; the "messy carpet sign". 67 additional patients with LGI1-antibodies, of which 47 with FBDS, and 65 patients with other forms of encephalitis or epilepsy were then questioned for the presence of the sign or related phenomena.

Table 1: Patient demographics

	LGI1 + FBDS	LGI1 no FBDS	Disease controls^
Number of patients	48	20	65
Mean age (median, range)	71.3 (71, 52-90)	64.1 (62.5, 44-92)	56.5 (62, 16-85)
Male	33 (68.8%)	13 (65%)	39 (60%)
Focal-onset seizure*	26 (54.2%)	16 (80%)	37/59 (62.7%)
Generalised seizure	10 (20.8%)	10 (50%)	28/59 (47.5%)
No seizures	0	2 (10%)	11/62 (18%)

*Excludes FBDS
^Other encephalitis = 58; focal-onset epilepsies = 7; denominator provided where data available for <65 participants

Patients were recruited from Oxford autoimmune and/or epilepsy clinics and via the Encephalitis Society between August 2016-June 2019.

Results: frequency and severity of FBDS

- 48/68 (**71%**) of LGI1-antibody patients had FBDS
- At disease nadir, these occurred very often, with a median frequency of 84 seizures per day (**Figure 1**)
- FBDS affected the face, arm, and leg and could be described as 'body jolts' by patients (**Figure 2**)

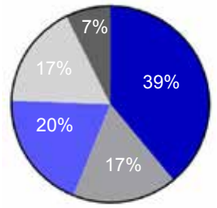

Figure 1. Number of FBDS at disease nadir in 41 patients

Figure 2. Excerpts from a family diary of a patient with active FBDS, detailing numerous incidents of the "messy carpet sign" and its variants, as well as high frequency of 'body jolts'. Reproduced with family permission, with thanks

Results: clinical signs associated with FBDS

- 24/48 (**50%**) recalled the messy carpet or a related sign compared to 1 (**1.5%**) of disease controls (adjusted p<0.0001)
- 26/48 (**54%**) LGI1-FBDS patients experienced falls compared to 3/54 (**6%**) of disease controls (adjusted p<0.0001). Eight falls in FBDS patients resulted in significant injury including fracture and head injury
- The sign highlighted the risk of falls: 18/26 (**69%**) of FBDS patients with falls were messy carpet sign positive compared to 6/22 (**27%**) who had the sign and no falls (odds ratio 5.8, 95% CI 1.5-25.6, p = 0.008, Fisher's exact test)

The carpet sign: patient descriptions & clinical value

In addition to tea or coffee on carpets or clothing, variants of the sign included wine spills in two ("glass of wine sign"), dropped sausage rolls, and tearing of trousers through a forceful FBDS. One patient sustained a burn, illustrating the sign's direct morbidity. Three patients described bathroom-based domestic accidents, two of whom were flung violently against a toilet cistern ("the cistern sign"). The box below displays patient accounts of the sign.

Messy carpet sign

(He) would "throw plates of food…had to have new carpets cleaned…would bring a cup of tea up and fling all over the carpet…had to have a new carpet" – 61-year-old man (index patient)

"In hospital…I was having jerks all the time. I spilt tea and burnt my abdomen" (M, 67)

"Due to "hand jerks" on the right side, I was wearing more tea than drinking it. It went all over the carpet and up the wall" (M, 75)

"I would have a sensation on the left side of my temple, which spread to my right temple, then both arms would jerk. I would try to control (it) but I couldn't. The occasional fall progressed…I broke a printer, and fell out of a car door, scuffed my knee and tore my trousers" (M, 53)

"On Monday he had a very bad turn – had a spasm while eating – he felt extremely unwell. This was the first sign of something serious, his arm went up violently, it was not just a little jerk, his dinner went everywhere" (M, 72)

Spilled drink sign

"My hand would let go of things…I threw a cup of tea up in the air, and spilt wine over my wife's shirt…I was dropping things…" (M, 76)

"I was out for lunch with friends, as I was putting my hand out I knocked over a glass of white wine…my hand just does a quick cramp" (M, 79)

Cistern sign

"I could be on the toilet and be thrown back…concern (that I would) break the cistern...it was scary…the force increased…" (F, 66)

"(I) would stop leaving the house as was concerned about having a violent event e.g. one time sat on the toilet, went to reach for loo roll, (FBDS was) so violent swang round and broke the cistern" (M, 59)

The odds ratio of FBDS in patients with the "messy carpet sign" was 62 (95% CI 9.1-2631.1) and, overall, the sign and its variants showed a 98.5% specificity and a PPV of 96% with a sensitivity of 50% (95% CI 35.4%-64.6) (Table 2). This persisted after adjustment for age (age: β=0.05, p=0.007, 'messy carpet sign': β=3.8, p=0.0003). Hence, this sign has a high specificity and PPV for patients with FBDS.

Table 2: Sensitivity, Specificity, PPV & NPV* of the carpet sign and its variants

	FBDS	Disease controls	
Sign positive	24	1	PPV: 96% (95% CI 77.7% to 99.8%)
Sign negative	24	64	NPV: 72.7% (95% CI 62% to 81.4%)
	Sensitivity 50% (95% CI 45.4-64.6%)	Specificity: 98.5% (95% CI 90.6-99.9%)	
Odds ratio FBDS : controls	61.7, 95% CI 9.1-2631.1, adjusted p<0.0001		

*Negative predictive value

Comparison to UK population statistics

In 2002, the last year with a published national Home and Leisure Accident Surveillance System report, an estimated 15,909 UK citizens experienced accidents with mugs of tea or coffee, 30,689 with a drinking glass, and 15,416 with a toilet in home or leisure environments.[7] Based on the 2002 UK population of 59,365,700[8] the odds ratio for being in cup-of-tea, drinking glass or toilet accident for FBDS patients compared to the population was 930 (95% CI 525.1-1832.5, p<0.0001). Since there was frequently a delay in detection of LGI1-antibodies in our cohort, with initial misdiagnoses including anxiety, panic attacks and depression (n=11), dementia (n=6), and cerebrovascular disease (n=4), the sign could represent a useful aide-memoire for general clinicians to help recognise this rare disease.

Conclusions

- The "messy carpet sign" is characteristic of a rare anti-epileptic drug refractory seizure type, FBDS, which is pathognomic of LGI1-antibodies
- It is associated with falls and carries a risk of associated physical and psychological morbidity
- It could help raise the index of suspicion for FBDS in individuals in middle to older age, particularly males, who present with an acute onset of 'jerks', 'jolts', 'spasms' or 'cramps' (as described by patients) combined with other relevant clinical features

References. [1]Binks S, Klein CJ, Waters P *et al.* LGI1, CASPR2 and related antibodies: a molecular evolution of the phenotypes. J Neurol Neurosurg Psychiatry. 2018 May; 89 (5): 526-534. [2]Irani SR, Michell AW, Lang B *et al.* Faciobrachial dystonic seizures precede Lgi1 antibody limbic encephalitis. Ann Neurol. 2011 May; 69 (5): 892-900. [3]Thompson J, Bi M, Murchison AG *et al.* The importance of early immunotherapy in patients with faciobrachial dystonic seizures. Brain. 2018 01;141(2):348-56. [4]Kuranuputsb S, Symmonds M, Knight RK *et al.* LGI1-antibody encephalitis is characterised by frequent, multifocal clinical and subclinical seizures. Seizure. 2017 May 30; 50:1 4-17. [5]Navarro V, Kas A, Apartis E *et al.* Motor cortex and hippocampus are the two main cortical targets in LGI1-antibody encephalitis. Brain. 2016 Apr; 139 (Pt 4): 1079-93. [6]Flanagan EP, Kotsenas AL, Britton JW, McKeon A, Watson RE, Klein CJ *et al.* Basal ganglia T1 hyperintensity in LGI1-autoantibody faciobrachial dystonic seizures. Neurol Neuroimmunol Neuroinflamm. 2015 Oct 1;2 (6): e161. [7]71 24th (final) report of the home and leisure surveillance system. 2000, 2001 and 2002 data. London; Department of Trade and Industry; 2003. [8]Office for National Statistics. Overview of the UK population: November 2018. 2018 [accessed 2019 July 18]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/articles/overviewoftheukpopulation/november2018

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Mouse models of Japanese encephalitis virus infection: a systematic review and meta-analysis using a meta-regression approach

Study Objectives
To perform a systematic literature review, meta-analysis and meta-regression of published Japanese encephalitis virus (JEV) mouse experiments to investigate the variation in model parameters, assess homogeneity and test the relationship of key variables against mortality.

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Background

- **JEV remains a leading cause of brain infection across Asia, resulting in considerable death and disability (1).**
- **Some randomized clinical trials have been performed to evaluate JE treatments, but no effective therapies discovered (2).**
- **High lethality and no treatment means animal models are crucial.**
- **Mice remain the most used model to evaluate novel treatments, due to their low-cost and timely reproduction (3).**
- **However, great variability exists across laboratories for mouse model reporting as they have not been standardized (4).**

Aims

- **To understand which parameters account for variation in mouse model reporting, we conducted a systematic review of published JEV experiments in mouse models.**
- **We hypothesized that the following variables would influence lethality: Virus strain, virus dose, administration route, mouse strain, mouse age and mouse sex.**
- **We aimed to test the relationship of these variables on mortality from JEV infection is mice.**

Methodology

- **A PubMed search was performed using key terms related to 'Japanese encephalitis' and 'mice', with results from 1935 (first JEV isolation) to August 2020.**
- **Abstracts and full texts were screened by 2 authors independently for the following exclusion criteria: 1) JEV inoculation in mice, 2) virus dose reported, 3) JEV strain/ source reported, 4) Immunocompetent mice and strain reported, 5) Mortality reported as death or humane endpoint, 6) English publication and 7) primary research.**
- **From 1991 studies identified and reviewed ,127 studies were included, of which included data for 5026 individual mice in 487 experimental groups challenged with JEV.**
- **Quality assessment and data extraction were performed by 2 authors independently. Quality was assessed using CAMARADES guidelines with additional criteria added by the authors for a total of 17 quality criteria.**
- **Data were analyzed using R Version 4.0.2.**
- **Variables of interest were plotted against mortality at the individual level of experiments. Meta-regression was used to quantify the impact of experiment level covariates on heterogeneity of outcomes.**
- **A multivariable analysis was performed using all the variables in a single model to estimate mortality.**

Key findings

- **The global estimate of mice mortality after JEV challenge (base meta-regression model) was 64.7 (95% CI 60.9 to 68.3).**
- **Heterogeneity was substantial between experimental groups (I^2 70.1% , df 486).**
- **Mouse strain: Incorporating mouse strain as a moderator in the base meta-regression model reduced variability of base model (I^2 63.6%). (See figures 1 A and B).**
- **Mouse age (months): Incorporating mouse age as a moderator in the base meta-regression model reduced variability of base model (I^2 65.2%). (See figures 1 C and D).**
- **Mouse sex: Incorporating mouse sex as a moderator in the base meta-regression model minimally reduced variability of base model (I^2 68.7%). (See Figure 1 E).**
- **Virus strain: Incorporating virus strain as a moderator in the base meta-regression model reduced variability of base model (I^2 56.5%). (See figures 2 A and B).**
- **Virus dose: Incorporating virus dose in PFU as a moderator in the base meta-regression model reduced variability of base model (I^2 65.9%). (See figures 3 A and B).**
- **Route of administration: Incorporating route of administration as a moderator in the base meta-regression model minimally reduced variability of base model (I^2 68.7%). (See figures 4, 5 A and B).**

Reduced dataset analysis

- **Subgroup analysis was performed using top 6 mice strains, top 13 virus strains and top 6 routes of administration. Reduced dataset include 49.7% of experimental groups and 50.1% of mice. Pooled estimate of mortality in mice after JEV challenge (base meta-regression model) for reduced dataset was 64.3 (95% CI, 58.9 to 69.4).**
- **Heterogeneity was substantial between experimental groups (I^2 70.0% , df 241).**
- **The final model reduced the heterogeneity substantially (I^2 37.8%, df 241).**
- **This confirms our starting hypothesis that mouse strain, mouse age, route of administration, virus dose and virus strain account for much of the variation in JE mouse model mortality.**

(1) Heffelfinger JD, Li X, Batmunkh N, Grabovac V, Diorditsa S, Liyanage JB, et al. Japanese Encephalitis Surveillance and Immunization–Asia and Western Pacific Regions,2016. MMWR Morb Mortal Wkly Rep. 2017;66(22):579-83, (2) Turtle L, Solomon T. Japanese encephalitis—the prospects for new treatments. Nature Reviews Neurology. 2018;14, (3) Buer J, Balling R. Mice, microbes and models of infection. Nature Reviews Genetics. 2003;4(3):195-205., (4) Ritskes-Hoitinga M, Leenaars M, Avey M, Rovers M, Scholten R. Systematic reviews of preclinical animal studies can make significant contributions to health care and more transparent translational medicine. Cochrane Database of Systematic Reviews. 2014.

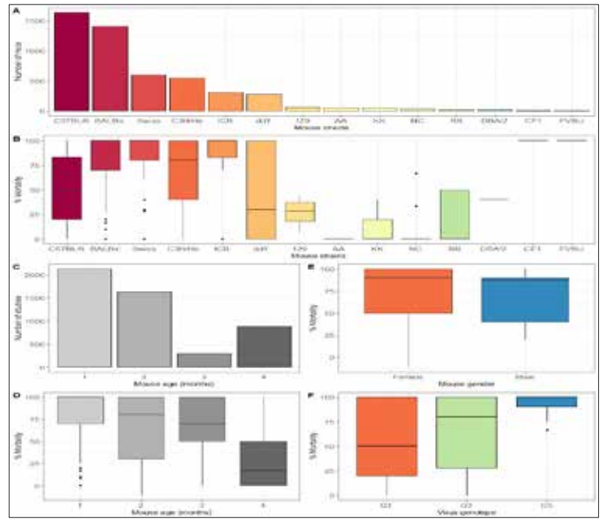

Figure 1: A) Number of mice vs mouse strain, B) Mortality vs mouse strain, C) Ages of mice used, D) Mortality vs mice age, E) Mortality vs mice sex, F) Mortality vs JEV genotype.

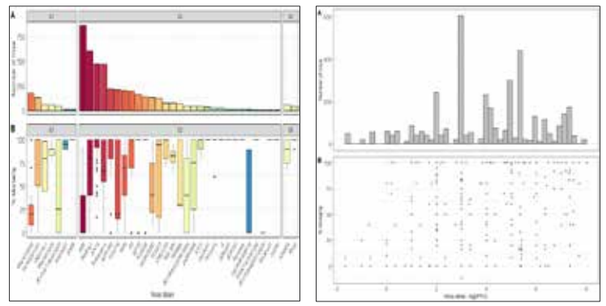

Figure 2 (Left): A) Number of mice vs different JEV strains, B) Mortality vs JEV strains. Figure 3 (Right): A) Number of mice vs Virus dose (PFU), B) Mortality vs JEV dose (PFU).

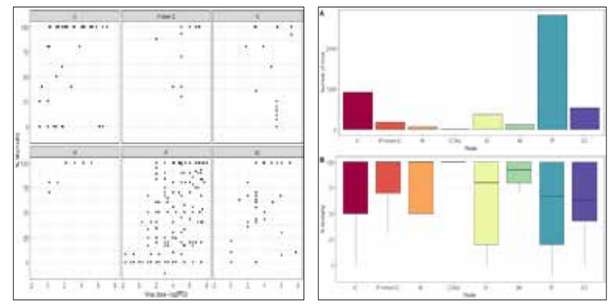

Figure 4 (Left): Mortality vs Virus dose (PFU) grouped in different routes of administration. Figure 5 (Right): A) Number of mice vs routes of administration, B) Mortality vs route of administration.

Final recommendations

- **Power calculations are crucial for accurate sample size estimations.**
- **Virus strains used in studies need to be sequenced and data included.**
- **Factors that effect variability in outcomes and need careful attention in study design include mouse strain and age and virus strain, dose and route.**

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A role for pathogen risk factors and autoimmunity in encephalitis lethargica?

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Background

The encephalitis lethargica (EL) epidemic swept the world between 1916-1926 and is estimated to have afflicted between 80,000 to one million people worldwide.

Presentation
- Prodrome of malaise, headache and fever
- Profound sleep disturbance 'pseudo sleep'
- Oculomotor palsies
- +/- almost any neuropsychiatric symptoms

Disease course
- Acute phase – mortality 30-40%
- Fully recovered ~30%
- Chronic EL – post-encephalitic parkinsonism ~30%

Possible Aetiology
- Environmental – unlikely
- Infectious – influenza 1918 H1N1, Herpes Simplex virus
- Autoimmune – anti-basal ganglia, anti-NMDAR

Methods and Results

We conducted a review of reported cases of EL-like syndromes published on PubMed between Jan 1, 2000, to Aug 1, 2020.

Our search revealed 30 reports describing 76 putative cases, 13 of whom were subsequently diagnosed with anti-NMDAR encephalitis.

Steroids and other immunotherapies were the most commonly used treatments, outcomes were mixed.

Influenza and other pathogens

- The epidemic approximately coincided with the 1918 influenza pandemic.
- No influenza RNA found in archival EL brain tissue.
- No pathogen has been definitively linked to EL.

An autoimmune encephalitis?

- Impossible to know whether contemporary cases of sporadic EL-like syndromes are the same as epidemic EL.
- Number of differences between epidemic EL and anti-NMDAR encephalitis
- Male predominance for EL (anti-NMDAR 8:1 female).
- Children with EL were more likely to present with psychiatric symptoms, opposite for anti-NMDAR.
- Known triggers for anti-NMDAR do not explain emergence and disappearance of EL epidemic.

Parallels with COVID-19

- A small proportion of patients infected with SARS-CoV-2 develop neurological and neuropsychiatric illness.
- A common infection can trigger an abnormal immune response.

Conclusions

- Important in the context of COVID-19 that we closely monitor neurological complications and long-term symptoms and take advantage of both history and novel evidence.
- Emergence and disappearance of EL during epidemic may well remain a mystery.

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The clinical diversity of anti-IgLON5 disease in the Dutch population

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Introduction

Anti-IgLON5 disease is a recently discovered, rare autoimmune disorder. A diagnosis is often made only after years, also complicated by the variety of symptoms. We describe clinical symptoms, clues for diagnosis, IgG subclass levels and effect of immunotherapy.

Methodology

In this observational cohort study (partly retrospective, partly prospective), all Dutch patients diagnosed with anti-IgLON5 disease were included. Most were seen and treated at Erasmus MC. Patient characteristics were collected, and serum and CSF samples were tested with immunohistochemistry and in house cell-based assay (CBA). Patients were prospectively followed over time, obtaining information about treatment.

Conclusions

- Anti-IgLON5 disease shows a widespread variability of symptoms
- Myopathy seems to be an important symptom in a considerable part of patients
- Some, albeit limited, improvement is seen in most of the patients, emphasizing the need for early recognition and treatment of this progressive disease.

Results

Baseline characteristics

Table 1. Demographics of patients diagnosed with anti-IgLON5 disease

Number of patients	14
Male	6 (43%)
Age at time of diagnosis (years, median)	62 (IQR 56-71, range 45-85)
Time symptom onset to diagnosis (months, median)	83 (IQR 29-182, range 7-280)
mRS at diagnosis	2.5 (IQR 2-4.5, range 1-6)
Time follow-up since symptom onset (months)	90 (IQR 53-185, range 13-282)
mRS at last follow-up	3 (IQR 2-6, range 1-6)

- All patients had a chronic presentation
- Three patients were known with systemic autoimmune disorders, consisting of rheumatoid arthritis, Bechterew and psoriasis.

Symptoms

Figure 1. Initial symptoms

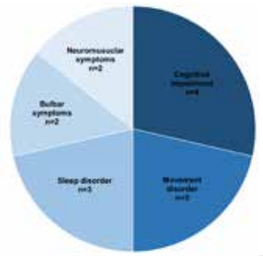


Figure 2. Predominant symptoms at presentation

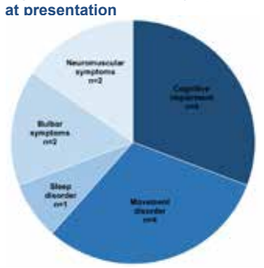
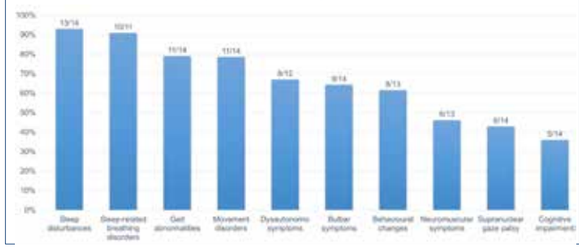


Figure 3. Most common symptoms during disease course



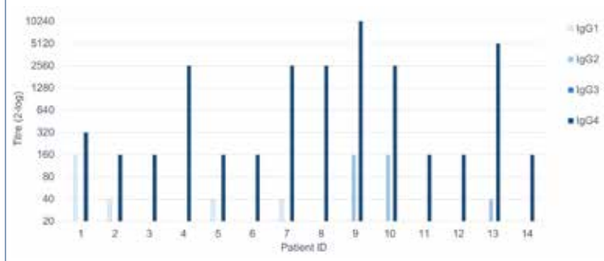
Ancillary testing

Table 2. Ancillary testing

Systemic tumor	14% (2/14)
CSF analysis	
Pleocytosis	8% (1/12)
Oligoclonal bands	50% (5/10)
Normal IgG index	100% (10/10)
CBA	
Serum	100% (14/14)
CSF	90% (9/10)
IHC	
Serum	100% (14/14)
CSF	73% (8/11)

- Breast cancer and bladder carcinoma were identified in 2 patients, respectively 6 and 4 years after symptom onset.
- In all patients with clinical neuromuscular signs, muscle biopsy showed myopathic changes.
- MRI-brain did not show specific encephalitis signs in all patients. Atrophy, in accordance with age, was seen, without a specific pattern.

