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Encephalitis Conference 2020

TUESDAY 8TH
DECEMBER 2020
09.00 - 16.45

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Poster Booklet

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I am a neurology trainee in Oxford who completed a year of registrar training in February 2019, and am now taking time out of programme for a full-time DPhil, with the goal of establishing myself as a clinician-scientist. In 2016-2017, I spent a year as an academic clinical fellow (ACF) within the Oxford Autoimmune Neurology Group of the Nuffield Department of Clinical Neurosciences, focusing on clinical and immunogenetic aspects of antibody-mediated encephalitides.

I am joint first author on a research paper about human leucocyte antigen (HLA) associations of these conditions published in Brain, and was awarded Wellcome Trust funding for a DPhil to continue this work. I had previously successfully completed an Academic Foundation Programme (AFP) 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, I graduated first in my cohort at Brighton and Sussex Medical School, obtaining the Professor Alasdair Smith 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. In 2011, I had the honour to be the inaugural first prize winner of the Encephalitis Society national undergraduate essay prize, cementing a professional interest and future clinical and research focus on this condition.

POSTER PRESENTATION

Factors predicting patient quality of life after LGI1-antibody encephalitis

*Binks SNM,[1,2] *Veldsman M,[3] Jacob S,[4] Maddison P,[5] Coebergh J,[6] Michael S,[1] Ramanathan S,[1,7] Easton A,[8,9] Scheller Nissen M,[10] Blaabjerg M,[10] Leite M Isabel,[1,2] Okai D,[11] *Husain M,[3,12] + Irani SR[1,2]

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Introduction

Leucine-rich glioma-inactivated 1 (LGI1)-antibody encephalitis presents with cognitive deficits and frequent seizures, with inflammation centred on the hippocampus.[1-4] It is a rare (1 per million/year in the UK) but treatable cause of cognitive decline in predominantly middle-aged and older men.

Although an early immunotherapy response in LGI1-antibody encephalitis is well documented, the question has been asked as to whether long-term outcomes are "good enough".[1, 3-7] The LGI1-QoL study has collected detailed cognitive, neuropsychiatric and quality of life (QoL) data on 60 patients. Assessments selected include validated instruments to examine aspects clinically observed as important to our patients, such as fatigue, mood, and emotional regulation.

Patient population

Table 1: Demographics of LGI1-QoL Cohort

Number of patients	60
Male : Female	40 (66%) : 20
Age at time of assessment / years	Range 44-92, mean 69, median 70
Time since onset / months	Range 4 – 179, mean 56, median 41

The LGI1-QoL assessment battery

Table 2: Study assessments and key domains probed by each

Mini-mental state examination (MMSE)	Cognition
Frontal assessment battery (FAB)	Executive function
Addenbrooke's cognitive examination (ACE)	Cognition
Pathological laughter & crying scale	Emotionality
Hospital anxiety and depression scale (HADS)	Affective disorder
Neuropsychiatric inventory questionnaire (NPIQ)	Carer-rated behaviour
Fatigue scale for motor and cognitive functions (FSMC)	Fatigue
Modified Fatigue Impact Scale (MFIS)	Fatigue
EQ5D5L – visual & numeric (index) scale (pre- & post-illness)	Quality of Life
Life Satisfaction Questionnaire (LSQ) (pre- & post-illness)	Quality of Life
Modified Rankin Scale (mRS)	Disability
Clinical Assessment Score for Autoimmune Encephalitis (CASE)	Disability

LGI1-antibody cohort deficits vs normative values

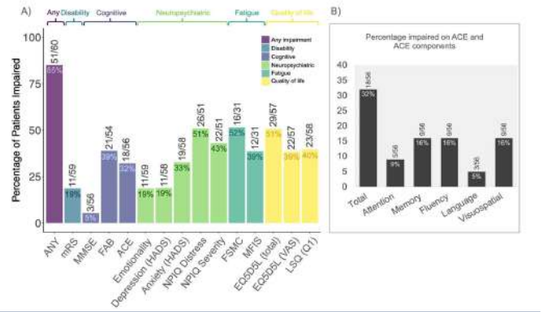


Figure 1. Impairments in the LGI1-antibody cohort, compared to age-appropriate normative values from the literature

- 85% of patients were impaired on any single measure (**Figure 1A**)
- Percent impaired on single tests ranged from 5% (MMSE) to 52% (FSMC)
- Carer distress was present in 51% of spouses or relatives surveyed
- Within cognitive screening (**Figure 1B**), memory, fluency and visuospatial capabilities were more greatly impacted than attention or language