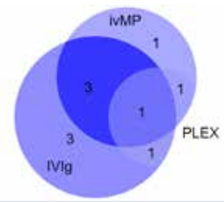
Figure 4. IgG subclasses pre-treatment



- IgLON5 antibodies were IgG4 in all (n=14), while 4 patients also harboured IgG1, and 3 also IgG2.
- No patients harboured IgG3.

Treatment and outcome

Figure 5. First-line immunotherapy (N=10)



- Four patients did not receive immunotherapy.
- Six patients received second-line therapy (all Rituximab).
- All patients who received second-line immunotherapy, also received first-line therapy.

Table 3. Effect of immunotherapy

After first-line therapy	N=10
Deterioration	N=1
Stabilization	N=0
Minimal or some improvement	N=9
Good effect	N=0
After second-line therapy	N=6
Deterioration	N=1
Stabilization	N=1
Minimal or some improvement	N=2
Good effect	N=0
Not accessible (yet)	N=2

- One patient with minimal improvement after first-line therapy (IVIg alone), had no muscle weakness anymore but gait abnormalities deteriorated.
- One patient with minimal improvement after second-line therapy (Rituximab), had less chorea, but respiratory and bulbar symptoms deteriorated.
- One patient died before response to Rituximab could be assessed.

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Non-interventional observational study
Autoimmune encephalitis in first episode of acute psychosis: pilot results

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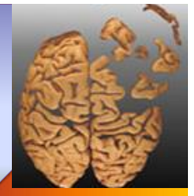


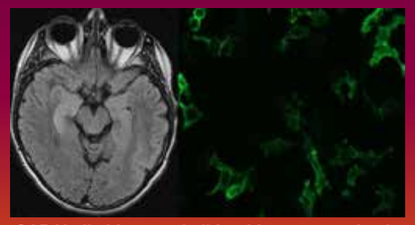
BACKGROUND AND AIMS

Autoimmune encephalitis (AE) comprises a group of non-infectious immune-mediated inflammatory disorders of the central nervous system.
The presence of antineuronal antibodies (Ab) can lead to psychiatric symptoms in the beginning of AE in 60% of patients (Herken et al., 2017).
3-7% of patients with first psychotic episode were suffered from AE (Al-Diwani et al., 2017). Due to severe course of AE without treatment and cases of post-mortem AE diagnosis in psychiatric ward, early AE diagnosis is very important.

The aim of the study was to describe clinical and laboratory findings in AE beginning with first episode of acute psychosis.

MATHERIALS AND METHODS

This study was approved by Moscow City Ethics Commission (Marth 2020).
Patients screening procedure was described in the study profile.
Inclusion criteria: age 18-60, with first acute psychosis with affective and psychotic symptomatics not more then 1 year ago, possibility to sign informed consent and PANSS score at this time <5.
Exclusion criteria: intoxication, brain trauma, RW, HIV, HCV, HBV, COVID19 + , somatic or infectious pathology, brain lesion at CT scan, pregnancy, other confirmed neurological pathology.
Clinical, MRI, psychotic and neurological status, PANSS score, MOCA score were assessed.
Special diagnostic tests were performed at LCC INVITRO Laboratory: oligoclonal bands, serum antineuronal antibodies (hu, ma2, ri, AMPH, yo-1, CV2), NMDA, CASPR2, LGi1, GABAb, AMPA1,2 (Euroimmune, Germany), thyroid serology, ANA, antibodies to dsDNA.
If AE diagnosis was confirmed we used immunosuppressive treatment according to current guidelines.



GABAb–limbic encephalitis with acute psychosis. MRI and CSF immunoreactivity in biochips with HEK-cells (Euroimmune, Germany)

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STUDY PROFILE

40 patients with acute psychosis admitted to Moscow City Psychiatric Hospital № 4

Included: 29 patients after signing of informed consent

Excluded: 11 patients due to symptomatic psychosis (intoxication or somatic pathology)

In all patients lumbar puncture was performed.

Clinical data: MRI, psychotic and neurological status, routine analysis, PANSS, MOCA score
«Basic» analysis:
- **Serum: antineuronal antibodies (hu, ma2, ri, AMPH, yo-1, CV2), NMDA, CASPR2, LGi1, GABAb, AMPA1,2, thyroid serelogy, ANA, antibodies to dsDNA.**
- **CSF: oligoclonal bands, protein level, cytotis**
- **Video of paroxismal events**

«Additional» analysis:
- **CSF: antineuronal antibodies, NMDA, CASPR2, LGi1, GABAb, AMPA1,2,**
- **MRI**

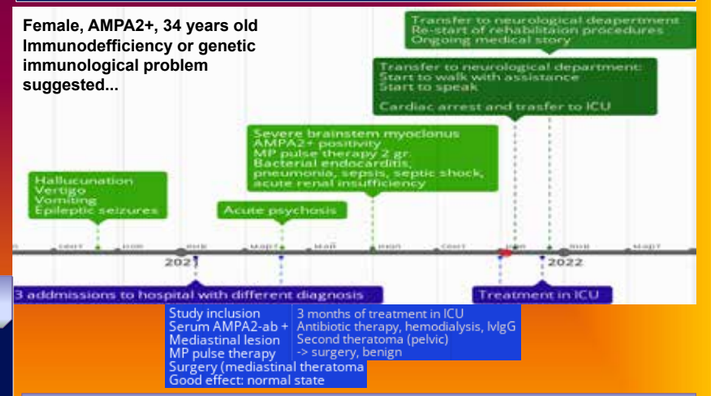
Discussion ? AE diagnosis ? Treatment ?

RESULTS:

In 24 % (n=7) of patients antineuronal Abs were detected: amphiphysin Ab (n=1), GABAb (n=2), AMPA2 (n=1), yo+GAD (n=1) and GAD (n=2).
We confirmed AE diagnosis in 3 female patients (10%):
- **AE with amphiphysin Ab (first symptoms were movement disorder with "stiff-person" phenotype and affective symptoms). She was successfully treated with MP pulse therapy, plasma exchange, cyclophosphamide. After one year she can return to work.**
- **AE with anti-AMPA2 Abs (first symptoms was hallucinatory delusional syndrome) with suggested immunodeficiency (see case below)**
- **AE with anti-GABAb Abs with acute polymorphic psychotic syndrome. She was successfully treated with MP pulse therapy, plasma exchange, rituximab.**

4 patients were diagnosed with possible AE.
All of these patients took upper-middle dosage of antipsychoic with a good response. Additionally we treated 2 of these patients (GAD+yo positive male patient with typical schizophrenic symptoms and female patient with low-GAD level and oligoclonal bands) with MP pulse therapy with partial effect.

Female, AMPA2+, 34 years old
Immunodefficiency or genetic immunological problem suggested...



CONCLUSION

This is a pilot result (we are planning to include up to 150 patients with acute psychosis) but we have already confirmed that is a time to change practice for diagnosis of acute psychosis in psychiatric ward.
This study was granted by LLC«INVITRO».

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Dr. Ganesh Chandra Sahoo is working in the area of molecular virology. He is currently looking after the molecular viral diagnosis and research activities of ICMR-RMRI, Patna. He has been involved in different nationwide epidemiological surveillance related to virology such as rotavirus surveillance throughout India. From time-to-time, outbreak of acute encephalitis syndrome (AES) has been seen in Bihar region. He is one of the active members of the AES team from RMRI, Patna, India.

He has guided doctoral students in screening different chemical compounds against various target receptors responsible for parasite survival. He has worked in drug discovery areas such as screening of chemical compound databases against Kala-azar and other viral diseases. As drug delivery is an important criterion for drug development and nanoparticle formulation of the compounds makes easy delivery of the compound at the target site (receptor), he has carried out different projects of Indian Council of Medical Research (ICMR) related to viral disease and drug discovery research.

Immuno-informatics Approach to predict Epitopes in Scrub typhus Fever (*Orientia tsutsugamushi*) (Acute Encephalitis Syndrome)

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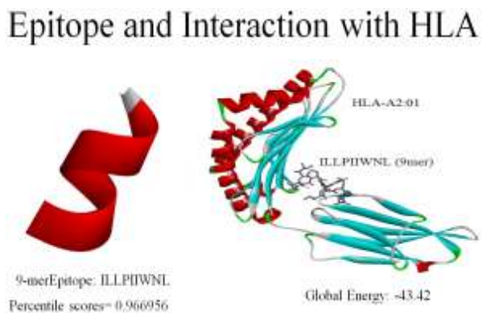
Presenter: Dr. Ganesh Chandra Sahoo, Scientist-E, DHR-ICMR, VRDLN, ICMR-RMRIMS, Agamkuan, Patna, India 800007. E-mail: ganeshiitkgp@gmail.com

Scrub typhus causes acute febrile illness, a zoonotic infection first described in Japan in 1899 caused by *Orientia tsutsugamushi*. It spreads to people through bites of infected chiggers (larval mites) from Trombiculidae family. It is moderately endemic in tropical part of Asian-Pacific region[1]. The current spreading of scrub typhus (*Orientia tsutsugamushi*) in Patna region during the year 2021 that a number of patients admitted to different medical colleges and hospitals such as AIIMS, Patna, PMCH, NMCH were detected to be positive for scrub typhus in Patna city, we have used both PCR and ELISA kits for detection. There is no vaccine available against scrub typhus; hence designing a novel peptide-based vaccine would be a better idea to combat the current spreading of scrub typhus in Bihar state. Full-length amino acid sequences of RodA protein of *O. tsutsugamushi* in NCBI database were retrieved, BLASTp (protein- protein) analysis was carried out. Linear B-cell epitopes were identified using IEDB analysis resource[2]. Predicted epitopes were analyzed for conserved regions across all available *O. tsutsugamushi* strain sequences. The 3D model of consensus RodA protein amino acid sequence prepared by using PEP-FOLD Peptide Structure Prediction Server and validation of modeled structure of RodA protein was carried out. Different 9-mer peptides of RodA protein were screened against different HLAs and further the peptides were scored, among which few peptides exhibited high binding affinity. The six nine mer-peptides are ILLPIIWNL, EVAKISVIL, QYSIVPLLL, ILLPIIWNL, IAIPITLVI and ELDPLGSGY.

Fig.1 Epitope prediction and scoring of RodA protein



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Dr Juan Carlos Garcia-Beristain graduated from the UNAM (National Autonomous University of Mexico) as a medical doctor. He became a medical specialist in pediatrics from the South-Central Specialty Hospital for Mexican Petroleum and is a subspecialist in pediatric neurology from the Children's Hospital of Mexico Federico Gómez (HIMFG). He is an AMSA fellow and has a master's degree in neuroimmunology from the Autonomous University of Barcelona. Currently, he coordinates the HIMFG´s Neuroimmunology Clinic, is part of the masters/ PhD program in Medical Sciences at the UNAM, is a member of the Mexican Academy of Neurology, and has authored books on neurodevelopment and refractory epilepsy.

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Autoimmune encephalitis following infection by SARS-CoV-2: a case report.

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Background:
Multiple neurological and neuroimmune manifestations have been described in association with infection by SARS-CoV-2.

Case: 11-year-old female with a 4-week history of:

- visual and auditory hallucinations
- irritability and psychomotor agitation
- somnolence
- impossibility to walk (tremor, weakness, increased muscle tone)
- insomnia and exacerbation of hallucinations
- generalized tonic-clonic seizures 4-5 times per day
- dysarthria, prosopagnosia, dysphasia, disorientation
- loss of working, procedural and semantic memory

Relevant history:

- **Infection by SARS-CoV-2 two months prior** to the beginning of current symptoms, which began 2 weeks after the remission of symptoms of COVID-19.

WORKUP

STUDY AND RESULTS

- Nasopharyngeal swab RT-PCR
  - **SARS-CoV-2 POSITIVE**
- Cerebrospinal Fluid
  - **SARS-CoV-2 POSITIVE** (4,200 copies/ml)
  - Anti-NMDAr and Anti-NR1 Antibodies: **NEGATIVE**
- Electroencephalogram and brain MRI
  - Normal
- Abdomino-pelvic CT
  - No ovarian tumor
- Nerve conduction and muscle enzymes
  - Normal

Treatment:
effective in the remission of the patient's symptoms

- steroids
- antipsychotics
- mycophenolate mofetil
- monoclonal antibodies (rituximab)
- antiepileptic drugs

Discussion:

We determined a case of autoimmune encephalitis with a history of COVID-19 and the presence of SARS-CoV-2 in cerebrospinal fluid at the time of diagnosis.

Conclusions:

Due to the epidemiological shift derived from the COVID-19 pandemic, we believe this diagnosis should be considered in patients presenting with encephalopathic symptoms weather or not they have a history of presenting classic symptoms of infection by SARS-CoV-2.

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Comparing Seasonality Trends of Infectious and Autoimmune Encephalitis

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Introduction

- Autoimmune diseases (ADs) affecting the central nervous system have been increasingly recognized in the pediatric population.
- Given existing patterns between seasonality and infectious disease, multiple etiologies have been hypothesized including molecular mimicry.
- This study retrospectively investigates whether seasonality relates to disease etiology within pediatric populations.
- As the peripheral immune system changes with the onset of puberty, this study also investigates whether adolescence correlates with immune system dysregulation to seasonal variations (Brenthouse et al. 2016).

Methods

- Medical records were extracted for pediatric patients (Age < 19) admitted to one of three metropolitan New York care centers (Weill Cornell Medicine, Columbia University Irving Medical Center, or Mount Sinai Health System) between 1/1/2010-12/31/2017.
- Records assigned ICD-9 or ICD-10 codes (neuroinflammatory condition) were evaluated against definitive diagnostic inclusion criteria for infectious and autoimmune diseases of the central neuroaxis.
- Children were categorized as having definitive diagnosis when a specific pathogen was detected, and the clinical presentation was consistent with consensus diagnostic criteria.
- Cases were grouped ages <11 and ≥ 11, then divided by seasonality. Diagnostic and demographic variables were extracted from the electronic medical records and analyzed using chi-squared tests.

Results

- A total of 201 pediatrics patients with encephalitis were identified with 129 (64.2%) patients < 11 years, and 72 (35.8%) patients ≥ 11 years.
- Within the <11 years cohort, 12 (9.7%) cases were found to be immune mediated (IMM), 41 (33.1%) cases infectious (INF). ≥ 11-year-olds showed 9 (12.5%) IMM cases and 24 (34.7%) INF cases.
- For patients <11 years, the highest number of cases were in the Summer (INF) and Fall (IMM), while for patients ≥ 11 years, highest cases were in the Summer/Fall (INF) and Winter (IMM).
- Chi-square test of independence demonstrated a significant relationship between seasonality and encephalitis etiology (χ^2 = 17.4, p<0.01) within the <11 years cohort, but no significant association for ≥11 years cohort (χ^2= 5.3, p = 0.15).

Data

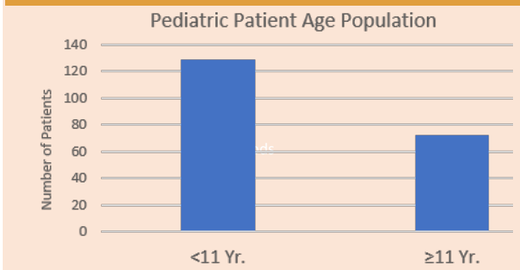

Figure 1: Number of patients over and under 11 Years

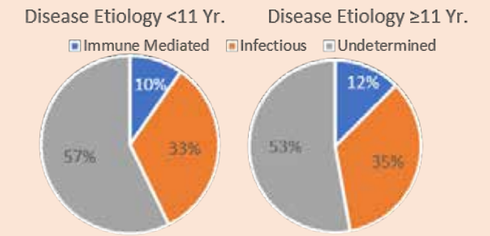

Figure 2: Distribution of Immune Mediated, Infectious, and Undetermined Disease etiologies.

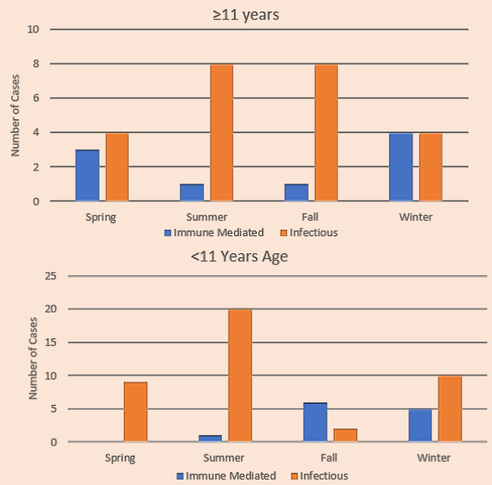

Figure 3+4: Number of cases with either infectious or immune mediated etiologies per change in seasons.

Conclusion

- A significant relationship between seasonality and disease etiology was found for patients under the age of 11, but not for those ≥11 years.
- This finding provides partial support for previously reported literature (Adang et al. 2014)- the existence of seasonal bias for certain disease etiologies.
- Improving knowledge of disease patterns will provide insight to potential triggers to serious autoimmune diseases.
- While evidence suggests seasonality as a mediating variable for disease etiology, the underlying cause of this phenomenon requires further investigation.

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Utilization of Routine Biomarkers for Prediction of an Infectious or Autoimmune Etiology in Encephalitis

Hai Ethan Hoang[1], Jessica Robinson-Papp[2], Lan Mu[2], Kiran Thakur[3], Carla Kim[3], Vivian Ssonko[3], Rachelle Dugue[3], Eileen Harrigan[3], Brittany Glassberg[2], Allison Navis[2], Jacqueline Sarah Gofshteyn[1], Mu Ji Hwang[1], Nathalie Jette[2], Anusha K. Yeshokumar[2]

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Background and Introduction

Encephalitis may be caused by infectious pathogens or autoantibodies.

Treatments and management strategies differ significantly based on etiology.

Delays in treatment initiation, while the underlying etiology is discerned, can negatively impact long-term outcomes.

Objective

To identify early clinical and laboratory data that may aid in predicting an eventual diagnosis of infectious (IE) or autoimmune encephalitis (AE).

Methods

Medical records for individuals with pathogen identified or autoantibody associated encephalitis were reviewed for patients admitted to 3 tertiary hospitals in New York, New York from 2010-2017.

When available, the below data were collected for patients:

- Demographics (including fever at presentation)
- Serum, cerebrospinal fluid (CSF), magnetic resonance imaging (MRI), and electroencephalogram (EEG) results

Statistical Analysis

- Descriptive analyses with median, range, and frequency
- Multivariate regression and exploratory analysis with imputed variables
- A p-value <0.05 was deemed significant

Results

Table 1: Differences in Diagnostic Evaluation Between Infectious Encephalitis (IE), including the viral subset, and Autoimmune Encephalitis (AE)

	IE n=246	Viral n=151	AE n=87	p-value (IE vs. AE)	p-value (Viral vs. AE)
Fever	163 (66.3%)	94 (62.3%)	21 (24.8%)	<0.001	<0.001
CSF Studies					
WBC (cells/µL)	100.0 (0-16150)	78.0 (0-2184)	8.0 (0-300)	<0.001	<0.001
Protein (mg/dL)	97.0 (13-5001)	76.5 (13-1123)	40.9 (14-171)	<0.001	<0.001
Glucose (mg/dL)	55.0 (0-221)	58.0 (14-221)	69.0 (24-160)	<0.001	0.001
CSF-specific OCBs	25.0%	5.9%	43.6%	0.091	0.142
Serum Studies					
WBC (cells/µL)	9.0 (1.2-38)	7.8 (1.2-34.3)	9.7 (2.7-21.3)	0.98	0.02
ESR (mm/HR)	27.0 (1-131)	19.5 (1-131)	13.0 (0-120)	<0.001	0.035
CRP (mg/L)	11.3 (0.1-362)	6.4 (0.2-236.4)	1.3 (0.1-145)	<0.001	0.005
Lactate (mmol/L)	1.5 (0.6-15.7)	1.4 (0.6-15.7)	1.2 (0.6-335)	0.049	0.285
ANA > 1:80	8.6%	11.5%	32.7%	<0.001	<0.001
Magnetic Resonance Imaging					
Contrast-enhancing	42.0%	24.7%	22.1%	0.003	0.709
FLAIR abnorm.	53.6%	54.5%	59.2%	0.426	0.56
Electroencephalogram					
Electrog. Sz	27.2%	33.3%	32.8%	0.464	0.949
EEG Abnorm.	90.1%	91.8%	91.4%	0.796	0.932

Table 2: Odds of Confirming an AE Diagnosis (As Compared to an IE Diagnosis)

	OR	95% CI	p-value
Fever	0.30	0.13-0.69	<0.050
Elevated CSF WBC	0.86	0.79-0.93	<0.001
Age 12-29 years (compared to > 65 years)	4.72	1.49-14.93	<0.050

Table 3: Predictive Value of 1) Fever, 2) CSF WBC ≥50 cells/µL, and 3) CSF protein of ≥75mg/dL in Evaluating a Diagnosis of AE

Take Away Message: the presence of two or three of these criteria suggest that an autoimmune etiology is unlikely

Evaluating a Diagnosis of AE When Two Criteria Are Present	
Sensitivity	83%
Specificity	84%
Negative Predictive Value	94%
Positive Predictive Value	63%

Evaluating a Diagnosis of AE When All Three Criteria Are Present	
Sensitivity	92%
Specificity	75%
Negative Predictive Value	95%
Positive Predictive Value	64%

Discussion

The following routine biomarkers are seen more in patients diagnosed with IE than AE:

- Fever at presentation
- Higher CSF WBC
- Higher CSF protein
- Higher inflammatory markers including ESR, CRP, and lactate
- Contrast-enhancement on brain MRI

Patients with fever at presentation and higher CSF WBC and CSF protein had a strong likelihood of being diagnosed with IE.

Prospective studies may determine whether this model leads to improvements in time-to-treatment, hospitalization costs, and morbidity and mortality.