Functional recovery but decline in QoL after LGI1-antibody encephalitis

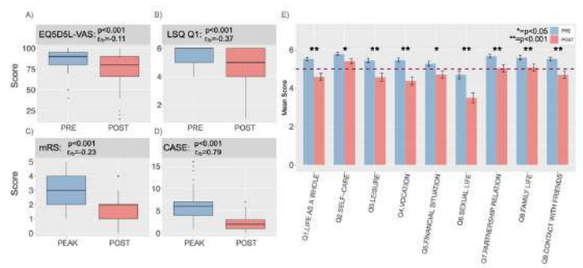
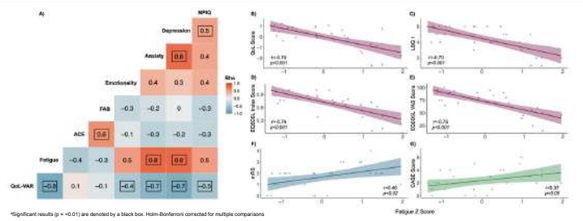


Figure 2 A-D: Box and whiskers plots of pre- to post-illness scores in QoL measures EQ5D5L-VAS (A) and LSQ-Q1 (B), and of peak to post-illness scores in functional outcomes mRS (C) and CASE (D). **Figure 2 E:** Bar chart showing pre- to post-illness scores in all components of the LSQ. Dashed line represents threshold for impairment. P values calculated using Wilcoxon signed rank nonparametric test, Holm-Bonferroni corrected

Peak to post-illness scores in clinician-rated functional outcomes (mRS and CASE) confirmed significant functional recovery (**Figure 2C-2D**). By contrast, the two patient-rated QoL measures (EQ5D5L-VAS and LSQ; **Figure 2A-2B and E**) showed a significant deterioration of QoL from pre- to post-illness.

Fatigue, mood and carer-rated outcomes correlate with QoL in single regression analysis



*Significant results (p < +0.01) are denoted by a black box. Holm-Bonferroni corrected for multiple comparisons

Figure 3. Correlations between outcomes in the LGI1-antibody encephalitis patient assessments. A: Diagram of single correlations (R values, Pearson's correlation) across patient-reported outcome measures. B-G. Correlations between fatigue and patient- and clinician-rated outcomes.

Single correlation analysis revealed several significant correlations, in particular between a composite measure of the three patient QoL measures (termed QoL-VAR) and the following: fatigue Z-score (r=-0.78), depression (r=-0.74), anxiety (r=-0.67), the NPIQ (r=-0.48) and emotionality (r=-0.43) (**Figure 3A**). Fatigue correlated significantly with both patient and clinical-rated outcome measures (**Figure 3B-G**).

Fatigue predicts QoL after LGI1-antibody encephalitis

To explore these relationships further, multiple regression analysis was performed. The model was adjusted for multiple collinearity and included the variables of age, time to immunotherapy, mood and months since onset. In this adjusted model, only fatigue (p=0.025) and the FAB (p=0.033) emerged as significant factors predicting QoL after LGI1-antibody encephalitis. A stepwise regression model was subsequently performed to confirm the finding. In this model, only the fatigue Z-score remained a significant predictor.

Finally, as the complete research assessment battery took ~3 hours to administer, its core components which best explained the QoL outcome were distilled. From exploratory factor analysis, most variance could be captured by five of the instruments: ACE, HADS, CASE, MFIS and EQ5D5L-VAS, cumulatively, taking ~30 minutes to complete.

Conclusions

- Detailed testing reveals deficits in almost all (85%) LGI1-antibody encephalitis patients in the recovery phase, despite a 'good' mRS score (mean post-illness score 1.6)
- Fatigue is the main predictor of long-term QoL in this cohort
- A simple battery of five tests, suitable for the clinic setting, can detect most of the post-acute phase variance after LGI1-antibody encephalitis

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References for study assessments and normative values available on request by e-mail to Dr Binks.

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ODENSE AUTOIMMUNE ENCEPHALITIS RESEARCH GROUP

Real-life use of the Cunningham Panel™ in a Danish cohort

SDU University of Southern Denmark

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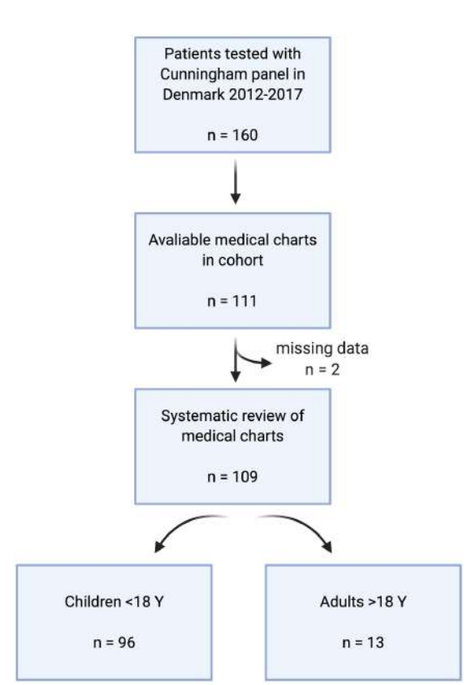
BACKGROUND