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Professor Sarosh Irani is a clinician scientist who leads the Oxford Autoimmune Neurology Group to better manage and study autoantibody mediated diseases of the nervous system. Professor Irani undertook clinical training in Oxford and London, a DPhil in Oxford and a Fulbright postdoctoral position in UCSF. He was awarded the Graham-Bull Prize in Clinical Science / Goulstonian Lectureship, from the Royal College of Physicians, and awards including the NIHR BRC Senior Clinical Fellowship and both Wellcome Intermediate and MRC Senior Clinical Fellowships. He runs the UK's major clinic for antibody mediated CNS diseases and continues to explore the immunobiology and neuroscience which underlie the autoimmune neurological diseases. He has made several clinical discoveries including the recognition of faciobrachial dystonic seizures and the distinctive psychopathological features associated with NMDAR-antibody encephalitis. In the laboratory, he has led the discovery of LGI1- and CASPR2-antibodies, their associated HLA associations and the roles of B cells in the pathogenesis of autoimmune forms of encephalitis and neuromyelitis optica.

Rozanolixizumab in Leucine-Rich Glioma-Inactivated 1 Autoimmune Encephalitis: The LEGIONE Study Design

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Objective

- AIE001 (LEGIONE) is a Phase 2 (NCT04875975) study designed to assess the efficacy, safety and pharmacokinetics of the neonatal Fc receptor (FcRn) inhibitor, rozanolixizumab, in adult study participants with leucine-rich glioma-inactivated 1 autoimmune encephalitis (LGI1 AIE)[1]

Introduction

- LGI1 AIE is a clinically homogeneous syndrome believed to be directly mediated by pathogenic autoantibodies against LGI1, predominantly of the immunoglobulin G4 (IgG4) subclass[2]
- LGI1 AIE patients are mostly male (66%), aged 60+ and present with neurological and psychiatric symptoms[3–5]
- No approved treatment options are available; however, one small-scale randomised controlled trial shows a benefit of intravenous immunoglobulin over placebo[2,6]
- Rozanolixizumab is a fully humanised, IgG4 monoclonal antibody that specifically inhibits the activity of FcRn by targeting its IgG-binding region, reducing the concentration of circulating IgG antibodies (Figure 1)[7]
- Rozanolixizumab treatment has been shown to reduce levels of IgG[7,8], and would be anticipated to reduce the level of pathogenic LGI1 IgG4 autoantibodies in patients with LGI1 AIE
- The removal of IgG antibodies by FcRn inhibition therefore provides the rationale for testing rozanolixizumab as a potential treatment option for patients with LGI1 AIE

Methods

Study design

- LEGIONE is a multicentre, randomised, double-blind, placebo-controlled Phase 2 study to evaluate the efficacy, safety, and pharmacokinetics of rozanolixizumab as a treatment for people with LGI1 AIE (Figure 2)

Study population

- The study will include approximately 68 adult patients with serum LGI1 autoantibodies; key inclusion and exclusion criteria are shown in Figure 2

Study treatments

- Eligible study participants will be randomised 1:1 to receive steroids and either rozanolixizumab or placebo, administered by a subcutaneous (SC) infusion over 24 weeks

Endpoints

- The primary endpoint is seizure freedom, defined as an absence of seizures for a minimum of 28 consecutive days, maintained until the end of the treatment period (Week 25)
- Secondary efficacy, safety and patient-reported outcomes endpoints are summarised in Figure 2
- Exploratory pharmacokinetic and pharmacodynamic endpoints will also be studied, including measurement of total serum IgG concentration and serum LGI1 autoantibody concentration

Analysis

- All planned primary and secondary efficacy analyses will be conducted on the Randomised Set RS/ITT, defined as all enrolled study participants who were randomised to study treatment and analysed according to randomised treatment. The Safety Set is defined as the Randomised Set; however, participants will need to have received one dose of study medication and be considered according to actual treatment received
- The difference in the proportions of the participants achieving the primary endpoint between treatment arms, measured by the common (rozanolixizumab/placebo) odds ratio, will be assessed with the Cochran–Mantel–Haenszel test conditional on the stratification factors

Conclusions

- The LEGIONE study will provide first insights into the efficacy, safety and pharmacokinetics of rozanolixizumab in the treatment of LGI1 AIE
- LEGIONE is the first Phase 2 study to evaluate efficacy of FcRn inhibition as a treatment for patients with LGI1 AIE
- The study is funded by UCB Pharma and is enrolling patients

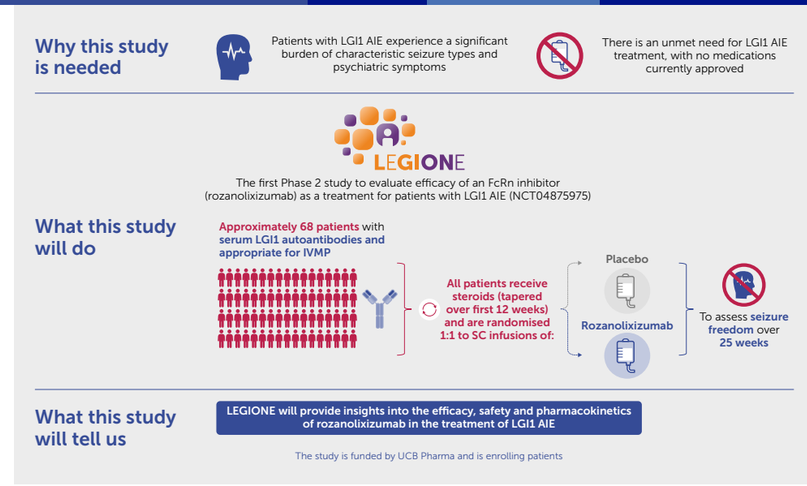


Figure 1 Inhibition of FcRn and IgG recycling by rozanolixizumab[8,9]

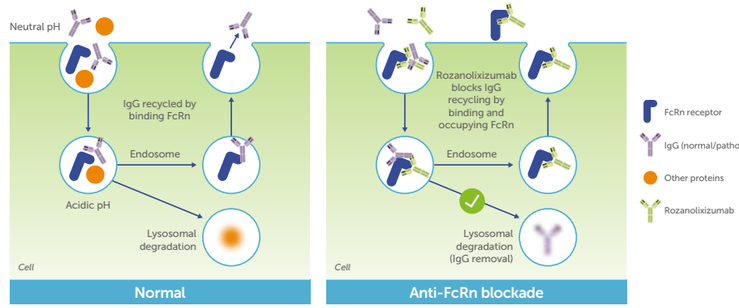


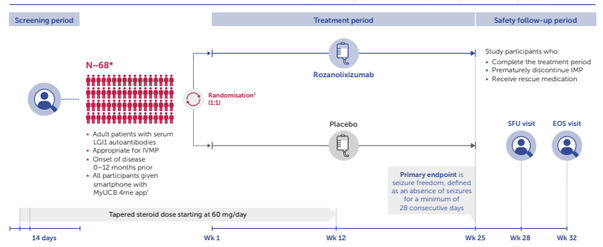
Figure 2 LEGIONE (NCT04875975) study design overview

Key inclusion criteria

- Adults aged ≥18 to ≤89 years
- Seropositive for LGI1 autoantibodies
- FBDS and/or other partial (focal) seizures with or without secondary generalisation (≥2 seizures/week) during the screening period, or have experienced such seizures that stopped as a result of IVMP initiation
- Currently considered for treatment with IVMP, or has initiated IVMP treatment (500–1000 mg/day) ≤14 days prior to randomisation
- Onset of disease 0–12 months prior to screening
- Weighs at least 35 kg at screening

Key exclusion criteria

- Prior diagnosis of epilepsy unrelated to LGI1 AIE
- Other medical conditions, including: Active or history of neoplastic disease; current or history of primary immune deficiency; active GI disorders; positive TB at screening; clinically relevant active infection or serious infection ≤6 weeks prior to first IMP dose
- Prior splenectomy
- Live vaccination ≤8 weeks prior to baseline
- Screening neutrophil count <1500 cells/mm³; IgG level ≤5.5 g/L
- Known hypersensitivity to any components of the study medication
- Prior treatment with prohibited immunosuppressants, biologics, and other therapies within the timeframe specified in the protocol



Primary endpoint

- Seizure freedom, defined as an absence of seizures for ≥28 consecutive days, maintained until the end of the treatment period (Week 25)

Secondary endpoints

- Change from baseline in cognitive function (RBANS)
- Proportion of participants requiring rescue medication
- Time to first occurrence of seizure freedom
- Incidence of TEAEs (until Week 32)

Patient-reported outcomes

- PGIS
- PGIC
- SF-36
- EuroQol-5D-5L

Other efficacy assessments

- Clinical Assessment Scale in AIE
- Modified Rankin Scale
- MRI evaluation of whole brain and hippocampal volume

*Patients will be stratified at randomisation by time from disease onset (≤6 months or >6 months from disease onset) and cognitive function (presence or absence of impaired cognitive function based on the RBANS score of ≤85 or >85). †MyUCB 4me app will be used to enter information about seizures experienced between scheduled visits to the site. The data recorded in the MyUCB 4me app will be available to the site investigator, who will use the information recorded to discuss with the patient and/or caregiver, and if necessary, to report seizure-related information in the eCRF. ‡An allowance of 10% has been made for drop-outs.

Abbreviations: AIE, autoimmune encephalitis; eCRF, electronic case report form; EOS, end of study; FBDS, faciobrachial dystonic seizures; FcRn, neonatal Fc receptor; GI, gastrointestinal; IgG, immunoglobulin G; IMP, investigational medicinal product; IVMP, intravenous methylprednisolone; LGI1, leucine-rich glioma-inactivated 1; MRI, magnetic resonance imaging; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Disease Severity; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; SC, subcutaneous; SF-36, 36-Item Short Form Survey; SFU, safety follow-up; TB, tuberculosis; TEAE, treatment-emergent adverse event.

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Author contributions: Sarosh R Irani: Contributor to study design, including ethics preparation and approval; chief investigator in the UK; contributed to review and editing of publication. Maarten J Titulaer: Contributor to study design and publication development. Anjana Dhar Koul: Contributor to study design and publication development. Robert Kozarski: Contributor to study design and publication development. Stephen Yates: Contributor to study design and publication development. Divyanshu Dubey: Contributor to study design and publication development. **Author disclosures:** Sarosh R Irani: Co-applicant and receives royalties on patent application WO/2010/046716 entitled 'Neurological Autoimmune Disorders' (the patent has been licensed for the development of assays for LGI1 and other VGKC-complex antibodies), and has filed two other patents regarding autoantibody diagnostic algorithms. Maarten J Titulaer: No disclosures. Anjana Dhar Koul: Employee and stockholder of UCB Pharma. Robert Kozarski: Employee of Cytel and contracted to UCB Pharma. Stephen Yates: Employee and stockholder of UCB Pharma. Divyanshu Dubey: No disclosures. **Acknowledgements:** This study is sponsored by UCB Pharma. Medical writing support was provided by Karen Mansfield and Imogen Millbank of Ogilvy Health, Oxford, UK, and funded by UCB Pharma, in accordance with Good Publication Practice (GPP) 3 guidelines (http://www.ismpp.org/gpp3). All costs associated with development of this poster were funded by UCB Pharma.

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Jakob Kreye studied Medicine at Charité-Universitätsmedizin in Berlin, Germany (2008 - 2016). Since 2013 he started to research on autoimmune encephalitides in Prof. Harald Prüss Lab at the German Center for Neurodegenerative Diseases (DZNE) Berlin.

As part of his MD thesis, he isolated and characterized first human monoclonal antidodies against NMDA receptor from patients with NMDAR encephalitis (Kreye et. al. Brain 2016, PMID: 27543972). He continued as a Postdoc in Harald Prüss Lab with further investigations of monoclonal antibodies in infectious diseases and autoimmune disorders with strong on antibody mediated neuronal dysfunction. During the COVID-19 pandemic he used his expertise in monoclonal antibodies to research the humoral reponse against SARS-CoV-2 in COVID-19 patients (e.g. Kreye et. al. Cell 2020, PMID: 33058755).

Encephalitis patient derived monoclonal GABA-A receptor antibodies cause epileptic seizures

Kreye J[1,2], Wright SK[3], van Casteren A[1], Stöffler L[1,2], Kaindl AM[2], Woodhall G[3], Garner CC[1] and Prüss H[1,2]

Introduction

Autoantibodies targeting the GABA-A receptor (GABA-A-R) hallmark an autoimmune encephalitis presenting with seizures, psychomotor disorders and MRI abnormalities (1,2,3). Previous studies have shown that patients' samples containing polyclonal GABA-A-R antibodies caused downregulation of surface GABA-A-R and electrophysiological changes in cultured neurons. However, patients with GABA-A-R encephalitis commonly harbor further established pathogenic autoantibodies such as those targeting LGI1, CASPR2, NMDAR (1,2,3). Hence it is unclear whether the observed effects exclusively relate to GABA-A-R antibodies. We aimed to characterize the intrathecal human monoclonal antibody (mAb) repertoire in acute GABA-A-R encephalitis.

Methods

In an unbiased approach we use established protocols (4) to isolate single cerebrospinal fluid cells of a pediatric GABA-A-R encephalitis patient (5) via fluoresence-activated cell sorting (FACS). From each single cell cDNA the variable region of the heavy and light chain immunglobulin (Ig) genes were amplified, sequenced and cloned into an expression vector containing the constant region of the respective genes. Human embryonic kidney cells (HEK) were transiently co-transfected with the pair of heavy and light chain vectors. The recombinant mAb containing supernatant was harvested and screened for GABA-A-R reactivity (Fig. 1).

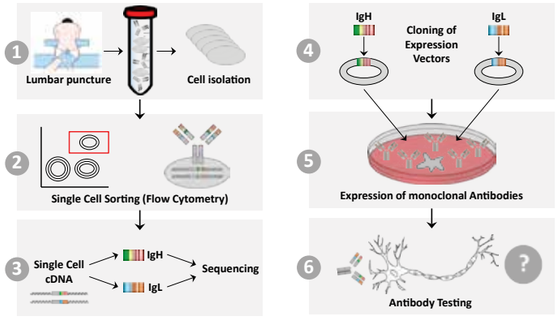

Fig. 1: Generation of human monoclonal antibodies from cerebrospinal fluid derived single cells.

From GABA-A-R mAbs we examined the binding properties on murine tissue sections and cell-based assays expressing individual GABA-A-R subunits or combinations thereof. Functional effects were investigated in vitro in cultured neuron systems using electrophysiological recordings and receptor level quantifications by Western blotting and reader-based immunocytochemistry. Finally, selected GABA-A-R mAbs were applied into rodent as IgG and Fab fragments continuous cerebroventricular infusion via osmotic pumps to study their pathogenicity in vivo including wireless EEG recordings to measure electric activity. For functional assays selected monoclonal antibodies were purified from HEK cell supernatant using Protein G sepharose beads and dialysed in PBS.

Results

We recombinantly isolated 67 mAbs from cerebrospinal fluid cells of a pediatric GABA-A-R encephalitis patient to identify five GABA-A-R mAbs with characteristic staining to murine brain tissue (Fig. 2A-B) and on live neurons (Fig. 2C). mAb binding showed the clustered distribution of GABA-A-R along neuronal dendrites (Fig. 2D) in co-localization with vesicular GABA Transporter (vGAT, Fig. 2E).

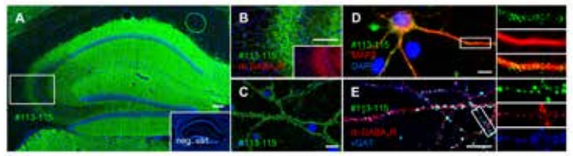

Fig. 2: (A-B) Immunofluorescence stainings of human GABAAR mAb #113-115 (green) on unfixed murine brain tissue; with binding to hippocampal neuropil. (B) Higher magnification of the hippocampal CA3 area showing the co-localization with a commercial anti-GABAAR antibody (red, nuclei in blue). (C) Live-cell staining of GABAAR mAb #113-115 on cultured cortical rat neurons. (D-E) Immunofluorescence staining on fixed cultured cortical rat neurons, with GABAAR mAb #113-115 (green) in (D) clustered binding pattern along MAP2+ (red) dendrites and in (E) co-localization with commercial antibodies against GABAAR (red) and the pre-synaptic marker vesicular GABA transporter (vGAT, blue). Scale bars indicate 100 µm in (A-B) and 20 µm in (C-E).

Five GABAAR mAbs bound to various epitopes involving the α1 and γ2 receptor subunits, with variable binding strength and partial competition (not shown). Strongest binding mAb #113-115 selectively reduced GABAergic currents in neuronal cultures (Fig. 3) without causing receptor internalization in vitro (not shown).

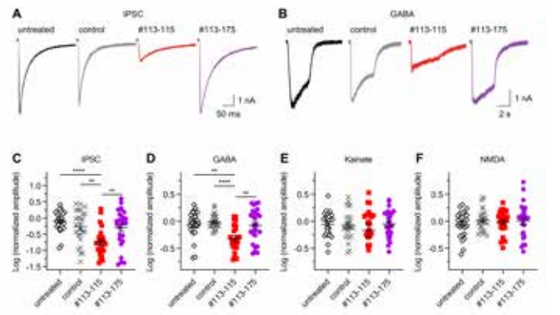

Fig. 3: mAb #113-115 selectively reduced GABAergic signalling in vitro, independent of receptor internalization. (A-B) Representative traces from (A) evoked or (B) GABA-dependent currents of murine autaptic neurons after pre-incubation with indicated human mAb. (C-F) Amplitudes of (C) evoked or chemically induced responses to (D) GABA, (E) kainate or (F) NMDA of murine autaptic neurons after mAb pre-incubation as indicated (values normalized to mean of untreated condition). Data was analyzed using Kruskal-Wallis, Dunn's posthoc tests (**, P ≤ 0.01; ****, P ≤ 0.0001; or not shown when P > 0.05). Each dot represents one neuron, n = 25 per condition. Bars indicate mean ± SEM.

Cerebroventricular infusion of #113-115 as IgG and Fab fragment into mice induced a severe phenotype with seizures and increased mortality (Fig. 4A), reminiscent of encephalitis patients' symptoms. Receptor expression levels remain unaltered (Fig. 4B-C). Application of GABA-A-R mAbs into rats at doses not causing mortality led to an increase of ictal events in wireless EEG recordings (Fig. 4D), that were detected even over the period of a 7-day continuous infusion (Fig. 5E) and even 14 days after termination of the infusion (not shown).

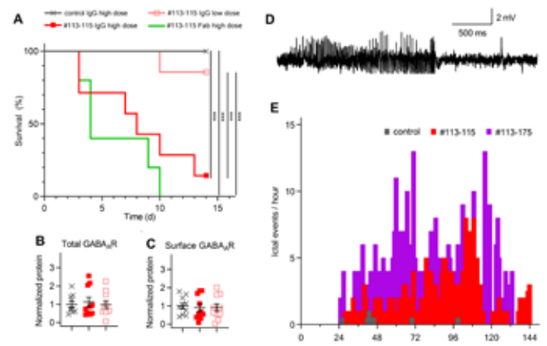

Fig. 4. (A) Kaplan-Meier plot for survival of C57BL/6 mice after cerebroventricular infusion over 14 days of indicated mAbs as IgG in high or low dose (1.5/0.3 µg IgG per hour) or as Fab in high dose. Survival was significantly different as analyzed using log-rank Mantel-Cox (P ≤ 0.0001), followed by ANOVA, posthoc Tukey's multiple comparisons (*** P ≤ 0.001; or not shown when P > 0.05; n = 5-7 animals per group). (B-C) Quantifications of the indicated surface proteins from murine brain homogenates after cerebroventricular mAb infusion as analyzed by Western blotting and normalized to mean of control IgG group. Each dot represents one hemisphere, n = 10 per condition. Bars indicate mean ± SEM. (D) (Representative EEG of an ictal event recorded from a CA3 depth electrode of a Wistar rat receiving GABAAR mAb infusion. (E) Comparison of hourly averages of coastline length between GABAAR mAb (#113-115 n = 3, #113-175 n = 3) and control (n = 6) infused animals, analyzed using Mann-Whitney (***, P ≤ 0.001; n = 900-905 average values per group). Horizonzal lines indicate mean and quartiles.

Conclusions

- Our results provide insight into the CSF antibody repertoire of acute GABA-A-R encephalitis and show that disease-specific mAb antibodies can be recombinantly generated from patients' cerebrospinal fluid to allow an in-depth in vitro and in vivo characterization of binding properties and functional effects.
- We established an animal model for GABA-A-R encephalitis that demonstrated direct pathogenicity of autoantibodies on GABA-A-Rs independent of Fc-mediated effector functions. Direct effects may include stabilization of the receptor in a desensitized state, allosteric modulation of the physiological GABA binding affinity and/or neurotransmission efficacy, and orthosteric GABA antagonism.
- These data provide the scientific rationale for clinical treatments using antibody depletion in GABA-A-R encephalitis patients.
- The identified GABA-A-R mAbs can serve as tools for the development of antibody-selective immunotherapies.

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Léonie Lesec

INSERM U1237, GIP Cyceron, Caen, France

Léonie Lesec is a PharmaD and PhD student in INSERM U1237 unit at the Caen University, France. She started in 2019 her thesis about the CD4 T cell response against N-Methyl-D-Aspartate receptor (NMDAR) in a mouse model of autoimmune encephalitis, under the direction of Olivier Toutirais and Brigitte Le Mauff.

The main goal of her work is to deepen characterization of immune response in anti-NMDAR autoimmune encephalitis and develop immunotherapy approaches. After her thesis, she wishes to continue in the research as pharmacist/researcher with a strong interest in the field of immunology.