Anti-basal ganglia antibodies and calcium calmodulin dependent kinase II activity (CaMKII-activity) have been implicated in Sydenham's chorea (SC), Encephalitis lethargica (EL) and more recently, Pediatric autoimmune neuropsychiatric disorder associated with Streptococcal infections (PANDAS) and Pediatric acute-onset neuropsychiatric syndrome (PANS). The Cunningham Panel™ measures five components (Antibodies towards Dopamine D1 receptor, Dopamine D2 receptor, Lysoganglioside GM1, and Tubulin and activity of CaMKII) and have been used in the diagnostic process. We investigated clinical relevance of the Cunningham Panel™, and its usefulness as a diagnostic tool or treatment guide.

METHODS

From 2012 to 2017, 160 patients were tested with the Cunningham Panel™ through the national antibody testing facility (Statens Serum Institute) in Denmark. We were able to obtain medical charts from 111 of these patients. Two cases had to be excluded due to missing data. The remaining 109 charts were systematically reviewed, registering general demographic, symptoms, ancillary testing including Cunningham Panel™ results. Based on these data the diagnosis was assessed and predictive values, sensitivity and specificity calculated.



CONCLUSIONS:

Our results indicate that in a real-life setting and even in a selected cohort of patients, the Cunningham Panel™ is not a good tool to aid diagnosis of PANDAS/PANS due to its low specificity and low PPV.

In our cohort, it did not add much to the diagnostic certainty compared to clinical evaluation, brain imaging and exclusion of other possible causes.

RESULTS

Demographics of the investigated cohort (*n* = 109)

Sex	Number of patients	Average age (range years)
Children	95	9 (0,5 -18)
Boys	56	8 (1-17)
Girls	39	10 (0,5 -18)
Adults	13	46 (19-69)
Males	5	44 (29-62)
Females	8	48 (19-69)

Number of positive tests of the Cunningham Panel™ (*n* (%))

Group	Neg.	1 Pos.	2 Pos.	3 Pos.	4 Pos.	5 Pos.
All	15 (14%)	36 (33%)	26 (24%)	16 (15%)	11(10%)	5 (5%)
Children	15 (16%)	31 (33%)	24 (25%)	11 (12%)	10 (11%)	4 (4%)
Boys	13 (23%)	20 (36%)	9 (16%)	6 (11%)	5 (9%)	3 (5%)
Girls	2 (5%)	11(28%)	15 (38%)	5 (12%)	5 (13%)	1 (3%)
Adults	0 (0%)	5 (38%)	2 (15%)	4 (31%)	1 (8%)	1(8%)
Males	0(0%)	4 (80%)	0 (0%)	1 (20%)	0 (0%)	0 (0%)
Females	0(0%)	1(13%)	2 (25%)	3 (38%)	1(13%)	1(13%)

Specific positive tests of the Cunningham Panel™ (*n* (%))

Group	CaMKII	Tubulin	D1	D2	LysGM1
All	84 (77%)	49 (45%)	33 (30%)	18 (17%)	23(21%)
Children	72 (76%)	42 (44%)	27 (28%)	14 (15%)	19(20%)
Boys	39 (70%)	22 (38%)	16 (27%)	6 (11%)	10(18%)
Girls	33 (85%)	20 (51%)	11 (28%)	8 (21%)	9(23%)
Adults	11 (85%)	6 (46%)	6 (46%)	4 (31%)	3 (23%)
Males	3 (60%)	3 (60%)	1 (20%)	0 (0%)	0 (0%)
Females	8 (100%)	3 (38%)	5 (63%)	4 (50%)	3 (38%)

Diagnosis based on diagnostic criteria after review of charts

Diagnosis	Number and sex	Average age
PANDAS	10 (7 male; 3 female)	9
PANS	5 (2 male; 3 female)	11
PANDAS & PANS	10 (5 male; 5 female)	7
Sydenhams chorea	4 (2 male; 2 female)	15

Positive tests on the Cunningham Panel™ based on diagnosis

Group	Neg.	1 Pos.	2 Pos.	3 Pos.	4 Pos.	5 Pos.
PANS	1 (20%)	2 (40%)	1 (20%)	1 (20%)	0 (0%)	0 (0%)
PANDAS	2 (20%)	2 (20%)	3 (30%)	0 (0%)	1 (10%)	2 (20%)
PANDAS & PANS	0 (0 %)	3 (30%)	3(30%)	3 (30%)	1(10%)	0 (0%)
Sydenhams Chorea	0 (0 %)	1 (25%)	2 (50%)	1 (25%)	0 (0 %)	0 (0 %)

Predictive values, sensitivity and specificity

PANDAS and/or PANS	PPV	Sensitivity	Specificity
Any Positive	27,5%	88%	17%
At least 2 positive tests	30,6%	60%	51,4%
At least 3 positive tests	32%	32%	75,7%
At least 4 positive tests	28,5%	16%	85,7%
	NPV	**Sensitivity**	**Specificity**
Negative Cunningham for excluding PANDAS and/or PANS	80%	80%	88%

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Iona graduated from Sussex University in 2012 with a 1st class degree in Medical Neuroscience. She spent a number of years working for the charity Rethink Mental Illness before settling into the field of research. Iona now works for the SINAPPS research group at the Department of Psychiatry, University of Oxford investigating the role of inflammation in psychosis. She is based in Exeter, Devon and coordinates recruitment in the South West of England. She is also a member of the Devon Partnership NHS Trust Research and Development team supporting other studies.

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Illness history and time to antibody testing in psychosis patients with anti-neuronal membrane antibodies

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Background

- Autoantibodies to neuronal cell surface receptors are considered pathogenic in autoimmune encephalitis and antibody-targeted immunotherapy has proved to be an effective treatment.[1]
- Psychiatric symptoms are common in the early phase of the disease[2] and cases of such antibodies have now been reported in purely psychiatric presentations where there is no progression to the neurological symptoms of encephalitis.[2]
- Antibodies were found in 8.8% of patients with first episode psychosis (FEP) compared with 4% in healthy controls.[2] The ongoing PPiP2 study is investigating prevalence in a broader group of patients with acute psychosis.
- We aim to investigate antibody prevalence in FEP and recurrent psychosis patients and association with time to antibody testing to further establish any characteristics of antibody positive cases of psychosis.

Methods

Participants 16-70 years old with acute psychosis lasting no longer than two years and without coexisting neurological disease were recruited in in 43 NHS mental health trusts across England.

Serum samples were tested via Live cell-based assays for NMDAR, LGI1, CASPR2 and GABA-A antibodies. Demographic data was collected including illness history and number of days between onset of symptoms and antibody testing (time to antibody testing).

Chi square tests were used to test difference in antibody prevalence between FEP and recurrent Psychosis and associations between serum test result (positive or negative) and time to antibody test. Significance level was set at p=0.05.

Results

	First Episode n= 1137 (57.6%)	Recurrent Psychosis n= 838 (42.4%)	p value
	n (%)	n (%)	
Age			
Mean (SD)	30 (12.06)	36.9 (13.11)	<0.001*
Median (range)	27 (16-70)	35(18-71)	
Sex			
male	661 (58.2%)	512 (61.3 %)	0.16**
female	474 (41.8%)	323 (38.7%)	
Ethnicity			
Black	120 (10.6%)	104 (12.4%)	0.09**
Aisan	118 (10.5%)	70 (8.5%)	
White	774 (68.5)	596 (71.4%)	
Mixed White and Aisan	13 (1.1%)	5 (0.6%)	
Mixed White and Black	35 (3.1%)	18 (2.1%)	
Other mixed background	15 (1.3%)	7(0.8%)	
Other Ethnic Group	19 (1.7)	21 (2.5%)	
Not stated	29 (2.6%)	13 (1.6%)	

Table 1. Demographics of FEP patients compared with recurrent psychosis patients.

	FEP n=1137	Relapse n=838	P value
Positive antibody test result	64 (5.6%)	49 (5.8%)	0.84**

Table 2. Prevalence of antibodies in FEP and recurrent psychosis patients.
*** t test ** chi square test**

- Data was collected for 1975 participants with acute psychosis. We identified 113/1975 (5.7%) participants with at least one antibody of interest.
- A significant difference was found in mean age 30 (SD 12.06) vs 36.9 (SD 13.11), p<0.001 between FEP and recurrent groups (table 1).
- No difference was found in prevalence of anti-neuronal antibodies between FEP (n=64/1137, 5.6%) and recurrent groups (n=49/838, 5.8%), p=0.84 (table 2).
- No difference was found in prevalence of antibodies between participants who were tested earlier in their illness and participants tested later (p=0.47) (figure 1).

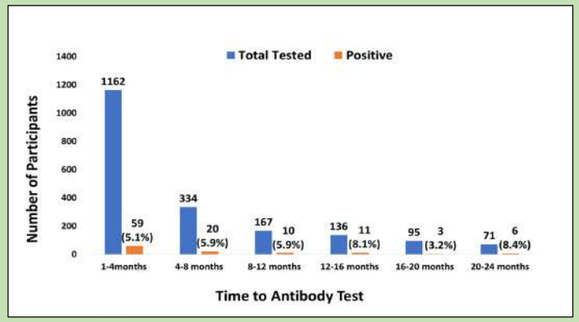

Figure 1. Number of tested and antibody positive participants grouped by time to antibody test.