CD4 T cell response against the N-Methyl-D-Aspartate receptor in a mouse model of autoimmune encephalitis

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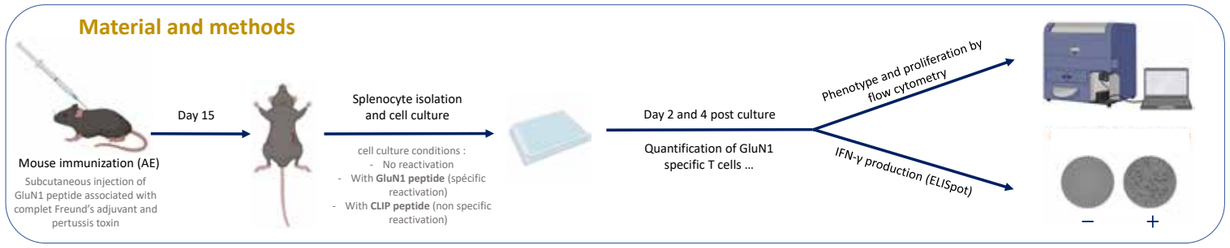
Introduction

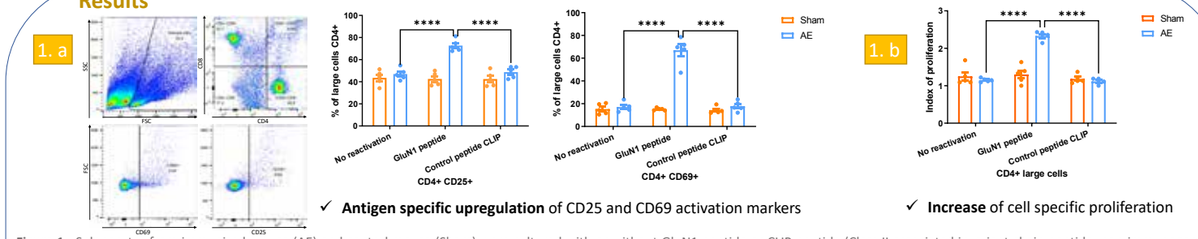
Anti N-Methyl-D-aspartate receptor (NMDAR) autoimmune encephalitis (AE) is a newly described neuropsychiatric disorder characterized by psychiatric disturbances, cognitive impairment and epileptic seizures[1]. It is a rare disease mediated by autoantibodies (aAbs) against the GluN1 subunit of NMDAR. The exact etiology of the pathology is unknown and immune mechanisms involved in this pathology are still misunderstood.
We have recently developed a mouse model of NMDAR-AE by immunization with a GluN1 peptide that drives a series of symptoms that recapitulate AE[2]. Importantly, anti-NMDAR Abs detected in the serum in our AE model are associated with B cell clusters in the meninges and choroid plexus, and with plasma cells in the cerebrospinal fluid. However, upstream immune processes that drive aAb production, especially the contribution of CD4 T helper cells, are still largely unknown.

⇨ **Our goal is to characterize the T CD4 cell response against the NMDAR in our mouse model of AE.**

Material and methods



Results



✓ **Antigen specific upregulation** of CD25 and CD69 activation markers

✓ **Increase** of cell specific proliferation

Figure 1 : Splenocytes from immunized mouse (AE) and control mouse (Sham) were cultured with or without GluN1 peptide or CLIP peptide (Class II-associated invariant chain peptide, non-immunogenic self peptide). After 2 days, cells were analyzed for CD25 and CD69 expression by flow cytometry (ANOVA, n=5, ****p<0,001) (a). Marked cells with CFSE (Carboxyfluorescein succinimidyl ester, cell proliferation tracer) were analyzed after 4 days for proliferation by flow cytometry (ANOVA, n=5, ****p<0,001) (b).

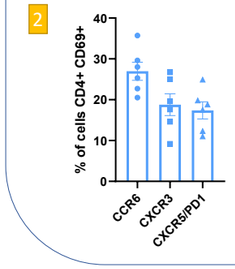
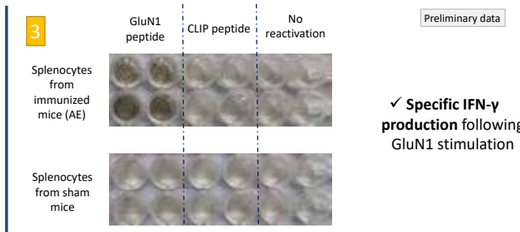


Figure 2 : Splenocytes from AE mouse were cultured with GluN1 peptide. After 2 days, T helper cells were identified among activated TCD4+ CD69+ cells by flow cytometry using subset specific chemokine receptor expression (n=6).

✓ Among the GluN1-specific CD4 T cells, we identified a subset of **T follicular** cells (help to B cell response), **Th1** cells (cellular response) and **Th17** cells (inflammatory response)

CCR6 : Th17 cells
CXCR3 : Th1 cells
CXCR5/PD1 : T follicular cells



✓ **Specific IFN-γ production** following GluN1 stimulation

Figure 3 : Splenocytes from AE mice and sham mice were stimulated with GluN1 or CLIP peptide. IFN-γ production is determined by ELISpot assay.

Discussion / Conclusion

In this study, we highlight **a systemic T cell response** in our mouse model of AE. Our data support the presence of GluN1 specific CD4 T cells, as suggested by the presence of IgG Abs with **T/B cell collaboration** for the production of anti-NMDAR Abs. These data provide a rationale for the development of novel **tolerogenic immunotherapies** (eg antigen-specific vaccines) in anti-NMDAR AE.
Currently, the specific T cell response is also analyzed in the central nervous system (meninges) using the same assays. In addition, we are also investigating the functional profile of T and B cells by determining their cytokine production in spleen, meninges and choroid plexus.

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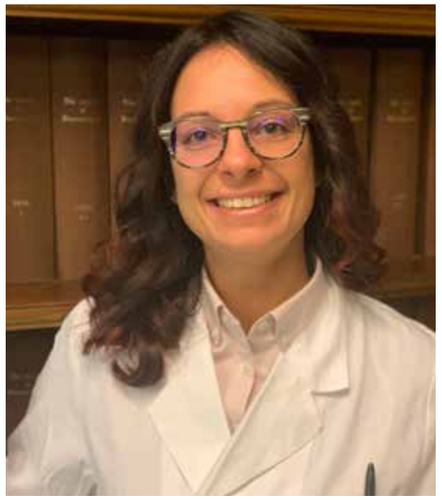
2. Wagnon Isabelle, Pauline Hélie, Isabelle Bardou, Caroline Regnauld, Léonie Lesec, Jerôme Leprince, Mikaël Naveau, et al. 2020. « Autoimmune Encephalitis Mediated by B-Cell Response against N-Methyl-d-Aspartate Receptor ». *Brain: A Journal of Neurology* 143 (10): 2957-72.



Dr. Sara Mariotto

Neurology Unit, Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Italy

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Sara Mariotto (MD, PhD) is a neurologist with expertise in the field of neuroimmunology/neuroinfection with a focus on autoimmune/paraneoplastic encephalitis and encephalomyelitis.

During her fellowship at the Department of Neurology, University of Innsbruck (March-October 2017) she studied CNS antibody-mediated disorders (supervisor Prof. Markus Reindl) learning autoantibody detection/IgG subclass analysis with cell-based assay and how to analyse the cytokines/chemokines profile of patients.

She also spent a period (October 2017) at the Institute of Neurology, Medical University of Vienna learning new techniques for the diagnosis of autoimmune encephalitis (supervisor Prof. Romana Höftberger). Since, she has diagnosed and managed adult and paediatric patients with suspected encephalitis referred to Neurology Unit, participated to multidisciplinary discussions of challenging cases, and analysed results of samples referred to Neuropathology Laboratory actively implementing the diagnostic process with new assays. Finally, she has become interested in biomarkers of disease activity (i.e. NfL) in autoimmune and infectious encephalitis and developed several collaborative studies on this topic.

Predictive value of serum neurofilament light chain levels in anti-NMDA receptor encephalitis

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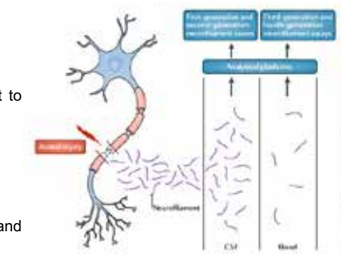
Introduction

Anti-NMDAR encephalitis

- Complex immune-mediated disorder
- Usually favourable long-term outcome
- Outcome and disease course are difficult to predict[1,2]

Neurofilament light chain (NfL)

- Released from axons after acute injury
- Useful biomarkers of disease activity and final prognosis in neurological disorders[3]



Aim of the study

To analyse NfL levels as markers of disease activity and prognosis in patients with anti-NMDAR encephalitis

Methods

Study subjects

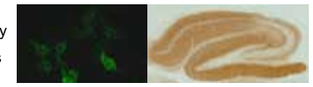
Dutch patients with anti-NMDAR encephalitis (n=71) with available pre-treatment sera, and follow-up sera (n=58 from 20 patients, and paired CSF (n=33). Comparison was made with 60 age-matched healthy controls.

NfL measurement

In duplicates using SIMOA Nf-light kit with SR-X immunoassay analyser (Quanterix, Simoa).

NMDAR antibody detection

Cell-based assay and confirmed by immunohistochemistry. All patients had NMDAR antibodies in CSF.



Results

Fig. 1. Serum NfL levels are higher in anti-NMDAR encephalitis patients and associated with age at onset (A), but not different based on disease severity (B).

Fig. 2. Serum and CSF NfL levels correlate well.

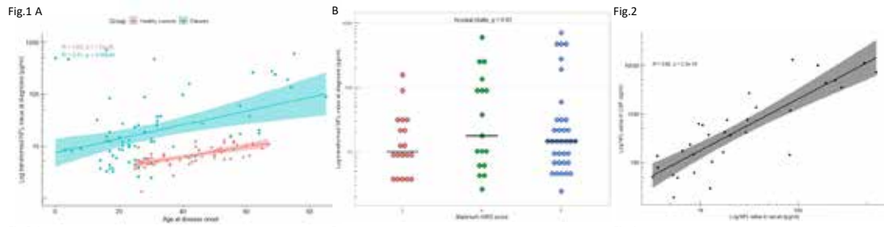


Fig. 3. Serum NfL levels are higher in anti-NMDAR patients with radiological signs of inflammation and tissue damage (A) or preceding HSV1 encephalitis (B).

Fig. 4. Serum NfL levels univariably seem associated with outcome at 12 months (measured by mRS).

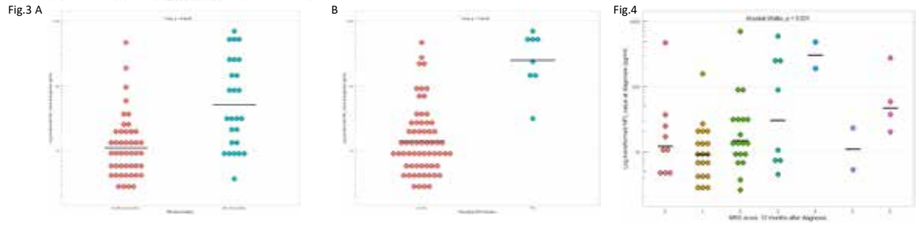
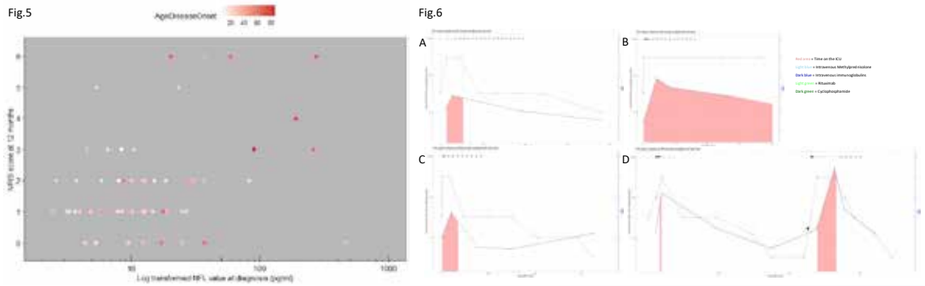


Fig. 5. Serum NfL levels are no longer an independent predicting factor for outcome (mRS at 12 months), once corrected for age.

Fig. 6. Serum NfL levels over time in individual patients, showing an increase during admission (A-C) and during relapse (D).



Discussion

- NfL levels are increased in anti-NMDAR encephalitis, suggesting that axonal damage is a feature of this condition.
- NfL values at time of diagnosis do not correlate with disease severity and final outcome, suggesting that they have no predictive value this early.
- NfL levels increase weeks after disease onset, suggesting that axonal damage is not the initial feature of the disease, but might be relevant to monitor recovery.
- NfL levels do not predict relapses but can help identifying them.
- NfL serum levels are influenced by age, previous anti-HSV1 encephalitis, and radiological signs of tissue damage.

Conclusions

Since axonal damage is a feature of active anti-NMDAR encephalitis, measuring serum NfL values is helpful in the clinical practice to identify an active disease and monitor recovery, although it is not useful for prognostic predictions.

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I am an infection specialist trainee working in East of England between Norwich and Cambridge, having completed my earlier training in Glasgow. I have completed the DTM&H at LSTM, and have experience of working as a doctor in Zambia and Malawi.

Limbic Encephalitis with Neurogenic Stunned Myocardium

Brian McCann, Khan Muhammad, Fernandez Cornelius, Arsalan Javaid, Shafia Khanum

United Lincolnshire Hospitals NHS Trust

Introduction

It is recognised neurological disease can cause cardiac abnormalities, such as in cases of stroke, or any other brain injury. Rarely, diseases such as limbic encephalitis can cause cardiac dysfunction, through a process involving autonomic stimulation, termed Neurogenic Stunned Myocardium (NSM).

Case Description

48 year old male presented with a vague few weeks history of odd behaviour, short term memory issues, and dry cough. Past medical history included type 1 diabetes mellitus, which patient was taking insulin for.

Examination showed GCS 14/15 due to confusion. Auscultation revealed crepitations at right mid and lower zones.

Investigations

Lab tests	Results	Range	Lab tests	Results	Range
CRP	90 mg/L	0-5	Troponin T	1273 ng/L	0-15
WCC	12.5 10^9/L	4.3-11.2	NT-pro BNP	1786 ng/L	0-300
Glucose	37.0 mmol/L	3.0-6.0	Lactate	2.1 mmol/L	0.5-1.0

- CXR showed bilateral pleural effusions, with superadded patchy right basal consolidation
- ECG showed non-specific lateral T-wave changes
- Trans-thoracic ECHO showed ejection fraction 26%
- CT head imaging did not reveal any abnormality. MRI did show features in keeping with limbic encephalitis (fig 1)

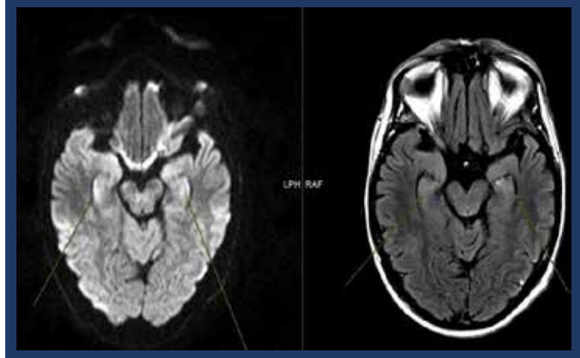

Figure 2: MRI brain showing hyper-intensities on T2-weighted FLAIR images (marked by arrows)

Management

Given antibiotics for community acquired pneumonia, and diuretics for decompensated cardiac failure.

Patient had borderline capacity, and was deemed able to refuse lumbar puncture. As LP could not be performed, diagnosis was challenging.

Following neurology review, patient commenced on IV methylprednisolone 1g/day. Repeat MRI at day 5 showed complete resolution of previous seen encephalitis.

Patient outcome

- Repeat MRI brain at day 5 showed complete resolution of previous seen encephalitis
- Cardiac MRI at four weeks showed normal ejection fraction
- Patient discharged home with reducing course of prednisolone. Following clinic review, he has ongoing issues with short term memory, but has returned to work.

Discussion

In cases of acute neurological disease, up to 40% have associated cardiac dysfunction[1]. Our case presents with Neurogenic Stunned Myocardium, a type of stress-cardiomyopathy. The limbic system contains baroreceptors involved in autonomic regulation. Brain insult can result in dysregulation of autonomic system, and result in increased catecholamine release[2].

Catecholamines bind to beta-adrenergic receptors on cardiac myocytes. The result is increased myofibril contractility, and tachycardia.

Blood tests typically showed raised troponin, and NT-pro BNP[2]. ECG typically shows widespread ST changes[2]. ECHO will show reduced left ventricular function. Crucially, coronary angiography will be normal, and cardiac dysfunction cannot be attributed to acute coronary syndrome of ischaemic origin.

Treatment is aimed at identifying and managing the underlying neurological disease.

Stress-cardiomyopathies are becoming more widely recognised. Takutsubo cardiomyopathy and NSM may be seen as a spectrum of the same disease, as the pathophysiological basis is thought to be similar[3].

In a patient presenting with unusual neurological symptoms and cardiac dysfunction, it is important to consider one unifying diagnosis.

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Dr. Mahtab Motamed got an MD from Tehran University of Medical Sciences (TUMS) in 2014 and then moved on starting her psychiatry residency there. She started her career as assistant professor in Roozbeh Hospital. Currently, she is the Director of Residency Training Program in the psychiatry department. At present she is also finishing up her Master degree in e-learning for medical education which she took at TUMS. Her field of interest is mental health of transitional age youth. This age group are at increased risk of mental disorders and first episodes of many psychiatric disorders including psychosis are at this age. Additionally, many disorders of childhood particularly neurodevelopmental disorders like autism and ADHD are left untreated when children age out into adulthood. Right now, she is codirector of the Adult Developmental Disorder Clinic in Roozbeh Hospital which tries to address the needs of this population.
As of 2018, they started a project on autoimmune psychosis in collaboration with Dr Saijo Jacob in Birmingham University. Dr Javad Alaghband-rad is the principal investigator of the project and Mahtab is running the day to day tasks of the project as the principal co-investigator. She won the Second Young Psychiatrists Davidian Awards in 2017 which is the annual national award of Iranian Psychiatry Association for early careers for her works with vulnerable children in collaboration with Médecins Sans Frontières/Doctors without Borders (MSF). She got Top Graduate Award of Alumni Office of TUMS and got the First rank of 65th national board of psychiatry in 2018.

Looking for Autoimmune Psychoses

A Preliminary Report from Iran

Javad Alaghband-rad, Arshia Seddigh, Aida Bavand Abbasabadi, Sajedeh Seyyed Alipour, Zahra Mirsepassi, Fatemeh Mohammadian, Vajiheh Aghamolaei, Mahtab Motamed*

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Introduction

There is increasing attention toward recognition of psychotic disorders with autoimmune etiologies especially among first episode psychosis (FEP).

Autoimmune Encephalitis may be underdiagnosed as the main presentations are psychiatric in nature unless patients develop a full range of neurological symptoms.

We, a referral psychiatric hospital in a developing country, aim to characterize the rate and clinical presentations of first episode autoimmune psychoses in our on going prospective study.

Methods

All patients referred to Roozbeh Hospital with FEP during last 3-months are recruited to the study.

The patients undergo comprehensive interview and physical and neurological examination along with a brain MRI and EEG study. A series of psychiatric assessment questionnaires are completed.

Serum and cerebrospinal fluid are assessed for a number of metabolic, inflammatory and autoimmune tests (Antibodies against intracellular antigens, synaptic receptors, ion channels and other cell-surface proteins).

Results

Participants

The project officially started in May 2020. However, the pilot phase had began in December 2019.
As predicted Covid-19 was a major blow to the process of patient's recruitment.

During these 13 months, **39** patients were recruited into the study. Twenty-one were males and eighteen were females. Mean age was 24 with twelve patients were being under 18 yrs.
We have enrolled four Afghan patients.
Most prevalent type of delusion was **persecutory delusion** with reference delusion coming afterwards and **auditory hallucinations** was the most prevalent type of hallucination.
Seven patients presented with **catatonic symptoms**.

Serum Study

Serum autoimmune antibodies were collected for twenty-three patients and six patients have undergone lumbar puncture.

THREE POSITIVE SERUMS
One for PNMA2 (Ma2/Ta)
One for Amiphysin and Yo/PCA-1
ONE for Anti CV2

A 28-year old female patient was admitted with irritability and persecutory and reference and being monitor delusion.
The first symptoms appeared two months earlier in the form of vegetative changes.
About 6 days after admission, the psychosis and the other symptoms subsided. Serum was positive for paraneoplastic factor **Ampiphysin, Yo/PCA-1**

A 46-year old female patient was referred to our hospital with irritability and persecutory and grandiosity delusion.
The first symptoms appeared two weeks earlier.
About 5 days after admission, the psychosis and the other symptoms subsided.
Serum was positive for paraneoplastic factor **Anti CV2**

A 35-year old female patient was referred with intense and impulsive aggression, commanding auditory hallucinations and suicidal thoughts. The onset of symptoms was about 3 months before and the symptoms worsened within two days before hospitalization. About 20 days after admission, the psychosis and the other symptoms subsided.
Serum was positive for paraneoplastic factor **PNMA2**

Discussion

In general, this group clinically resembles the common population of FEP in their presentations.
Certain sample features making our cases unique regardless of their autoimmune status , are

- *younger population*
- *high rate of prodromal symptoms*
- *catatonic features*
- *formal thought disorders*

Number of Afghan patients is proportionally higher than expected.
All the three patients with positive serums were women.

This patients represent a potentially promising group for whom early detection and interventions may reduce morbidity while experiencing their first episode of psychosis.

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João Moura is a first-year neurology resident at Centro Hospitalar Universitário do Porto, where he also completed the foundation program (2020). He concluded the Master's degree in Medicine at Instituto de Ciências Biomédicas Abel Salazar (ICBAS), University of Porto, in 2019, with the final grade of 17 values (scale: 0-20). He participated in more than 15 courses and 7 congresses in neurology, immunology, infectious diseases, and statistics.

Anti-GAD65 associated neurological syndromes in adults: a single center retrospective study

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Introduction

Antibodies against glutamic acid decarboxylase 65 (anti-GAD65) is correlated with with several auto-immune phenotypes, with variable response to immune suppressive therapy.[1,2]
Our aim was to describe clinical, analytical, imaging and therapeutical aspects of an anti-GAD65 cohort from a tertiary referral hospital.