Discussion

- Antibodies were found in 113/1975 (5.7%) participants with acute psychosis. The prevalence rate is in line with previous findings in FEP cohorts [3,4] although our sample was larger and included patients with recurrent psychosis.
- Prevalence of antibodies was similar in FEP and recurrent psychosis suggesting antibody testing may be equally relevant for both groups.
- 1162/1975 (59%) of study participants were tested within four months of symptom onset however there was no association found between prevalence of antibodies and time to testing. This may encourage testing of patients who have not responded to antipsychotics even if in a later phase of their psychosis episode.
- A limitation of this study is antibody testing at a singular time point. Testing at regular time intervals might help further understand the relationship between antibodies and psychosis symptoms.
- The results emphasise the importance of widespread antibody testing in psychosis patients. The ongoing SINAPPS2 trial investigating immunotherapy vs placebo in antibody-associated psychosis [5] is crucial for confirming the pathogenicity of these antibodies in a substantial number of patients for whom antibody-targeted treatments could have significant implications.

References

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Arielle Coughlin is a second year medical student at the Icahn School of Medicine at Mount Sinai. She received her BA in Biology from Columbia University. At Columbia, she conducted research on cytoskeletal dynamics in the Department of Cell Biology. She later worked as a clinical coordinator in the Division of Nephrology, where she was part of a research team studying the genetic causes of kidney disease. Since matriculating to medical school at Mount Sinai, she has been involved in neurology research investigating the burden of seizures in autoimmune encephalitis, under the mentorship of Dr. Anusha Yeshokumar and Dr. Nathalie Jette.

Seizures in Autoimmune Encephalitis: A Systematic Review

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OBJECTIVES

To study the prevalence of seizures and demographics in different types of autoimmune encephalitis (AE).

INTRODUCTION

AE refers to a group of diseases caused by autoantibodies against various neuronal receptors or cell surface proteins that result in a broad range of symptoms, including seizures, cognitive deficits, and psychiatric symptoms.

This study aims to improve the understanding of the clinical burden of seizures in AE.

METHODS

- PRISMA standards were followed.
- Databases: PubMed (Medline All), Embase, and PsychINFO from inception to June 7, 2019.
- Eligibility criteria: studies reporting seizure(s) and/or EEG data in ≥10 AE patients.
- Data collected: demographics, antibody type, seizures, and EEG findings.
- Abstract/full text review and data extraction were performed in duplicate.
- We performed descriptive analysis, logistic regression, and Chi-square analyses by antibody subtype.

RESULTS

- Of 3,856 abstracts reviewed, 1,616 underwent full text review, and 123 studies met full eligibility criteria **(Fig 1)**.
- Seizure data were available for 3,147 individual patients; 779 had demographic data and 1,962 had EEG data available.
- For patients with all AE subtypes and in the anti-NMDA receptor encephalitis (anti-NMDARE) subpopulation, seizures were more common in younger patients ($p<0.05$) **(Fig 3)**.
- For all AE subtypes, seizures were more common in males ($p=0.03$). There was no significant difference in sex for the anti-NMDARE or anti-LGI-1 subpopulations.

Figure 1: Screening for Study Inclusion

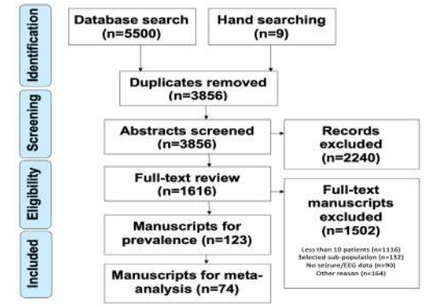


Table 1: Demographics for Patients with AE Subtypes with More Than One Manuscript Reporting Data

Antibody Type (n = # of Patients with Demographic Info)	# of Manuscripts Reporting Demographic Info	Age (years, Mean ± Standard Deviation)	Percent Female (%)
All Subtypes (n=779)	74	40.4 ± 23.6	52.80%
Anti-NMDAR (n=314)	23	20.8 ± 14.6	67.80%
Anti-LGI-1 (n=151)	11	57.2 ± 14.4	36.40%
Anti-GABA-B (n=99)	8	59.8 ± 11.8	30.3%
Anti-CASPR-2 (n=23)	3	63 ± 7.8	4.3%
Anti-VGKC* (n=43)	6	50.7 ± 23.2	39.5%
Anti-TPO or Anti-TG (n=49)	5	47.2 ± 18.1	79.6%
Anti-GAD-65 (n=28)	4	12.1 ± 13.9	50%
Anti-Glycine Receptor (n=16)	2	40.4 ± 16.4	75%
Anti-AMPA (n=13)	2	57.7 ± 13.7	76.9%