Methods

We retrospectively studied patients with neurological disfunction and a positive anti-GAD65 result in either serum or CSF. Automated ELISA and radioimmunoassay (RIA) where used for quantitative analysis. The sample was characterized based on clinical phenotype, anti-GAD65 concentration, treatment regiments and disease course. SPSS Statistics version 27 was used for statistical analysis. A p value <0.05 was considered significant.

Results

14 anti-GAD65 positive cases

Mean age of onset: **57.9** ± 14.5 years; 57.1% **female.**
Other autoimmune disorders: 3 type 1 diabetes mellitus (21.4%) and 2 myasthenia gravis (14.2%).

Limbic encephalitis	Psychosis	Epilepsy	Cerebellar ataxia	Stiff person syndrome
35.7%	28.6%	28.6%	21.4%	7.1%

6 (42.8%) overlap syndromes
4 (28.6%) non-consensual presentations

Median follow up time: **28 (3-132) months; 3 patients died (21.4%).**

Anti-GAD65 antibodies

Serum	CSF
12 (85.7%)	10 (71.4%)

Mean concentration: 21140.19 U/L

No correlation between serum anti-GAD65 and:
- Clinical phenotype (p=0.6)
- mRankin Scale (mRS) values (p=0.5).

Imaging

Brain MRI revealed T2/FLAIR hyperintensities in 50% of cases, most commonly parietal (35.7%) and frontal (28.6%) in location.

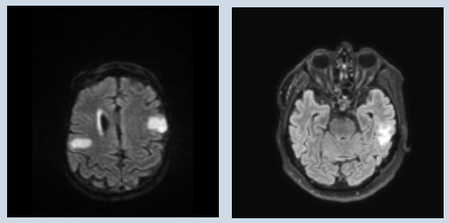

Figure 2 – Brain MRI of patients 9 (left) and 6 (right) from figure 1 showing FLAIR hyperintense tumefactive frontal and temporal lesions, respectively, attributable to autoimmune encephalitis related to anti-GAD65.

Disease course and treatment

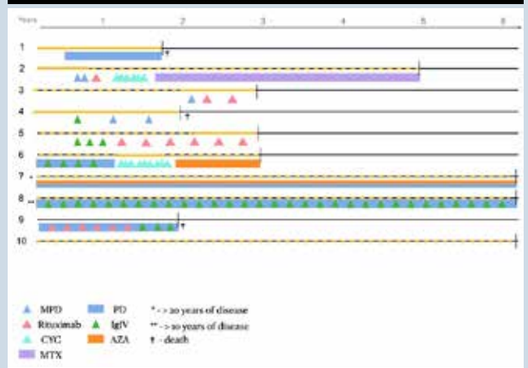

Figure 1 - Disease course and treatment for the patients with classical anti-GAD65 associated neurological syndromes (unscaled timepoints). Orange lines in full represent periods of symptomatic worsening and dotted lines refer to periods of clinical stability. MPD – methylprednisolone; PD – Prednisolone; IgIV – Intravenous immunoglobulin; CYC – cyclophosphamide; AZA – azathioprine; MTX – methotrexate

The 10 classical anti-GAD65 associated syndromes all underwent full body CT, with only the stiff-person patient showing a suspicious mediastinal nodule .

Conclusions

Anti-GAD65 mediated neurological disorders have a variable clinical presentation and disease course, in agreement with previous studies.[2]
The majority of patients require continuous treatment with immunosuppressors.
In this small cohort there was no correlation between serum anti-GAD65 levels and clinical phenotype or mRS.

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Increasing knowledge and promoting right attitudes and practices is one of her key interests both in research and practice. She has published articles in national and international journals and believes that for change to happen, one has to be part of the process and contribute their bit.

PSYCHOSOCIAL RESEARCH IN THE FIELD OF BRAIN INFECTIONS IN THE LAST DECADE: A SCOPING REVIEW

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Introduction

Encephalitis is an uncommon but serious condition characterized by the inflammation of the brain requiring immediate care. WHO recognizes neurological disorders as "one of the greatest threats to public health".

(World Health Organization, 2008)

Objective

Research Question:
'What are the Psychosocial factors explored in Brain Infections in the Last Decade?'

AIM:

1. To understand the psychological factors in Brain Infections in acute and chronic phases.
2. To understand the social determinants that influence Brain infections
3. To understand the factors influencing recovery in Brain Infections in the Last Decade.

Methodology

Synthesis Methodology: Prisma Scoping Review (PRISMA – sCR)

Data Bases searched: PubMed, EBSCO, ProQuest, Scopus, Google Scholar and Web of Science

Framework: Arksey and O'Malley (2005)

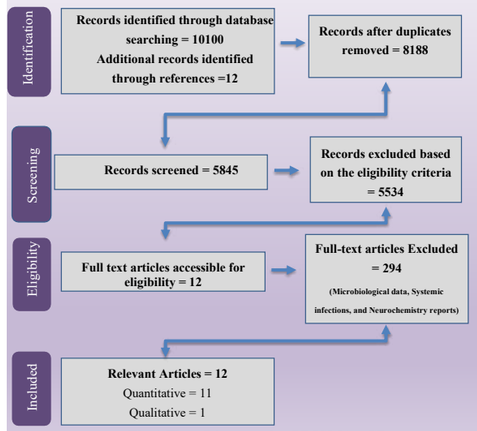


Fig.1 Flow Diagram for PRISMA-sCR

Results

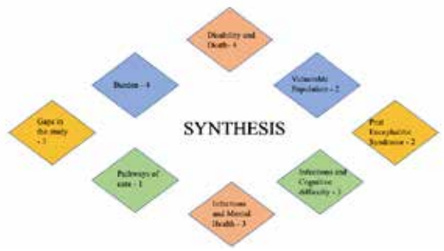


Fig.2 Major themes generated from the Review

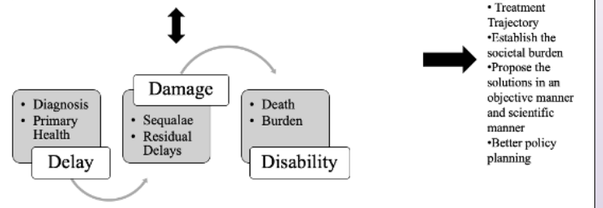
Results

Author	Burden	Vulnerable Population	Gaps in the study	Pathways of care	Infections and Mental Health	Infections and Cognitive difficulty	Disability and Death	Post Encephalitic Syndrome
Abdullahi et.al., 2020	X							
Adinolfi et.al., 2015	X					X		
Davis et.al.,2019	X		X				X	
John et.al., 2015	X	X			X	X		
Kakooza et.al., 2018		X						
Lesta et.al., 2018			X				X	
Nath, A, 2015			X					
Desmond et.al., 2013				X			X	
Olea et.al., 2017					X		X	
Wiedlocha et.al., 2015					X	X		X
Morano & Holt,2017								X

Fig.3 Synthesis -Table

Discussion

Predisposing Factors	Precipitating Factors	Perpetuating Factors
Genetic Inheritance	Lack of equipments	Burden in healthcare
Poor KAP	Behavioral patterns	Poor Lifestyle choices
Lack of health care services	Poor KAP	Risk services
Disability Adjusted Life years	Poor Quality of Life	Global health care concern
High societal costs	Overall Anxiety	Community Disruption



Findings

- The social determinants of health are commonly understood as the milieu in which humans are born, live, work, reproduce, worship, and age that profoundly affect physical and mental health indicators and overall quality of life.
- 8 major themes were identified from the review.
- Predominantly – systematic review was found.
- Psychosocial factors: Not pure in nature but were predominantly done along with other studies which were mainly -: Bio-medical and Psycho-pharmacological in nature.
- Social Causation as a relevant factor.
- Entire review provided only western literature.
- There is a need for the convergence of literature and practice and the need of the practice to inform the Policy.

Limitations

- Unpublished literature, other types of articles and grey literature are excluded.

Conclusions

- The Barriers and Facilitators in seeking care range on awareness, availability, accessibility, and affordability of care across levels which either increases or decreases the delay, disability, and the residual damage of the Acute Brain Infections.
- In the growing context of Brain Infections, it becomes imperative, to focus on all the factors of the condition for quality care through a multi-disciplinary approach.

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Additionally, she studies neurology at the Loginov MCSC, Department of Neurology in Moscow, where she carries out scientific activities under the guidance of scientific advisers and help in the implementation of scientific research.

Anti-Yo associated paraneoplastic encephalitis: neurological syndromes and successful treatment

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INTRODUCTION:

Paraneoplastic neurologic syndromes are a group of disorders resulting from immune-mediated mechanism effects of malignancy on the nervous system and associated with antibodies against intracellular antigens.

CLINICAL CASE:

Did not present any complaints due to mental disorders;
Subacutely developed psychomotor retardation
Rapidly progressive cerebellar syndrome
Opsoclonus-myoclonus
Oculogiric dystonia
Right laterocollis
Mental disorder in the form of a lack of spontaneous speech

61 years old

Instability in Romberg posture
Walking ataxia
Impossibility of tandem walking

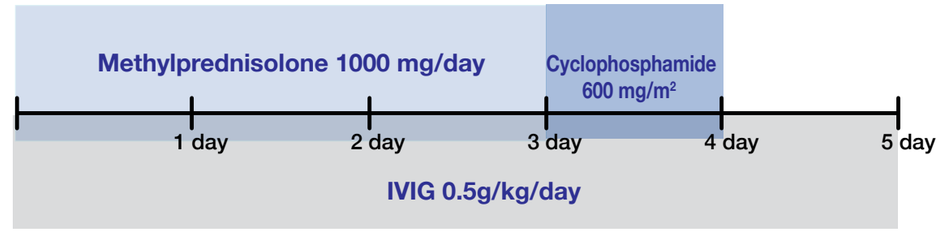
Multiple foci of vasogenic glyosis

Anti-Yo antibodies

PNS-Care Score

7 points (Probable)
- High-risk antibodies
- High-risk phenotype
- Cancer was not found but follow-u < 2 years

Polytheraphy:



The patient prescribed this therapy every month for 6 courses

The patient returned to speech, opsoclonus was regressed and ataxia was decreased after 2 courses

CONCLUSION:

In this case, we would like to show the successful experience in a patient with a difficult clinical situation and various symptoms.
When we meet with a case without cancer on PET-CT, it could be difficult to choose the right therapy if the glucocorticoids were ineffective.
It requires new randomized control studies for creating treatment algorithms.

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New clinical features of paraneoplastic encephalitis and encephalomyelitis: case reports of four patients

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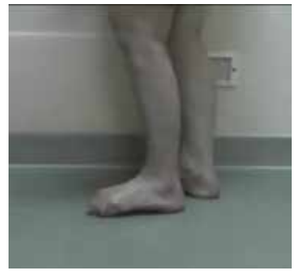
INTRODUCTION:

Paraneoplastic encephalitis is a rare disease involving the structures of the central nervous system. Recent data on paraneoplastic encephalitis in the medical literature is presented mainly by individual case reports or small case series, and therefore there are no published guidelines, nor is there a recommended standard approach to the diagnosis.

FINDINGS:

	Patient 1 woman, 61 y.o.	Patient 2 woman, 42 y.o.	Patient 3 woman, 55 y.o.	Patient 4 woman, 45 y.o.
Antibodies	anti-Yo	anti-Ri	anti-amphiphysin	anti-Hu anti-Yo
Clinical syndromes	- rapidly progressive cerebellar syndrome - opsoclonus-myoclonus - oculogyric crisis - mental disorder in the form of a lack of spontaneous speech	- multifocal dystonia - seizures	hemihypesthesia	encephalomyelities: asymmetric distal weakness in both hands
Onset	subacute	subacute	subacute	subacute
MRI	Vasogenic gliosis in the white matter, periventricular and subcortical nuclei	Area of inflammatory nature	Intramedullary mass Th_3-Th_8 Contrast accumulation: Th_5-Th_7 Multiple demyelination foci in the white matter of the brain	N
CSF	N	N	N	N
Associated cancer		breast cancer	ovarian teratoma	small cell lung cancer
Treatment	Immunoglobulins 0,5 g/kg/day for 5 days Glucocorticoids 1 g/kg/day 1-3 day Cyclophosphamide 600 mg/m^2 4 day	Glucocorticoids 1 g/kg/day for 5 days Cyclophosphamide 600 mg/m^2	Glucocorticoids 1 g/kg/day for 5 days	IVIG 0,5 g/kg/day for 4 days Cyclophosphamide 750 mg/m^2
Response	It was possible to achieve clinical remission against the background of polytherapy	Remission was not achieved	Completely responded to glucocorticoids	2 courses were completed

Patient 1



Patient 2

Patient 2

CONCLUSION:

These clinical cases confirm a wide range of clinical manifestations in patients with paraneoplastic encephalitis and encephalomyelitis. Probably, any uncharacteristic combination of neurological syndromes with a rapid increase in symptoms requires the exclusion of diseases of autoimmune genesis.

Patients' consent to the publication of data was obtained

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Elise Peter is resident in Internal Medicine and clinical Immunology in the Hospices Civils de Lyon (France). During her Master internship in “synaptopathies and auto-antibodies” team at the Institut NeuroMyogene, she started to work on the mechanisms of immune tolerance breakdown in paraneoplastic neurological syndrome with a focus on paraneoplastic cerebellar degeneration (anti-DNER and anti-Yo). She is now undertaking PhD studies in the same team on an integrative approach of tumour cells characterisation in anti-Yo gynaecological malignancies.

Ataxia with anti-DNER antibodies: from immunological characterization to new clinical insights

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Background

Paraneoplastic cerebellar degeneration with anti-DNER antibodies (**DNER ataxia**) is classically associated with Hodgkin’s disease. Few cases have been published, and **the long-term outcomes are unknown**.
Furthermore, little is known about DNER, besides that it is expressed specifically by the cerebellum’s Purkinje cells**. It is still debated if DNER is a surface antigen that can be reached by pathogenic anti-DNER antibodies.**

Objectives

We aimed to refine the **clinical description** of DNER ataxia, study the **patients’ outcomes** and correlate it with cerebellar atrophy. In addition we characterized the patients’ anti-DNER antibodies and studied **whether DNER is a surface antigen**.

Methods

A. Clinical study

Retrospective data

28 patients with DNER antibodies

French National Cohort

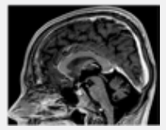
Diagnosis 2001 - 2020

B. Volumetric studies

Cerebellum volume

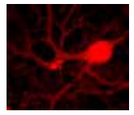
Longitudinal study

10 patients ; at least two available follow-up MRI



C. Antibody target localisation

1. Live immunostainings on **organotypic cerebellar slices** (OCS)



Purkinje cell from an OCS (anti-Calbindin staining)

2. Assessment of **DNER expression in cell membrane fractions** from rat brain lysates (western blots)

D. Antibody studies

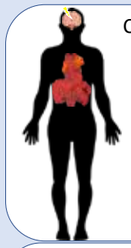
24 patients
9 paired serum/CSF DNER IgG subtypes & titers

DNER IgG intrathecal synthesis

Proteomic analysis (5 CSF samples vs.40 healthy controls)

Results

Clinical features



Men (82%)

Median age : 52 years

Acute cerebellar ataxia (96%)

Localised Hodgkin’s disease (60%)

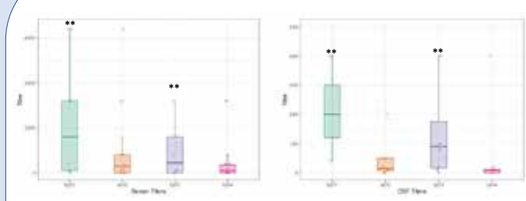
Severe but sometimes reversible

Median follow-up time : 24m
8 (29%) with no significant disability (mRS≤2) at last visit

Disability at onset correlate with long-term outcomes (p=0.03)

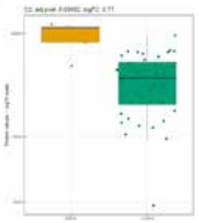
Type of treatments = no difference

DNER Antibodies are IgG1 and IgG3 isotypes with high CSF titers



Higher IgG1& IgG3 titers

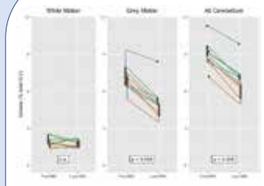
Intra-thecal synthesis in 8/8 patients(Reiber 2015)

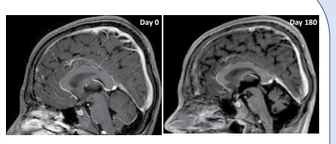


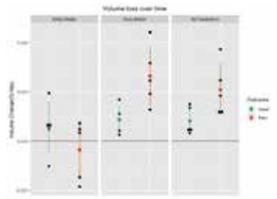
Proteomic analysis
Overexpression of the classical pathway components of complement activation

➡ **Complement activation** favoured by CSF **IGG3 antibodies** ?

Loss of cerebellum gray matter over time

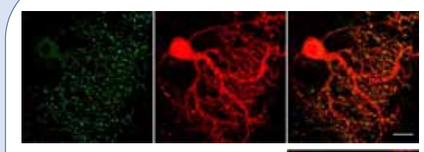


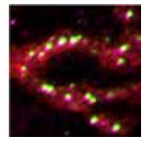




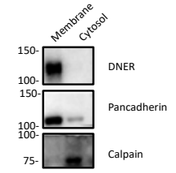
Volume loss is **lower and slower** in patients with **good clinical outcomes**

DNER-Ab reach their target on Purkinje cell surface





DNER ab of patients **CSF** reach their target on live Purkinje cells marked with **calbindin**
DNER ab of patients **CSF** colocalise with anti-**DNER** commercial ab



DNER is found in cell membrane fractions

Possible pathogenic effect of DNER-Ab (functional effect ?) may explain reversibility in patients with good prognosis

Conclusion

DNER-PCD presents as a **severe and acute ataxia** that **can be reversible**. Early detection is mandatory. **Anti-DNER IgG1 and IgG3 reach their target at the surface of Purkinje cell** and may trigger complement-dependant cytotoxicity, resulting in Purkinje cell death.

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Murphy, Kenneth, and Casey Weaver. *Janeway’s immunobiology*. Garland science, 2016.

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Thomas Pichl is a medical doctor training in Internal Medicine at Aberdeen Royal Infirmary. He developed an interest in infectious diseases and global health during his foundation years in Germany and moved to the UK to study an MSc at the London School of Hygiene and Tropical Medicine. Dr Pichl focused on research early in his career, investigating neurotoxic effects of ketamine at the Department of Paediatrics and Adolescent Medicine at the University of Cologne.

He currently works on various research projects with the Aberdeen Fungal Group as an Honorary Clinical Research Fellow.

Brain imaging in neurological infection with Japanese encephalitis virus compared with Dengue virus: A systematic review

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INTRODUCTION

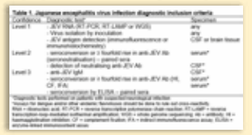
BACKGROUND: Japanese encephalitis virus (JEV) and dengue virus (DENV) represent important causes of encephalitis and significant public health threats in Asia. There are acknowledged limitations in diagnosis of the two diseases, with RNA rarely detected in cerebrospinal fluid, and poor specificity of serological tests. Brain imaging may provide diagnostic clues about the aetiology of infectious encephalitis and is increasingly available worldwide. Thalamic lesions are suggested to be common in Japanese encephalitis virus infection (JE)[1], but it is not clear if there are radiological findings that are pathognomonic for either neurological infection.

AIM: To elucidate whether there are characteristic brain lesions that differentiate between the diseases and improve diagnostics.

METHODS

SEARCH STRATEGY: Five databases (EMBASE®, MEDLINE®, Cochrane Library, Global Health, Web of Science™) were systematically searched

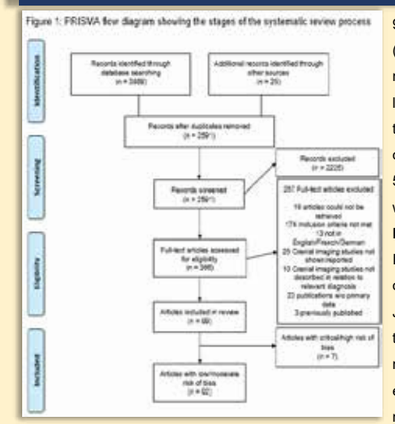
INCLUSION CRITERIA: All study types were considered suitable. PICO: **P**opulation: Patients of any age with confirmed JEV infection who underwent MRI or CT head scan or other brain imaging. **C**omparator: Patients of any age with confirmed acute dengue infection who underwent MRI or CT head scan or other brain imaging. **O**utcome: Pathologic features detected on brain imaging, differences between CT and MRI or other brain imaging as well as distinguishing findings for either flavivirus infection. Diagnostic tests were categorised into three confidence levels (see tables 1 and 2).



EXCLUSION CRITERIA: Concurrent brain disease other than JE or dengue; CNS infection in previous six months; brain imaging was performed 30 days or more after diagnosis; diagnosis based on single serum anti-dengue or anti-JEV IgM reading or single high titre; studies with high/critical risk of bias.

QUALITY ASSESSMENT: Systematic risk of bias assessment of all studies was performed with the Joanna Biggs Institute's (JBI) checklists for observational studies.

RESULTS



92 included studies provided brain imaging data on 336 patients (JE: 211, dengue: 125). Case reports and case series were the most common study type (64/92 and 20/92 resp.). More focal lesions were detected on MRI than on CT. Thalamic lesions were the most reported MRI finding in both diseases but appeared to occur more often in JE (74% in 23 studies) than dengue (29.4% in 58 studies), followed by basal ganglia lesions in JE (42.5%) and white matter lesions in dengue (28.4%) (see table 3).

KEY FINDINGS:

In cases with high diagnostic confidence and laboratory evidence of encephalitis, thalamic lesions were reported frequently in both JE (76.5% in 17 studies) and dengue (65.2% in 23 studies) (see table 4). Further MRI lesions (cerebral white matter, cerebellum, minor haemorrhage) were reported more often in dengue encephalitis compared with other dengue-associated neurological manifestations (not shown).