*Further Classification as LGI-1 or CASPR-2 not available
Abbreviations: NMDAR=N-methyl-D-asparate receptor, LGI-1= Leucine-rich Glioma-Inactivated 1, GABA-B= γ-Aminobutyric Acid-B, CASPR-2= Contactin Associated Protein 2, VGKC= Voltage-Gated Potassium Channel, TPO= thyroid peroxidase, TG= thyroglobulin, GAD-65= Glutamic Acid Decarboxylase, GFAP= Glial Fibrillary Acidic Protein, AMPA= Alpha-amino-3-hydroxyl-5-Methyl-4-isoxazolepropionic Acid

Figure 3: Prevalence of Clinical Seizures by Age Group

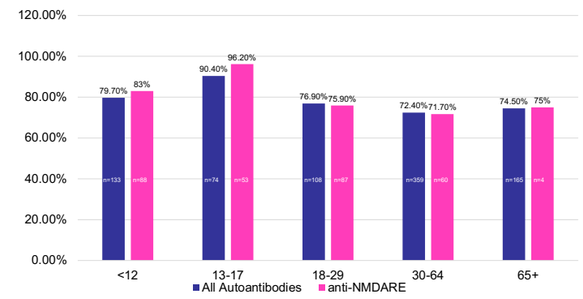
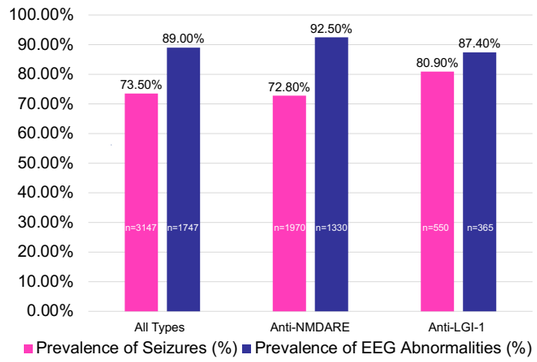


Figure 2: Prevalence of Clinical Seizures and EEG Abnormalities in AE

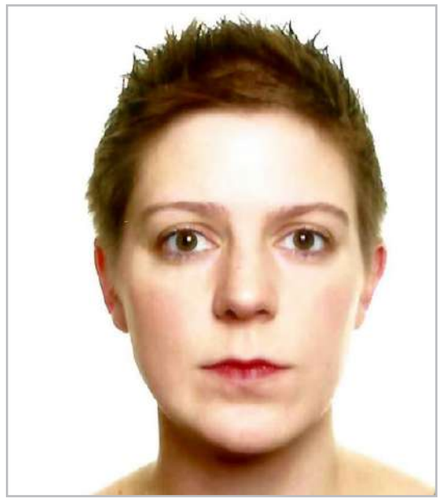


CONCLUSIONS

- Results of this systematic review provide an estimate of the prevalence of seizures in AE, confirming the magnitude of seizure burden in this population.
- Prospective studies are needed to identify factors associated with seizures and to evaluate the role of particular EEG findings as biomarkers of seizures and outcomes in AE.

FUNDING & CONTACT INFO

- AKY receives American Epilepsy Society funding, NJ holds the Professor of International Medicine Chair, Icahn School of Medicine, Dept of Medical Education provided funding
- Contact: arielle.coughlin@icahn.mssm.edu



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Adult-onset Rasmussen Encephalitis: An Association with Systemic Autoimmune Disorders?

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Background

Rasmussen encephalitis is a rare chronic inflammatory disease characterised by **gradual focal cortical atrophy**, **intractable focal-onset seizures**, and **progressive neurological deterioration**. While it predominantly affects children, it can also present later in adult life. The pathogenesis remains unclear, although it is believed to be linked to a cytotoxic T-cell mechanism with a potential contribution by autoantibodies. Treatment options are limited to antiepileptic drugs, immunomodulatory therapy, or surgery. However, there remains debate in the literature as to the association of Rasmussen encephalitis with other autoimmune diseases and the effect of immunomodulatory therapy.

Methodology

We hereby report two cases of adult-onset Rasmussen encephalitis associated with an inflammatory bowel disease, followed by a systematic literature review.

Case 1: 69 year-old woman

- Presentation: Refractory focal-onset seizures and *epilepsia partialis continua* from the age of 52yrs, accompanied by a progressive-onset left-sided hemiparesis, hemianopsia, neglect and cognitive deterioration.
- EEG: Seizures originating in the right mesio-postero-temporal regions
- MRI: Right mesio-postero-temporal atrophy
- PET-CT: Hypermetabolic segment in the left iliac fossa, highly suggestive of an **inflammatory bowel disease**.
- Treatment: Corticosteroids and azathioprine.
- Outcome: Gradual weaning of her antiepileptic medication and seizure freedom for the past 5yrs.

Case 2: 59 year-old woman

- Presentation: Drug-resistant complex partial seizures and *epilepsia partialis continua* from the age of 47yrs, who went on to develop a mixed aphasia, ideomotor and visuo-constructive apraxia, right-sided hemianopsia and neglect.
- EEG: Seizures originating in the left tempo-parietal area
- MRI: Left tempo-parietal atrophy
- Past medical history of **Crohn's disease** since the age of 31yrs for which she was treated with corticosteroids, azathioprine, and infliximab.
- Outcome: Corticosteroids had a transient beneficial effect on seizure frequency. The patient however died at the age of 59yrs following urinary sepsis due to an infected perianal fistula.

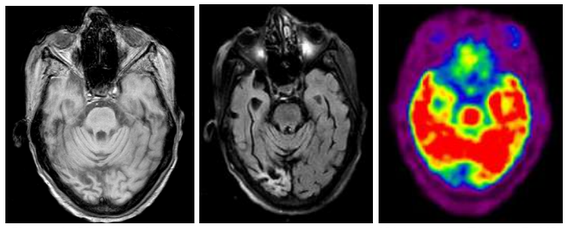

Figure 1: Right mesio-postero-temporal atrophy on MRI imaging (T1 and FLAIR sequences) and corresponding hypometabolic activity on FDG-PET.

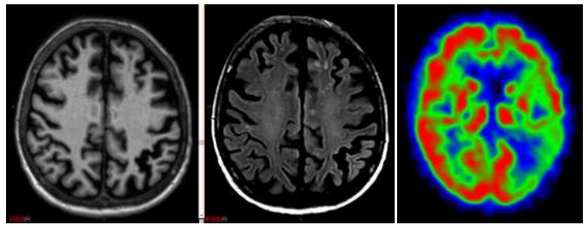

Figure 3: Left tempo-parietal atrophy on MRI imaging (T1 and FLAIR sequences) and corresponding hypometabolic activity on FDG-PET.

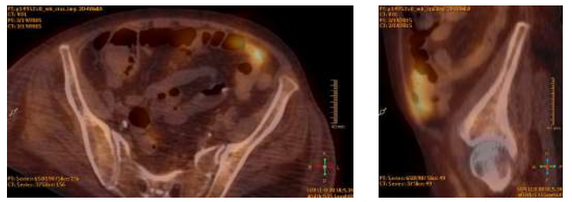

Figure 2: FDG-PET/CT imaging showing a hypermetabolic segment in the left iliac fossa, highly suggestive of inflammatory bowel disease.

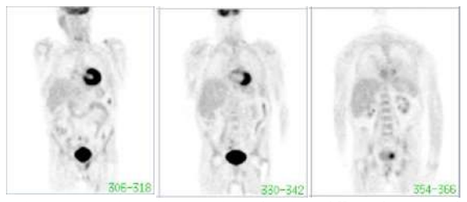

Figure 4: FDG-PET/CT imaging showing diffuse hypermetabolism along the transverse and left descending colon up to and including the peri-anal region.

Discussion

These cases illustrate the possible association of adult-onset Rasmussen encephalitis with a systemic autoimmune disorder and the potential beneficial effects of immunotherapy. Although other such cases have been described in the literature, a specific association with autoimmune diseases or autoantibodies has not yet been found. However, there is evidence that immunomodulatory therapies (including intravenous immunoglobulins, plasmapheresis and steroid therapy) may improve outcome in 61% of adult-onset Rasmussen encephalitis, even when performed at a late stage. This favours the idea of an immune-mediated process, with promising new therapies including those reducing T-cell entry into the CNS.

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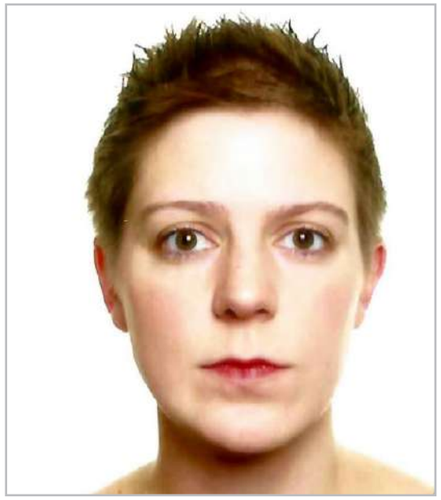

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Peripartum GAD65 Antibody-associated Autoimmune Encephalitis: A Case Report and Literature Review

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Background

Autoimmune limbic encephalitides rarely presents during or after pregnancy. They pose a real diagnostic challenge, with the main differentials being (pre)-eclampsia and perinatal psychosis. Furthermore, little data exists to guide treatment, adding to the complexity of the management of these cases, with potential repercussions on both mother and child.