Table 3. MRI and CT imaging findings according to diagnosed flavivirus infection

	JE (N=211)		Dengue* (N=125)	
	MRI	CT	MRI	CT
Total NF (%·F)	185 (85.8%)	37 (17.5%)	102 (81.6%)	42 (33.6%)
Normal scan n (%N)	6 (4.4%)	9 (24.3%)	27 (26.5%)	15 (35.7%)
Focal lesions				
Thalamus	134 (74.0%)	11 (29.7%)	30 (29.4%)	6 (14.3%)
Cerebral cortex	21 (11.6%)	4 (10.8%)	9 (8.8%)	-
Cerebral white matter	11 (6.1%)		29 (28.4)	2 (4.8%)
Basal ganglia	77 (42.5%)	1 (2.7%)	6 (7.8%)	1 (2.4%)
Brainstem	59 (32.6%)	1 (2.7%)	20 (19.6%)	3 (7.1%)
Medial temporal lobe	32 (17.7%)	1 (2.7%)	5 (4.5%)	-
Cerebellum	5 (2.8%)	-	19 (18.6%)	-
Intracranial haemorrhage				
major	1 (0.6%)	1 (2.7%)	6 (5.6%)	14 (33.3%)
minor	-	-	12 (11.7%)	-

† Includes all dengue cases with various neurological manifestations; ‡ N total number of patients who underwent respective neuroimaging; F = Total number of included participants; MRI = magnetic resonance imaging; CT = computed tomography; ADEM = acute disseminated encephalomyelitis; ns = not specified.

Table 4. MRI findings of JE and dengue encephalitis cases in which a CNS infection was detected in CSF or brain tissue, according to diagnostic confidence level

	Japanese encephalitis*		Dengue encephalitis†	
	L1/2	L3	L1/2	L3
Total NF	17	78	22	36
Focal lesions (%N)				
Thalamus	13 (76.5%)	62 (79.5%)	14 (63.6%)	3 (8.3%)
Cerebral cortex	4 (23.5%)	16 (20.5%)	3 (13.9%)	1 (2.8%)
Cerebral white matter	-	4 (5.1%)	9 (40.1%)	2 (5.6%)
Basal ganglia	6 (35.3%)	37 (47.4%)	2 (9.1%)	1 (2.8%)
Brainstem	4 (23.5%)	32 (41.0%)	8 (36.4%)	1 (2.8%)
Medial temporal lobe	11 (64.7%)	2 (2.6%)	3 (13.9%)	-
Cerebellum	-	2 (2.6%)	9 (40.1%)	3 (8.3%)
Intracranial haemorrhage (%N)	-	-	8 (36.4%)	2 (5.6%)
major	-	-	-	-
minor	-	-	8 (36.4%)	2 (5.6%)

* Studies in which a diagnosis was based on serum non-negative alone were excluded. See Tables 1 and 2 for details on levels of diagnostic confidence. † N total number of patients with respective flavivirus infection and diagnostic confidence level who underwent magnetic resonance imaging. MRI = magnetic resonance imaging, CT = computed tomography, ADEM = acute disseminated encephalomyelitis, ns = not specified.

CONCLUSION

Thalamic lesions appeared to occur frequently in both JE and dengue encephalitis. No radiological findings were found to be pathognomonic of either disease, yet there was a lack of high-quality studies. **JEV-specific IgM** in CSF correlated with the presence of lesions on brain imaging, but this was not the case for DENV-specific IgM. When DENV was detected by antigen or nucleic acid test, the rate of brain lesions was markedly higher. This possibly suggests a difference between JEV and DENV CSF IgM assay performance or perhaps that DENV neurological disease indeed comprises distinct entities with specific pathogenic mechanisms. **Current diagnostic standards**[2,3] for dengue encephalitis are insufficient. Our findings suggest that the specificity of the diagnostic method is key in identifying brain lesions.

LIMITATIONS: High selection bias likely as majority of data derived from case reports and case series. Participants in this study are not representative of any population. Relevant reporting bias likely due to differing MRI sequences of included studies. Comparability between different levels of diagnostic confidence in JE and dengue may be limited.

OUTLOOK: Prospective studies on these two flavivirus infections combining specific laboratory methods with a thorough reporting on clinical presentation and brain imaging is needed. This would contribute to establishing brain imaging as a valuable additional diagnostic tool benefitting clinicians and patients alike.

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Medicine is not like studying history, it's taking part in history. So much was discovered, and so many are to be explored further.

Clippers, pepper, slippers – what do all these have in common?

Background

Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS), first described in 2010, is a rare, poorly understood inflammatory disease involving the central nervous system.

It has a time pattern of subacute onset, progressive chronic course, and the symptoms relapse without treatment. Gait ataxia, dysarthria, diplopia, nystagmus are usual clinical manifestations suggestive of brainstem involvement.

At MRI, we can find multiple, bilateral, curvilinear, small nodular, or punctate enhancing lesions ”peppering” the pons; these lesions are usually smaller than 3mm in diameter.

CSF analyses can show mildly elevated protein, pleocytosis, or oligoclonal bands. None of the CSF changes help frame the disease.

Pathologically, the disease is inflammatory, with marked lymphocytic infiltration around the small blood vessels, involving white and gray matter. In contrast with prominent inflammation, there are no signs of vasculitis or myelin loss.

Patients show rapid clinical improvement and resolution of the MRI lesions under large-dose corticosteroid treatment. Symptoms reappear after tapering so that patients need chronic steroid treatment for disease control. Immunosuppression with azathioprine or methotrexate was successfully used in selected cases as a steroid-sparing strategy.

Diagnosis is made in a patient with brainstem symptoms and signs, subacute onset and progressive evolution, pons ”peppering” at MRI, T-lymphocyte infiltration around small blood vessels in biopsy samples, and sensitivity to steroid treatment. No biomarker is available. A definite diagnosis requires the exclusion of a broad spectrum of possible alternatives. Tobin et al. proposed diagnosis criteria based on clinical, radiological, and pathological features after studying 23 CLIPPERS cases.

In 2015 Armand et al. introduced the term SLIPPERS for a limited, supratentorial, but otherwise similar disease.

In 2016 Blaabjerg et al. found widespread perivascular inflammation in brain tissue appearing normal on conventional 3.0T MRI in an autopsy case of CLIPPERS. Also, other patients had supratentorial lesions visible at 7.0T in brain regions appearing normal on 3.0T MRI. These findings give a possible explanation for the cases with lesions in the midbrain, cerebellum, spinal cord, and supratentorial regions.

Thus, SLIPPERS may be just one form of presentation for the disease. Perhaps, the ”pontine” P will be dropped in the future, and the term CLIPERS will include the supratentorial and all other-than-pontine forms.

Methods

We will present the clinical case of a 44 years old woman with a history of one month of gait problems and weakness in the left leg.

The case

At the neurological examination, she was perfectly oriented, with left leg paresis, left Babinski sign, bilateral, brisk reflexes, and nystagmus. She had a broad-based gait and needed assistance to walk. No signs of peripheral nervous system involvement were found.

She had no weight loss, fever, meningism, lymphadenopathy, uveitis, or oral/genital ulcers.

MRI revealed bilateral T2/FLAIR hyperintense lesions with punctiform and linear enhancement in the pons, midbrain (symmetrical, Fig.1), thalamus, and basal ganglia (asymmetrical, more on the right, Fig. 2 and 3).

The workup we've done included angiotensin-converting enzyme, antinuclear antibodies, cANCA, pANCA, anti-AQP4, anti-MOG, antineuronal, anti-NMDA, anti-GAD, and anti-NMPA antibodies - all the results were negative.

Mild pleocytosis and oligoclonal bands were found at CSF analysis. The protein level was in the normal range. The cytologic analysis described lymphocytes without signs of atypia.

We started high-dose steroid treatment.

After five days of treatment, she had no gait problems, motor impairment, or nystagmus. There was marked improvement of lesion extension and reduced contrast enhancement at the control MRI, lower cellular count at the repeated CSF analysis. At two months follow-up, the MRI showed marked resolution of the lesions (Fig.4).

We put her on prolonged low-dose steroid treatment to prevent relapses. She had no neurological symptoms after three months of follow-up.

Discussion

CLIPPERS is a relatively ”young” entity with distinctive clinical, radiological and pathological characteristics. The emergence of new data helps to draw the lines between CLIPPERS and other entities. Being a rare disease, keeping a high level of suspicion is crucial, as patients show rapid resolution of symptoms under steroid treatment.

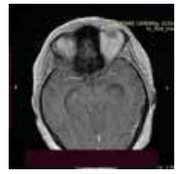

Fig.1: Punctate and curvilinear, bilateral enhancing lesions in the midbrain.

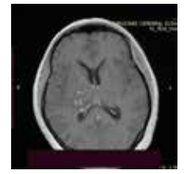

Fig.2: Similar lesions were found in basal ganglia, internal capsule and thalamus, more prominent on the right.

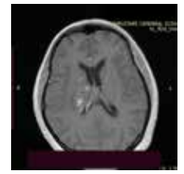

Fig.3: Some lesions had a slight confluent pattern but did not exceed 3mm in diameter.

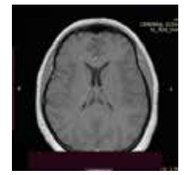

Fig.4: Control MRI after two months of treatment showed marked resolution of the lesions (in number and size).

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ISOLATED ANTI-AMPHIPHYSIN AUTOANTIBODY ASSOCIATED PARANEOPLASTIC VESTIBULO CEREBELLAR SYNDROME

Dr.Shivaram Rao K[1], Kousik Vankadari[1], Milap Milap[1], Hemanth V[1], Rukmini Mridula Kandadai[2]

Introduction

- Paraneoplastic cerebellar degeneration (PCD) is an immune mediated neurological disease characterized by adaptive immune response against onco-neural antigens physiologically expressed in the cerebellum.
- It is characterized by presence of highly specific onco-neural auto-antibodies like anti-Yo, anti-Hu, anti-Ri, and anti-Ma2 in the serum and cerebrospinal fluid as diagnostic biomarkers.
- Anti-amphiphysin autoantibody related paraneoplastic encephalitis is a less commonly seen autoimmune neurological disorder usually presenting as stiff person syndrome.

Unique Findings In This Case

- Isolated anti-amphiphysin antibody associated paraneoplastic cerebellar degeneration
- Vestibulocerebellar syndrome with associated sensorineural hearing loss and pure sensory neuropathy.
- Non secretory extragonadal germ cell tumor in the retroperitoneum.
- To the best of my knowledge, description of these symptom complex in non seminomatous, non secretory, extra gonadal germ cell tumors is probably the first time.

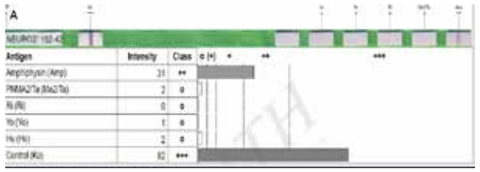
Case Description

34yr old male patient presented with following symptoms

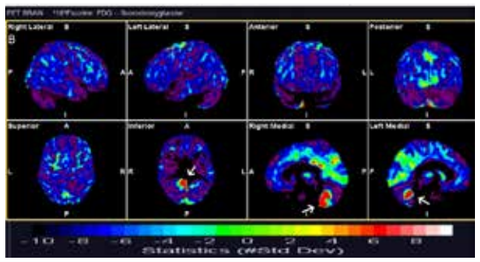
- Initially symptoms started with giddiness and swaying while walking associated with occasional nausea and vomiting.
- Oscillopsia was present with associated hearing loss and tinnitus.
- Symptoms slowly progressed over 5months with worsening of gait (was unable to walk without support).
- Examination showed predominantly broad based gait and opsoclonus in eyes.

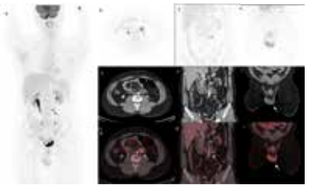
Investigations

- All Lab parameters were within normal limits.
- Pure tone audiometry showed moderate to mixed hearing loss of 46dbHI with downward sloping curve.
- CHAMP (cochlear hydrops analysis and masking procedure) test revealed latency and ratio values were higher than normal.
- Nerve conduction studies – Sensory neuropathy with completely absent sensory nerve action potentials in all four limbs with normal compound muscle action potentials.
- Contrast MRI – Normal
- CSF analysis – Normal
- Encephalitis panel showed – Amphiphysin antibodies positive (2+).

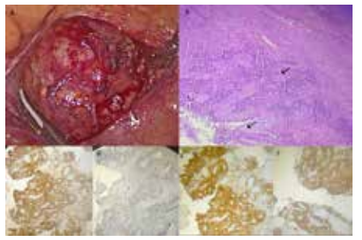


- F-18 FDG PET- CT - Stereotactic surface projection map of brain images following age adjusted normalization of metabolism show increased metabolic activity in the vestibulocerebellum and adjacent vermis





- Whole body F-18 FDG PET-CT revealed an area of focal tracer uptake (A, MIP; solid arrow) in the left lumbar region.
- Axial (B-D) and coronal (E-G) PET, CT, fused PET-CT images localize the increased tracer uptake to solid-cystic lesion (dashed arrows) in the left para-aortic region.
- Sagittal PET, CT and fused PET-CT images (H-J) show no evidence of functional or morphological abnormality in bilateral testis (dashed filled arrow).
- Further workup with LDH, serum hCG – 0.1 (< 2 mIU/ml) and AFP– 2(< 6 ng/ml) were normal.



- Intra-operative photograph of solid-cystic lesion was shown (A).
- Photomicrograph of sections from solid-cystic lesion reveals oval to round tumor cells (B; solid arrow) arranged in clusters and nests admixing extensive necrosis (B; dashed arrow)(Original magnification x 10; hematoxylin-eosin stain).
- On immunohistochemistry, tumors cells were diffusely positive for CD30 (C), Oct 3/4 (D), SALL-4(E) and focally positive for CK (F) confirming a diagnosis of non-seminomatous germ cell tumor having predominant component of embryonal carcinoma.

Discussion

- Anti-amphiphysin antibodies are autoantibodies directed against amphiphysin protein, a 128 kd nerve terminal protein located on the synaptic vesicles widely distributed in the nervous system including cerebellum (1).
- Isolated anti-amphiphysin antibodies are seen in association with small cell lung carcinoma and breast cancer (2).
- Extragonadal germ cell tumors (EGCT) are less commonly seen accounting for 2-5% of all germ cell tumors and arise from ectopic germ cell precursor cells that fail to complete normal embryogenic migration (3,4).
- Even though elevated serum levels of AFP and hCG help in diagnosis of yolk sac tumors and choriocarcinoma, seminomas and embryonal germ cell tumors are generally negative for these tumor markers as seen in our case. Detection of circulating miRNA in body fluids seen to be novel promising diagnostic biomarker for all types of germ cell tumors irrespective of age and location (5).
- Recently Brehm et al reported the association of novel paraneoplastic antibody named kelch like protein -11 antibody related encephalitis with seminomatous testicular germ cell tumors (6). Serological presence of these novel autoantibodies were not tested in our patient due to lack of availability in our region

Conclusion

- With expanding spectrum of autoimmune encephalitis, new antibodies are being discovered along with unique clinical spectrums.
- More clinical studies and unique diagnostic methods have to be developed for early detection to reduce the disability of the patients.

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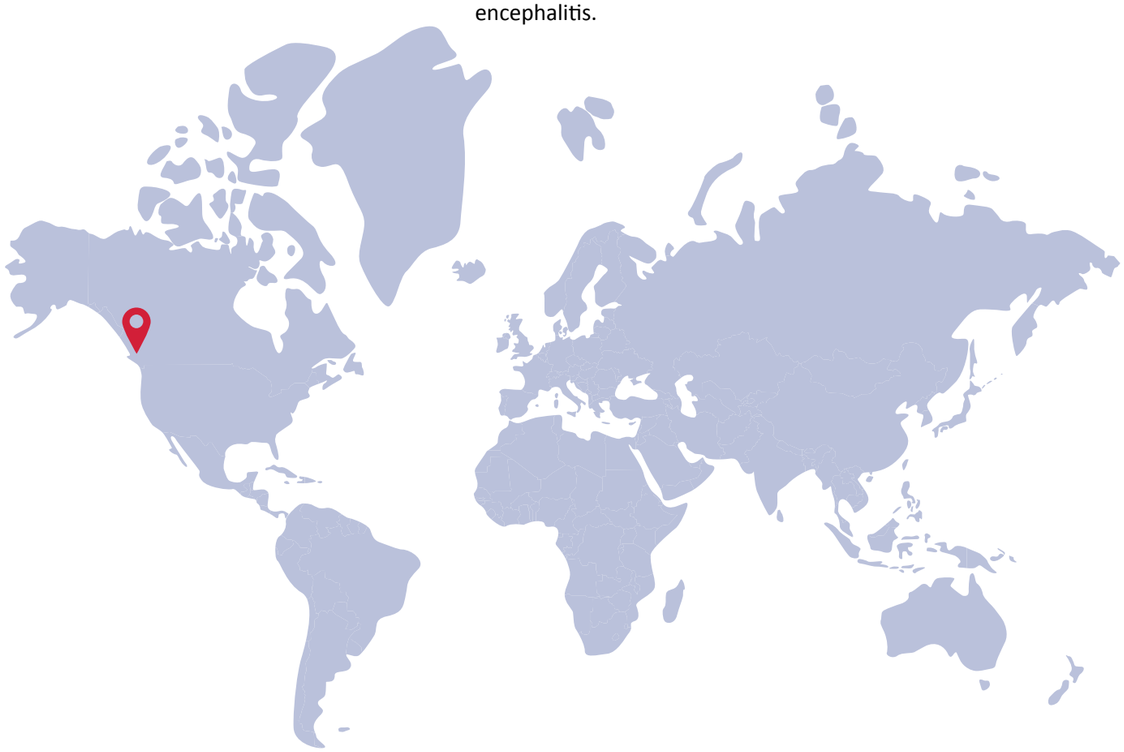

Major Factors Contributing to Long-term Reduction in Quality of Life in CASPR2-antibody Associated Syndromes

Christopher E. Uy, Sanchit Turaga, Babak Soleimani, Giacomo Portaro, Sudarshini Ramanathan, James Varley, Sophie Binks, Sarah Wright, Eleanor Grant, Patrick Waters, Sarosh R. Irani

Background

Autoantibodies to Contactin-Associated Protein 2 (CASPR2) are associated with neurological syndromes including limbic encephalitis, Morvan syndrome, peripheral nerve hyperexcitability, and ataxia. Although antibody-mediated neurological diseases are largely thought of as immunotherapy-responsive with good outcomes, previous studies in these disorders have relied on the modified Rankin Scale (mRS) as the main measure of disability. Emerging data in related disorders suggests long-lasting symptoms and ongoing disability, poorly reflected by mRS.

Findings

Table 1. Clinical Characteristics of patients (n=82) with serum CASPR2 antibodies

Age, median (range)	63.5 (21-82)
Male, n (%)	67 (81.7)
Median follow-up, years (range)	2.6 (0-13)
History of autoimmunity, n (%)	14 (17.1)
Myasthenia Gravis	7 (8.5
Thyroid Disease	4 (4.9)
Coeliac Disease	2 (2.4)
Other	1 each (1.2%) pernicious anemia, AIHA/pancytopenia/ITP, IgG4, psoriasis, polymyalgia rheumatica, pemphigus
Tumour at any stage	18 (22.0)
BPH, n (% of male patients)	16/67 (23.9)
Prostate Cancer, n (% of male patients)	5/67 (7.5)
Thymoma, n (%)	11 (13.4)
Other	1 pancreatic microcystic serous cyst adenoma + intraductal papillary mucinous neoplasm, 1 NSCLC, 1 Duke's B colon cancer
Main Syndromes	
Morvan Syndrome	30 (36.6)
Limbic Encephalitis	22 (26.8)
Isolated Neuromyotonia	5 (6.1)
Ataxia/Movement Disorder	2 (2.4)
LE/NMT	1 (1.2)
MoS/LE	1 (1.2)
Unrelated	5 (6.1)
Unknown	16 (19.5)
Relapsing Course	11 (13.4)
No. of episodes, median (range)	1 (1-4)

Table 2. Clinical Features throughout course of disease in patients (n=82) with serum CASPR2 ab

Feature (n=82)	Proportion of patients (%)
Sleep Disturbance	56 (68.3)
Autonomic Dysfunction	55 (67.1)
Peripheral Involvement	55 (67.1)
Cognitive Symptoms	49 (59.6)
Behavioural/Personality Change	43 (52.4)
Seizures	39 (47.6)
Psychiatric Symptoms	39 (47.6)
Movement Disorder	11 (17.1)
Ataxia/Cerebellar Symptoms	23 (28.0)

Table 3. Demographic Data, Time-Course, and Duration of Follow-up for longitudinal subgroup (n=57)

Clinical Information (n=57)	Total	Immunotherapy (IT)	No IT
Median age at onset, y (range)	66.5 (17.5 – 81)	68 (17.5 - 81)	64 (19 – 75)
Male (%)	49/57 (86%)	40/44 (90.9%)	9/13 (69.2%)
Immunotherapy	44/57 (77%)	44/44 (100%)	0/13
Mean time to peak severity, weeks (range)	20.0 (4.1 – 165)	21.3 (2-86.9)	16.8 (4.1-87.3)
Mean time to immunotherapy, weeks (range)	28.6 (4.1 – 178.1)	28.6 (4.1 – 178.1)	–
Patients with relapsing course, n (%)	9/57 (15.8%)	9/44 (20.5%)	0/13
Relapses in cohort	14	14	0
Mean duration of follow-up, y (range)	5.5 y (0 – 26.3)	5.7 (0.1 – 26.3)	5.7 (0.3 – 9.9)

Methods

We identified a cohort of 82 patients with CASPR2 antibodies identified by cell-based assay. Clinical phenotypes were determined by clinical interview and review of electronic patient records in 73. In a subgroup of 57 patients, temporal evolution of the main features of disease, and quality of life scales (EuroQol-5D5L and Visual Analog Scales) were analyzed after 6-months and then at annual intervals post-peak disease severity or after initiation of immunotherapy. For deceased patients, dates of death and proximal causes of death. Where available, surviving patients & families were contacted for most recent status. Those treated with immunotherapy (IT) were compared to those without (no IT).

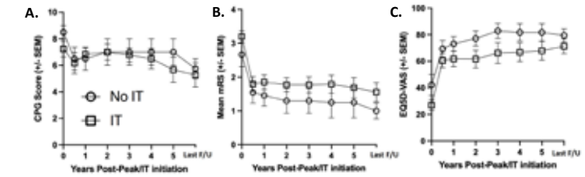

Figure 1. Patients with CASPR2-ab treated with immunotherapy had higher mean modified Rankin scores and lower EQ5D-visual analog scale scores at onset and throughout the course of illness compared to those who were untreated. There did not appear to be a difference in chronic pain grade score between the two groups.

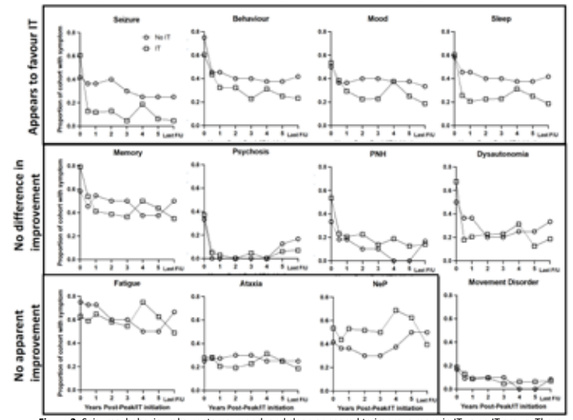

Figure 2. Seizures, behavioural symptoms, mood, and sleep appeared to improve more in IT vs no IT group. There were no obvious differences in memory, psychosis, peripheral nerve hyperexcitability (PNH), dysautonomia, or movement disorders which improved in both groups. Fatigue, ataxia, and neuropathic pain did not improve over time with or without IT.

Table 4. Characterization of Deaths in CASPR2-ab cohort

	Total	IT	No IT
Deaths, n (%)	20/57 (35.1%)	16/44 (36.3%)	4/13 (30.7%)
Mean age at death, y (range)	67.5 (29 – 83.5)	66.1 (29 – 83.5)	76.8 (75 - 78.7)
Median duration from onset to death, y (range)	2.6 (0.3 to 18)	2.6 (0.3 to 18)	4.5 (0.3 to 8.7)
-Cause of death unknown	10/20	6/16	4/4
-Infectious complications	5/20*	5/16*	0/4
-Metastatic disease	2/20*	2/16*	0/4
-Respiratory failure	2/20*	2/16*	0/4
-Sudden death during PLEx	1/20	1/16	0/4
-Basilar thrombosis (?IVIG related)	1/20	1/16	0/4
-Left ventricular failure due to ischemic heart disease	1/20	1/16	0/4

*1 patient with cause of death listed as respiratory failure due to pleural metastases and candidiasis hence total number of causes of death total >20.

Key Points

These preliminary data suggest that although many features of CASPR2-antibody related disease are immunotherapy responsive, there are some long-term residual symptoms which affect quality of life and lead to disability.

Those receiving immunotherapy had more disability at peak disease severity compared to no IT (mRS 3.26 vs 2.5) and had more residual disability at latest follow-up (mRS 1.5 vs 1). Quality of life at peak severity and most recent follow-up was worse in those receiving IT vs not (EQ5D-VAS peak 26.9 vs 42.2 and latest 71.3 vs 79.4).

Throughout the course of illness (mean duration 5.5 y), there were residual deficits across all major symptom categories. There was a trend toward lower rates of seizures, abnormal behaviour, mood disorders and sleep disorders in those receiving IT vs no IT. Memory complaints, psychotic symptoms, peripheral nerve hyperexcitability, dysautonomia, and movement disorders improved over time without clear differences between IT vs no IT. There was a high proportion of residual fatigue, ataxia and neuropathic pain in both groups.

Future Directions

Ongoing analysis will aim to examine effect of first versus second-line immunotherapy on individual disease symptoms, outcomes (residual disability and relapses) and quality of life components. Statistical analysis will follow descriptive statistics to determine if significant differences between subgroups exists. We also aim to examine any associations with serum antibody titres and subclasses and HLA genotype.

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Javier did his trainee in Neurology at Hospital Universitario de La Princesa. Since the beginning of the residency, he has shown interest and been involved in the field of Neuroimmunology, especially in the study of antibodies against neuronal antigens. Thus, he decided to do a training rotation in the Neuroimmunology lab at National Hospital for Neurology and Neurosurgery (Queen´s Square, London, UK), where he learnt different laboratory techniques such as ELISA, cell-based assays, immunohistochemistry, immunoblot, flow cytometry, SIMOA, etc. Furthermore, he actively collaborated in several research projects and participated in assistance of patients with immune-mediated diseases.

Regarding academic experience, he has shown a proactive attitude. He participated in the publication of seven scientific articles (five of them as first or second author), and he did thirteen presentations of studies or clinical cases as first author in many national and international congresses. In order to expand his knowledge about neuroimmunology he has successfully completed a master and currently doing another one. He has participated in two clinical trials (about treatment of stroke and multiple sclerosis). He is working as neurologist principally involved in neuroimmunology in Hospital Universitario Rey Juan Carlos. He is going to initiate a complementary rotation in the Immunology laboratory with the proposal of keeping learning the different techniques used in this field.

Infectious vs autoimmune encephalitis: a multidisciplinary challenge

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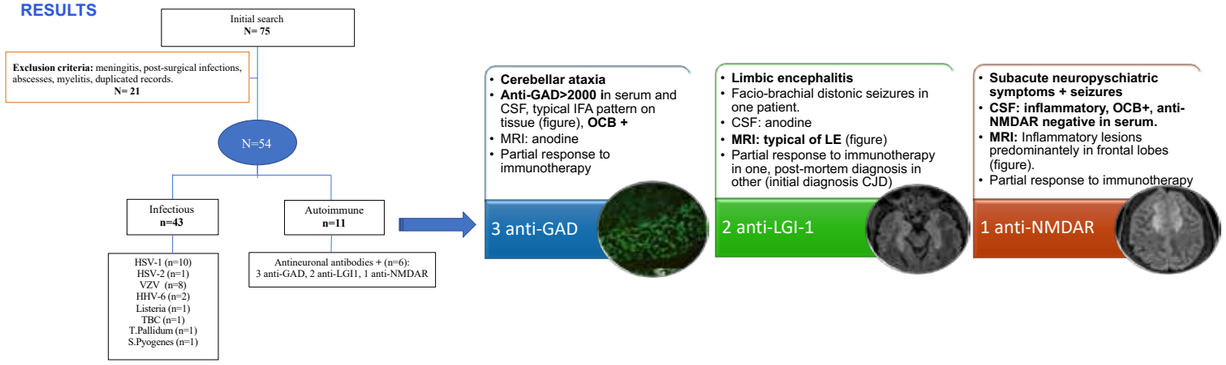
INTRODUCTION

The differential diagnosis of autoimmune and infectious encephalitis is notoriously difficult and requires a multidisciplinary management. The aim of this study is to analyze differences between both causes of encephalitis.

METHODS

We retrospectively reviewed the patients diagnosed of encephalitis in our hospital from 2012 to 2021. We collected different variables categorized as demographic, clinical, therapeutic, and prognostic, and they were compared between autoimmune encephalitis (AE) and infectious encephalitis (IE). SPSS 15.0 and R were used for statistical analysis.

RESULTS



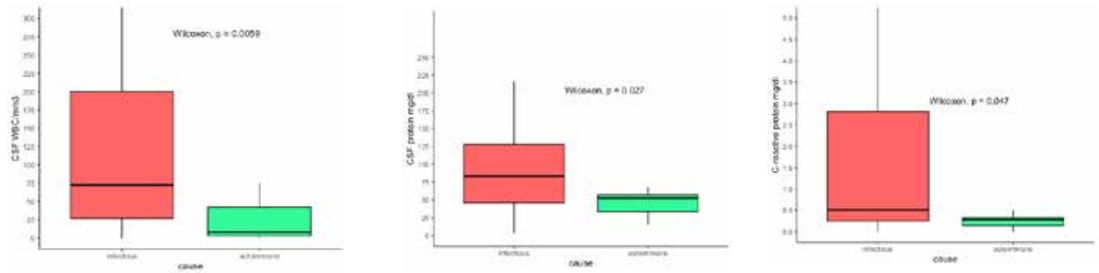
Demographic and clinical features	Total N=54	Cause		p
		Infectious N=43	Autoimmune N=11	
Female sex N (%)	23 (42,6)	20 (46,5)	3 (27,3)	n.s
Age (years) M ± SD	57 (22)	59,8 (21,1)	45,6 (22,5)	n.s (0,055)
Autoimmune diseases N (%)	10 (18,5)	7 (16,3)	3 (27,3)	n.s
Headache N (%)	18 (33,3)	15 (34,9)	3 (27,3)	n.s
Fever N (%)	28 (51,9)	25 (58,1)	3 (27,3)	n.s (0,068)
Memory impairment N (%)	6 (11,1)	2 (4,7)	4 (36,4)	**0,012**
Psychiatric symptoms N (%)	20 (37)	16 (37,2)	4 (36,4)	n.s
Focal deficits N (%)	37 (68,5)	29 (67,4)	8 (72,7)	n.s
Seizures N (%)	8 (14,8)	6 (14)	2 (18,2)	n.s
Movement disorders N (%)	6 (11,1)	2 (4,7)	4 (36,4)	**0,012**

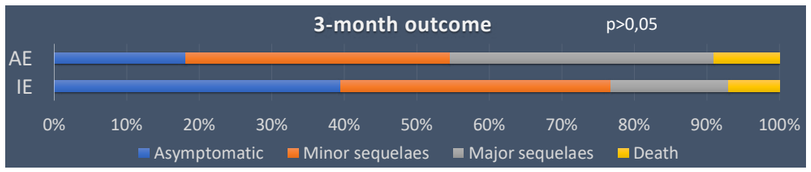
	Total N(%)	Cause		p
		Infectious N (%)	Autoimmune N (%)	
Ancillary testing				
→Abnormal MRI N (%)	33 (61,1)	27 (62,8)	6 (54,5)	n.s (0,089)
→Abnormal EEG N (%)	40 (74,1)	34 (79,1)	6 (54,5)	n.s

Infectious encephalitis: 43,5% HSV-1

Interestingly, two patients with autoimmune encephalitis had positive virus PCR in CSF:
- Anti-NMDAR: HHV-6 +
- One anti-GAD patient: HSV-2+

OCB +:
- 4/8 patients with AE
- 0/3 patients with IE





CONCLUSIONS

In our study, patients with AE showed movement disorders and memory impairment more frequently than IE. Patients with IE developed more inflammatory changes in CSF (cell-count and protein concentration) and serum (C-reactive protein). These results could be useful to distinguish infectious and autoimmune encephalitis, thus improving the management of these patients.

Dr James Varley

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James is a neurologist working in London. He completed his DPhil with the Oxford Autoimmune Neurology Group looking at various clinical and immunological aspects of autoimmune encephalitis.

Neuropsychiatric Systemic Lupus Erythematosus does not appear to be caused by antibodies

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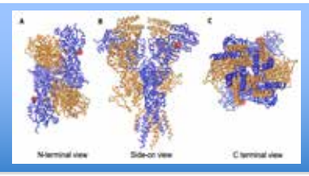
Background: Systemic lupus erythematosus (SLE) is a multi-system autoimmune disease primarily affecting young women. Neuropsychiatric SLE (NPSLE) is common and can be hugely debilitating though it is extremely broadly defined clinically, creating the impetus for better biomarkers to aid in diagnosis and measuring response to treatment. Antibodies to the N-methyl-D-aspartate receptors (NMDA), detected with peptide-based ELISAs which utilise a pentapeptide (DWEYS) expressed in the NR2A/B extracellular loop (background figure 1), have been implicated in NPSLE by several studies. However, patients with NPSLE have few clinical features seen in those with NMDAR-antibody encephalitis, whose antibodies are detected by binding to the extracellular domain of native NMDARs. This study aimed to characterise neuronal autoantibodies in NPSLE and explain this apparent clinical paradox.

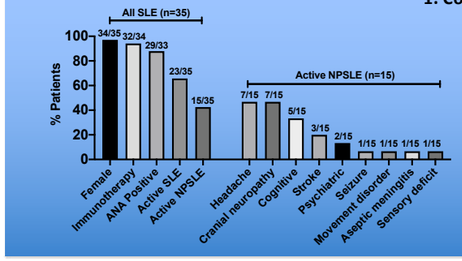
Methods: Clinical data, plasma and CSF from 35 patients with a mixture of SLE and active NPSLE were collected. 104 controls were used as comparators and included healthy individuals (n=36), patients with multiple sclerosis (n=32), neuroinflammation (n=4) and neuroglial surface targeted antibodies (n=36). Samples were tested on live NMDAR cell-based assays, hippocampal cultured neurons and peptide ELISAs.

Background figure
Three views of the NMDA receptor with the DWEYS peptide region highlighted in red



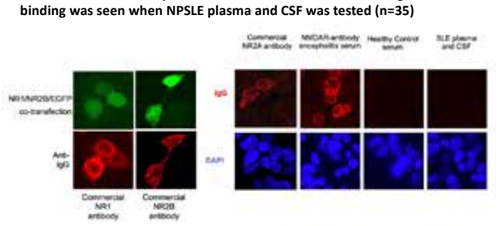
Results

1. Cohort characteristics

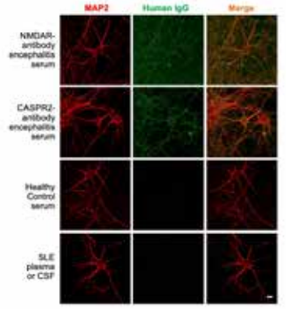


	SLE patients
Immunotherapy	32/34 (94.1%)
•Prednisolone	24/34 (70.6%)
•Hydroxychloroquine	14/34 (41.2%)
•ASA	13/34 (38.2%)
•AZA	9/34 (26.5%)
•MMF	5/34 (14.7%)
•Biologic	3/34 (8.8%)
•Ciclosporin	2/34 (5.9%)
•Methotrexate	1/34 (2.9%)

2. NMDAR cell based assay contained relevant NR1 and NR2 antigens but no binding was seen when NPSLE plasma and CSF was tested (n=35)



3. Cultured hippocampal neurons were use as an unbiased source of diverse brain antigens. Testing of known autoimmune encephalitis serum showed binding (green) but SLE patient plasma and CSF did not bind



4. Reconstruction of the DWEYS ELISA from the literature did show significant differences between SLE and controls in plasma and CSF

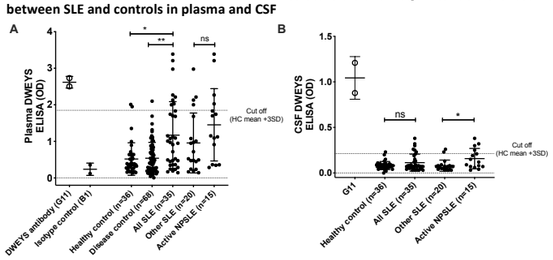


Figure 4. A) Optical density (OD) results from the DWEYS ELISA, using G11 (humanized anti-DWEYS antibody), an isotype control (B1), and plasma from disease controls (n=68), healthy controls (n=36) and SLE patients (n=35), including those with active NPSLE. Significant differences (Kruskal Wallis, post-hoc Dunn's correction) were observed between SLE patients and healthy controls (p=0.0316*) and disease controls (p<0.0085**), but not between active NPSLE and other cases of SLE (ns). Cut-off for positivity (dotted line) represents the mean plus three standard deviations of healthy control values. **B)** From CSFs, the DWEYS ELISA showed no difference between HCs and SLE, and modest significance within a comparison of SLE patients with active NPSLE versus others (p=0.0207, Mann Whitney U test).

5. Using the same ELISA, however, we demonstrated near identical binding in the presence of two different scrambled peptides and no peptide at all – suggesting the antibodies are binding the test plate

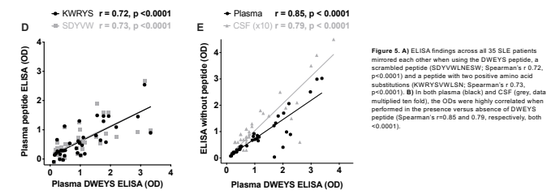


Figure 5. A) ELISA findings across all 35 SLE patients mirrored each other when using the DWEYS peptide, a scrambled peptide (SDYVWLNESW; Spearman's r 0.72, p<0.0001) and a peptide with two positive amino acid substitutions (KWRYSVWLSN; Spearman's r 0.73, p<0.0001). **B)** In both plasma (black) and CSF (grey, data multiplied ten fold), the ODs were highly correlated when performed in the presence versus absence of DWEYS peptide (Spearman's r=0.85 and 0.79, respectively, both <0.0001).

Discussion

The brain disease associated with SLE is not associated with detectable antibodies against neuronal surface proteins, including NMDARs. NPSLE is likely to have alternative pathological drivers. Our findings mandate a search for novel biomarkers in this condition.

Ms. Ana Vasconcelos

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Ana is currently a researcher at the "Synapse Biology" group at the CNC - Center for Neuroscience and Cell Biology, University of Coimbra. She has a master's degree in Cellular and Molecular Biology (University of Coimbra, Portugal, 2020) and a bachelor's degree in Biomedical Sciences (University of Aveiro, Portugal, 2018). Her laboratory studies the cellular and molecular mechanisms that regulate synaptic transmission and synaptic plasticity in the mammalian central nervous system.

She is interested in uncovering how encephalitis-associated autoantibodies targeting synaptic proteins disrupt synapse function and lead to disease. The aim of her research is to uncover the pathogenic mechanisms elicited by antibodies targeting CASPR2 in autoimmune synaptic encephalitis.

Concentration-dependent effects elicited by CASPR2 autoantibodies in the regulation of AMPA receptor trafficking and synaptic plasticity

Ana Vasconcelos*,[1], Dominique Fernandes*,[1], Sandra D. Santos[1], Ester Coutinho[2] & Ana Luísa Carvalho[1,3]

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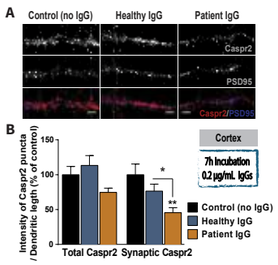
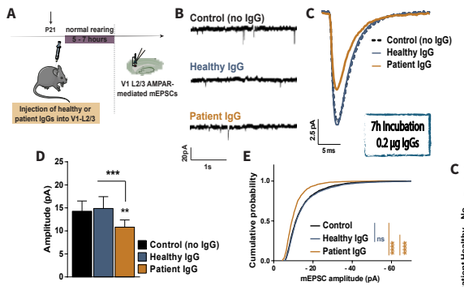
[2]Department of Basic and Clinical Neuroscience, King's College London, UK;
[3]Department of Life Sciences, Faculty of Sciences and Technology, University of Coimbra, Portugal

Previous findings[1]

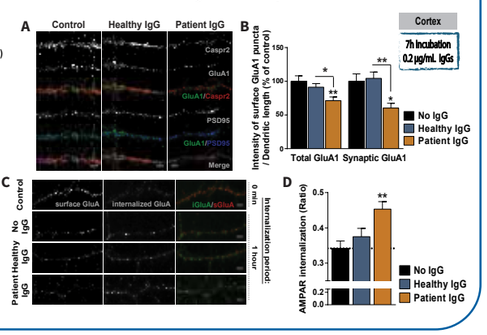
CASPR2 autoantibodies significantly alter the synaptic distribution of Caspr2



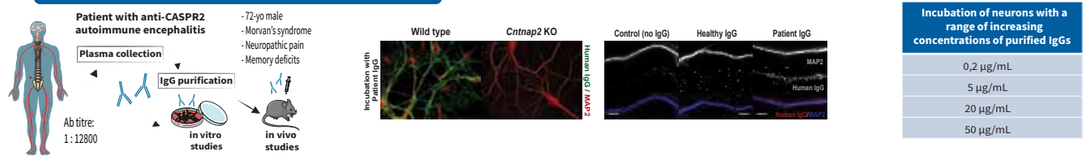
CASPR2 autoantibodies disrupt AMPAR function in vivo



CASPR2-Abs decrease the synaptic expression of surface AMPARs by increasing their endocytic rate

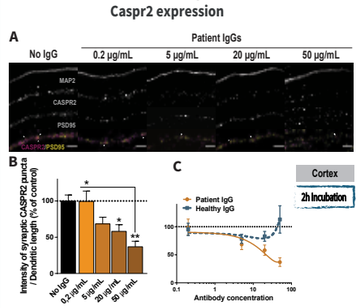


Methodology

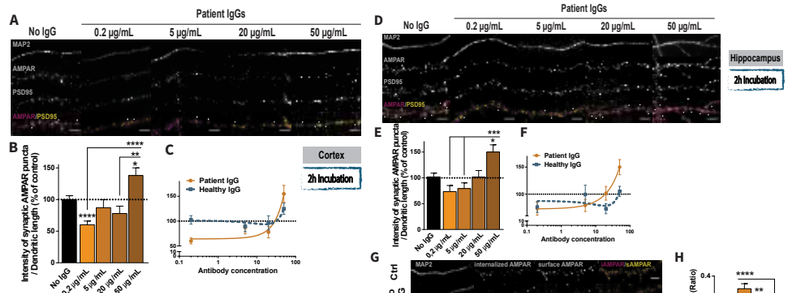


Results

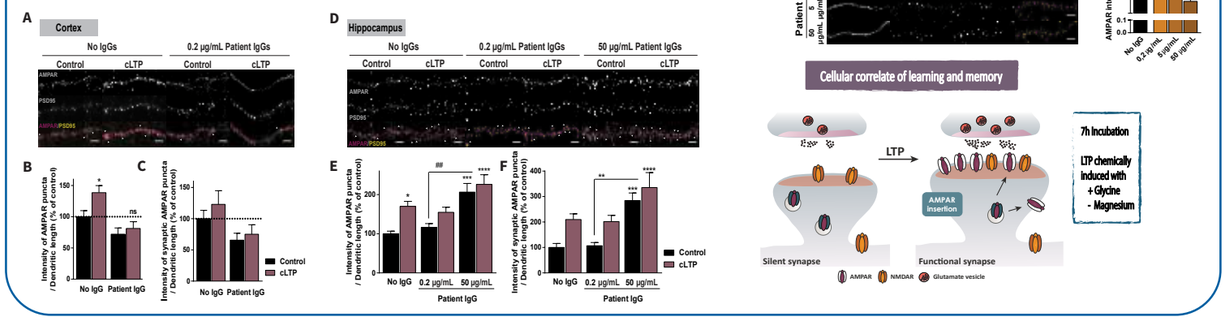
1. CASPR2-Abs elicit a dose-dependent decrease of Caspr2 expression



2. Different concentrations of CASPR2-Abs elicit oposing effects in AMPAR surface traffcking



3.CASPR2-Abs disrupt cLTP-mediated trafficking and surface insertion of AMPARs in a concentration-dependent manner



CASPR2 autoantibodies elicit concentration-dependent effects that perturb the role of CASPR2 in regulating AMPAR trafficking and synaptic plasticity phenomena.
Our findings pinpoint the glutamatergic system as a target for pathogenesis ensuing from an antibody-mediated disruption of CASPR2 function, and elucidate the possible mechanisms driving the cognitive and psychiatric symtopms presented by anti-CASPR2 encephalitis patients.

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References: (1) Fernandes D, Santos SD, Coutinho, E, Whitt JL, Rondão T, Leite MI, Buckley C, Lee HK, Carvalho AL. (2019) Disrupted AMPA receptor function upon genetic or antibody-mediated loss of autism-associated CASPR2. Cerebral Cortex DOI: 10.1093/cercor/bhz032 [Epub ahead of print].

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Juna de Vries, MD, PhD, works as a consulting neurologist at the department of Neurology of the Erasmus University Medical Center Rotterdam. The Erasmus MC serves as the national Academic Center of Excellence for autoimmune encephalitis caused by neuronal antibodies targeted at extracellular antigens (AE). She started her medical training at the Faculty of Medicine of the University Medical Center Utrecht in 1999, and obtained her medical degree in 2006. She temporarily worked as a research physician at the Utrecht Institute for Pharmaceutical Sciences, Division of Pharmacology of Utrecht University. In 2008 she started her PhD concerning the effects and safety of enzyme replacement therapy with recombinant human acid α-glucosidase in Pompe disease under the supervision of Prof. dr. Pieter van Doorn, neurologist and Prof. dr. Ans van der Ploeg, paediatrician, both working at Erasmus MC University Medical Center. In her thesis she also investigated the effect of antibodies against enzyme replacement therapy on treatment efficacy and safety. From 2011 until 2018 she worked as a resident in Neurology at the same center. Her main focus in her daily clinical work is on the care for patients with AE in close cooperation with Dr Maarten Titulaer, Furthermore, she is involved in the care for patients with paraneoplastic syndromes and various other neuro-immunological diseases. She received the AEA Community 2021 Seed Grant for the PROMISE study, a study on the (long-term) clinical outcome and disease burden in patients with AE. Another objective of this study is to develop valid and relevant patient reported outcome measures (PROMs). At the Encephalitis Society 2021 she will present the data of a retrospective cohort study that evaluates the Graus 2016 criteria for seronegative AIE and determines the occurrence of AIE mimics and how to differentiate these from AIE. She started this study in 2018 and Robin van Steenhoven, neurologist has continued the work under guidance of Juna de Vries and Maarten Titulaer.

Mimics of autoimmune encephalitis (AIE): a retrospective cohort study

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Conclusions and implications

- Common mimics of AIE are other CNS inflammatory disorders, primary psychiatric disorders, epilepsy with non-inflammatory etiology, CNS infections and malignant tumors.
- Potential confounding factors are non-specific antibodies (e.g. VGKC positivity in the absence of LGI1/CASPR2 antibodies), false positive cell-based assays and mesiotemporal lesions on MRI.
- Criteria for 'possible AIE' should be regarded as an entry criterion for ancillary testing, and not as a diagnostic category, since specificity for AIE tends to be low.

Introduction

Autoimmune encephalitis (AIE) is an important consideration in the differential diagnosis of acute encephalitis, especially in view of the beneficial response to immunotherapy. In 2016, newly formed clinical criteria for the diagnosis of AIE were proposed. In this study, we introduce a novel diagnosis of 'probable neuroinflammatory disorder (PNID)'.

Aims

- to describe mimics of AIE
- to evaluate the clinical criteria for AIE
- to identify pitfalls in the diagnosis of AIE

Methods

Design: retrospective cohort study, tertiary center (July 2016 - December 2019)

Patients: children and adults with strong suspicion of AIE

Testing: CSF, MRI brain, EEG, extensive antibody testing in serum and CSF when indicated cerebral biopsy

Evaluation: according to clinical AIE criteria (Table 1).

Results

Figure 1 Diagnosis (n=235) AIE mimics (n=78)

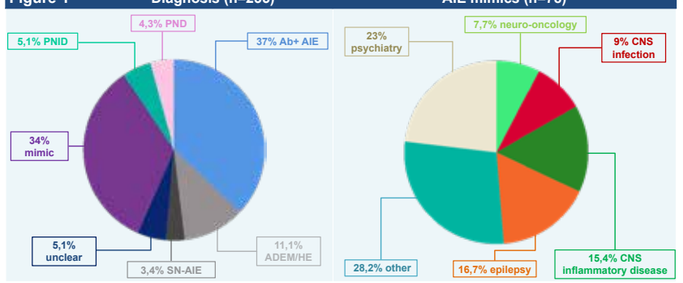


Table 1: Clinical criteria AIE (Graus 2016)

Possible AIE	
I Subacute onset (<3 months) of working memory deficits altered mental status, or psychiatric symptoms	
II ≥ 1 of the following: - new focal CNS findings - new onset seizures - CSF pleocytosis - MRI abnormalities suggestive of encephalitis	
Definite autoimmune LE	**Seronegative AIE**
I Subacute onset (<3 months) of working memory deficits altered mental status, seizures or psychiatric symptoms	
II MRI brain (T2/FLAIR) bilateral temporal lobe abnormalities	II Exclusion of well defined syndromes of AIE
II ≥ 1 of the following: - CSF pleocytosis - EEG abnormalities involving the temporal lobes	III Absence of autoantibodies in serum or CSF IV ≥ 2 of the following: - MRI abnormalities suggestive of AIE - CSF pleocytosis, OCB/ ↑ IgG index - compatible brain biopsy
Probable neuroinflammatory disorder (proposed)	
I Subacute onset (<3 months) of working memory deficits altered mental status, seizures or psychiatric symptoms	
II Not fulfilling the criteria for 'definite autoimmune LE' or 'seronegative AIE'	
III ≥ 2 of the following - pleocytosis - OCB / ↑ IgG index - similair staining pattern on immunohistochemistry in serum and CSF without known antibody - repeated clinically steroid responsiveness	
Reasonable exclusion of alternative causes (all categories)	

Table 2: evaluation clinical AIE criteria

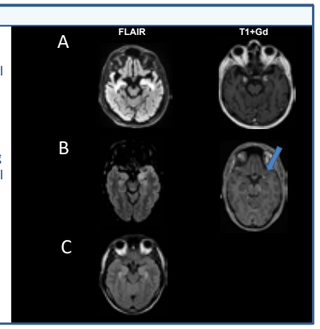
	possible AIE	definite AI-LE	SN-AIE
Ab+ AIE	85,5%	11,5%	0%
PND	90%	0%	0%
SN-AIE	100%	37,5%	100%
PNID	100%	0%	0%
Mimic	72,5%	3,8%	1,3%

Figure 2: Three patients with mimics of AIE

A. 69 year old male patient presenting with rapid progressive dementia. MRI demonstrating bilateral mesiotemporal lobe FLAIR-hyperintensities and parenchymal enhancement in corresponding regions.
Diagnosis: CNS Whipple's disease.

B. 47 year old female patient presenting with generalized seizures, memory disorders and aphasia. MRI demonstrating left mesiotemporal FLAIR-hyperintensity and leptomeningeal enhancement (arrow).
Diagnosis: glioblastoma multiforme (GBM).

C. 27 year old male patient presenting with subacute amnestic syndrome. MRI demonstrating bilateral mesiotemporal lobe FLAIR-hyperintensities.
Diagnosis: 3,4-methyleen-dioxymethamfetamine (MDMA) intoxication.



235 patients were referred, 56% female. The median age was 43 years (range 1-85). 23% of the patients were younger than 18 years at symptom onset. Neuronal antibodies were identified in 87 patients, while 26 patients fulfilled criteria for specific neuro-inflammatory disorders, including acute disseminated encephalo-myelitis (ADEM) and Hashimoto encephalopathy (HE). Seronegative AIE was diagnosed in 8 patients and 78 patients were classified as AIE mimic.
58 (72,5%) and 3 (3,8%) of AIE mimics fulfilled criteria for 'possible AIE' and 'definite autoimmune limbic encephalitis (LE)', respectively. One patient (1,3%) with an AIE mimic was classified as 'probable seronegative autoimmune encephalitis' (Table 2).
Most frequently AIE mimics were CNS inflammatory disorders other than ADEM or HE, primary psychiatric disorders, epilepsy with non-inflammatory etiology, central nervous system (CNS) infections and malignant CNS tumors. Common confounding factors were non-specific antibodies (e.g. anti-VGKC positivity in the absence of LGI1/CASPR2 antibodies), false positive cell-based assays and mesiotemporal lesions on MRI (Figure 2).

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Mr Wondim is a PhD student in Biomedical Research and Biostatistics and works as an assistant researcher.

Mulugeta is the fellow of Marie Curie through the European Unions Horizon 2020 research grant with a project on the molecular characterization of tick-borne encephalitis. His educational background goes back to Ethiopia where he had conducted BSc and Masters degrees in Nursing.

Mulugeta also studied Master of Public Health Methodologies in Belgium at the Université Libre de Bruxelles.

Epidemiological Trends of Trans-Boundary Tick-Borne Encephalitis in Europe, 2000-2019

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Introduction

- Tick-borne encephalitis (TBE) is a viral infectious disease that affects the central nervous system
  - Caused by the Tick-Borne Encephalitis Virus (TBEV)
- It has outcomes of mild to life threatening health conditions[1]
- Transmitted by tick bite and raw milk consumption
- Transmission involves ticks-rodent/animals-human
- Has three common sub-types; European (TBEV_Eu), Siberian (TBEV_Sib), and Far-Eastern (TBEV_FE)
- Two newly found subtypes-Baikalian (TBEV-Blk) and Himalayan (TBEV-Him) [2,3]
- *Ixodes ricinus* carries the TBE-Eu subtypes
- *Ixodes persulcatus* ticks (Siberian and Far-Eastern subtypes)
- *Ixodes ricinus* ticks are prevalent throughout Europe
- The Euro-Asia region is traditionally known for the prevalence of TBE
- TBEV-Eu causes neurological sequelae in up to 10% of cases with a mortality rate of <2%.
- TBEV-Sib causes prolonged infection
- TBEV-FE patients show high rates of neurological sequelae outcomes[3,4]

Factors Affecting TBEV Transmission

- Healthy ticks got infected while co-feeding
- Factors
  - Socioeconomic change, Climate change, Seasonal variations, Altitude
  - Individual characteristics
  - The capacity of ticks to survive harsh conditions
  - Virus can survive morphological changes of ticks
  - Availability of hosts and their interaction with human
    - NB: Surveillance conducted and emerging diagnostic protocols has helped identify more cases [5]

Trans-boudary Migration of TBE

- Recently, the European strain of TBEV has spread into non-endemic areas
- A phylogenetic analysis in Hungary appeared with contents of Finland, Germany, and Russia.
- The TBE-Si is seen in Finland and Estonia
- All subtypes were seen in the Crimean Peninsula
- There are new cases appeared in new places like
  - In 2019 in England and in Germany reappeared after 15 years
- Migratory birds are responsible as a transporter of infected ticks [6,7]

Aim

- To examine the epidemiological trends of TBE, data from European CDC and Poland National Polish National Public Health Institute

Epidemiological Trends of TBE 2000-2019

- The number of countries included across 2000-2019 has increased from 12-25

Table 1. The number of confirmed cases reported to ECDC and the number of countries involved in each year 2000-2019

Year	Number of countries reported	Number of confirmed cases reported
2000	12	2629
2001	14	2497
2002	14	1952
2003	14	3225
2004	14	2481
2005	15	2651
2006	15	3756
2007	15	2267
2008	16	2513
2009	16	3513
2010	16	3155
2012	21	2149
2013	22	2904
2014	24	1985
2015	24	1908
2016	25	2680
2017	25	2916
2018	26	3092
2019	25	3246
Total		51519

Source: Data from ECDC (https://register.ecdc.europa.eu/)

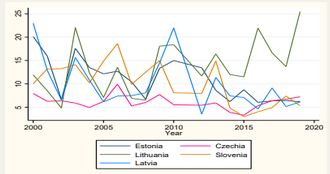

Figure 1. Annual incidence rate of TBE in most affected countries 2000-2019

- The number of cases reported varies with season.
- The number starts to rise in March and got its peak in August and decline in October

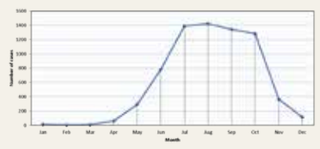

Figure 2. TBE Seasonality: Number of TBE cases by month of onset reported in nine EU/EFTA countries, 2000–2010 (n= 7 883) source: *Data from ECDC (https://register.ecdc.europa.eu/)*

- As age rises the number of cases with TBE also rises
- The likely reason could be
  - vulnerability to infection because of either their declined immunity or vulnerability of being infested by ticks
- People with age >50 years move across Europe without enough awareness about TBE and protecting themselves as compared to the other age groups.

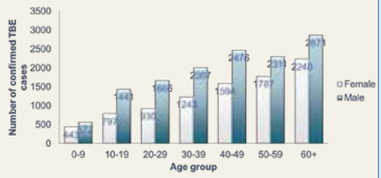

Figure 3. TBE Key risk groups: Number of TBE cases by age group and gender reported in 16 EU/EFTA countries, 2000–2010 (n=22,378). *Source: Data from ECDC (https://register.ecdc.europa.eu/)*

TBE Trend in Poland

- According to the Polish National Public Health Institute, the total number of TBE cases reported from the 16 voivodships of Poland from 1999 to 2019 was 4791.
- Most of the cases were reported from the three eastern and northeastern regions.
- Podlaskie had the most with a 2263 total number of cases that encompasses 47.23% of the total cases reported in the past 21 years.
- The second most affected region that borders Podlaskie in the North is Warminisko-Mazurskie with a case number of 1246 from 1999-2019.

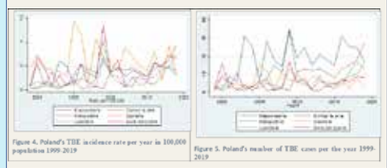

Figure 4. Poland's TBE incidence rate per year in 100,000 population 1999-2019

Figure 5. Poland's number of TBE cases per the year 1999-2019

Conclusion

- The geographical distribution of TBE has been changing over time.
- A combination of climate change, socioeconomic changes, seasonal variation, and individual characteristics like increased age and occupation are key factors for the spread of TBE.
- There was an increasing pattern in the second half of the 1990s, 2000, and after 2015.
- Generally, an integrated public health intervention is important to deter TBE within Europe including vaccination, disease detection, and consider TBE as a travel public health important disease.

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UNIVERSITY OF LIVERPOOL

Development and validation of a clinical scoring system for seizures in encephalitis: analysis and modelling of 436 patients from two independent multi-centre cohorts

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BACKGROUND

Acute seizures in encephalitis are common, associated with worse outcome, and potentially amenable to treatment. However, it is unclear which patients are at greatest risk and therefore may benefit from primary anti-epileptic prophylaxis.

AIM

We aimed to determine the demographic, clinical and investigatory factors associated with seizures in encephalitis and develop a risk-stratification score.

METHODS

We performed an analysis of 203 patients from 24 English hospitals (2005-2008) (Cohort 1). Outcome measures were seizures, inpatient seizures, and status epilepticus. A binary logistic regression risk model was converted to a clinical score and independently validated on 233 patients from 31 UK hospitals (2013-2016) (Cohort 2).

RESULTS

1. ASSOCIATED FACTORS

In Cohort 1, 121 (60%) patients had a seizure including 103 (51%) with witnessed inpatient seizures. Seizures were associated with fever (OR [95%CI] 2·21[1·13-4·34], p=0·019) and aetiology (antibody-associated OR 5.23[1.16-23.7] and herpes simplex virus OR 2.17[0.99-4.75], p=0·003) (Figure 1). Admission Glasgow coma score (GCS) ≤8/15 was predictive of subsequent inpatient seizures (OR 5·55[2·10-14·64], p<0·001), including in those not presenting with seizures (OR 6·57[1·37-31·5], p=0·025). Status epilepticus occurred in 19 (9%) and was associated with fever (p=0·009).

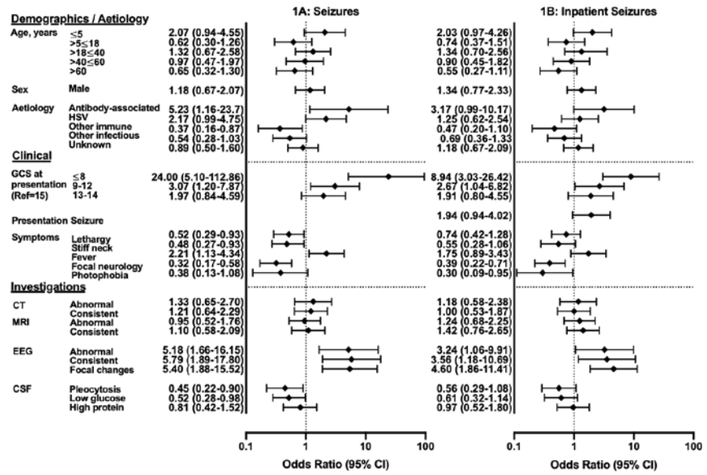

Figure 1: Demographic, clinical and investigatory factors associated with acute seizures in encephalitis

2. OUTCOMES

Although patients with seizures had a shorter pre-admission symptom duration (5[1-12] vs. 9[4-24] days, p=0·01), they had a worse outcome (GOS<5 OR 1·81[1·01-3·23], p=0·04) (Figure 2).

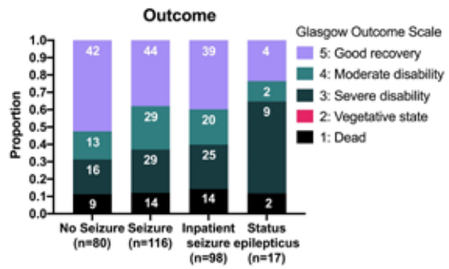

Figure 2: Glasgow Outcome Scale at 6 months stratified by presence and nature of seizures

3. MODEL DEVELOPMENT

A clinical score of seizure risk identified aetiology and admission GCS (AUROC = 0·775 [0·701-0·848]). The same model was validated in Cohort 2 (AUROC = 0·744 [0·677-0·811], p<0·001) (Figure 3). A second clinical scoring system for inpatient seizure risk (SEIZUre Risk in Encephalitis score (SEIZURE score); Figure 4) performed well (AUROC = 0.738 [95% CI: 0.657-0.820]). Of patients with a low-risk score 14/57 (25%) had an inpatient seizure, of medium-risk 22/46 (48%; OR 2·82[1·22-6·49], p=0·015), of high-risk 23/31 (74%; 8·83[3·23-24·14], p<0·001) and of very high-risk 13/15 (87%;19·96[4·00-99·50], p<0·001).

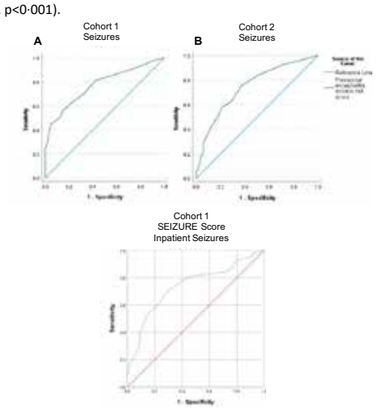

Figure 3: Receivers operating characteristics (ROC) curve for seizure risk according to Provisional encephalitis seizure risk score in derivation cohort (cohort 1) (A), Area under ROC = 0·775 [0·701-0·848], and validation cohort (cohort 2)(B), Area under ROC 0·744 [0·677-0·811]· ROC curve for seizure risk according to SEIZUre Risk in Encephalitis (SEIZURE) score (A) in derivation cohort (cohort 1).

SEIZUre Risk in Encephalitis (SEIZURE) score

Aetiology	Score
Antibody-associated	11
Infection (other)	7
Bacterial	6
Unknown	6
HSV	5
ADEM/ Immune	4
Mycobacterium tuberculosis	3
VZV	0
Glasgow Coma Scale	
3	12
4	11
5	10
6	9
7	8
8	7
9	6
10	5
11	4
12	3
13	2
14	1
15	0
Total Score	
	0-23

SEIZURE score	Probability of inpatient seizure	Odds radio (95% CI)
0-6	25%	-
7-10	48%	2·82 (1·22-6·49)
11-13	74%	8·83 (3·23-24·14)
14-23	87%	19·96 (4·00-99·50)

Figure 4: SEIZUre Risk in Encephalitis (SEIZURE) score based upon aetiology of encephalitis and Glasgow Coma Scale

INTERPRETATION

A small number of variables can effectively stratify acute seizure risk in patients with encephalitis. These findings can support the development of targeted interventions and aid clinical trial design.

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