Methodology

We hereby report a case of GAD65 antibody-associated encephalitis occurring during the last trimester of pregnancy, followed by a literature review.

Case: 26 year-old primiparous woman at 32-weeks of gestational age

Clinical presentation

She initially presented to the emergency department due to fatigue, loss of appetite, hand tremor and recurrent pre-syncopal events. She then went on to have recurrent tonic-clonic seizures, prompting the need for an emergency caesarean section. Despite this, she continued to have **refractory seizures**, needing rapid escalation of anti-epileptic drugs (AEDs) to include lorazepam, levetiracetam, lacosamide and sodium valproate. Over the subsequent weeks, she developed **anterograde amnesia**, **fluctuating behavioural changes**, **cerebellar ataxia** and **downbeat nystagmus**.

Investigations:

- Brain MRI: Right mesial-temporal and temporo-parietal hyperintensities on DWI and FLAIR imaging without contrast enhancement.
- FDG-PET/CT imaging: Hypermetabolism in the right hemisphere and left cerebellar cortex with no evidence of systemic neoplasia.
- EEG: Generalised slowing, with seizures starting in the right temporal lobe.
- Lumbar puncture: CSF-specific oligoclonal bands and intrathecal synthesis of IgG.
- GAD65 antibodies: 519280 IU/ml in serum; 10680 IU/ml in CSF.

►Diagnosis of GAD65 Antibody-associated Autoimmune Encephalitis

Treatment:

She received prompt treatment with high-dose pulse intravenous **methylprednisolone**, followed by two cycles of **rituximab** therapy.

Follow-up:

At 6-month follow-up, she has recovered well. She no longer has any cerebellar ataxia or nystagmus. She retains some cognitive difficulties (maintaining attention, usage of working memory, forward planning). She is now on three AEDs, including levetiracetam, lacosamide and sodium valproate, the latter being weaned progressively.

The baby, born prematurely, is in good health.

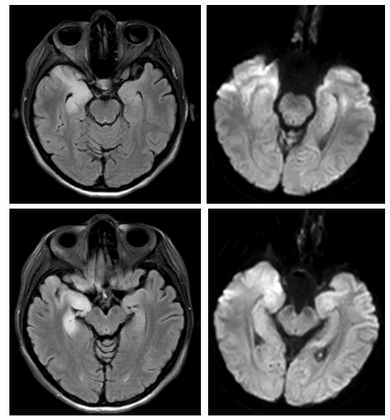

Figure 1: Right mesial-temporal and temporo-parietal hyper-intensities on FLAIR (left) and DWI (right) MRI-imaging.

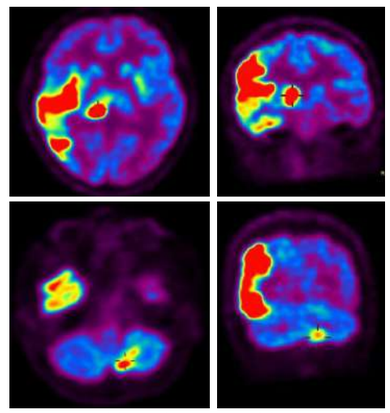

Figure 2: Hypermetabolism on FdG-PET/CT imaging of the right temporo-parieto-occipital region, the right thalamus and putamen, and the left cerebellum.

Discussion

To the best of our knowledge, this is the first reported case of a GAD65 antibody-associated encephalitis occurring in the peripartum period. **GAD65 antibodies** are known to be associated with diverse neurological syndromes, including **limbic encephalitis** (characterised by the presence of focal and secondary generalized seizures, memory impairment and psychiatric or behavioural symptoms), **cerebellar ataxia**, and **stiff-person syndrome**. Other cases of autoimmune encephalitis have been described during pregnancy, mainly with anti-NMDAR antibodies. The underlying mechanism is unclear, although hormonal and/or immunomodulatory effects during pregnancy may act as potential trigger for such autoimmune processes. Early diagnosis is however key to initiate prompt immunosuppression so as to limit long-term sequelae. A close collaboration between obstetricians, anaesthetists, neurologists and psychiatrists is of the utmost importance to offer the best care for these patients.

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EXPANDING THE CLINICAL SPECTRUM OF ANTI-GFAP ASTROCYTOPATHY: SEVERE MENINGOENCEPHALOMYELITIS WITH REMAKABLE HYPEREKPLEXIA, MYOCLONUS AND STIFFNESS

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INTRODUCTION

The autoimmune glial fibrillary acidic protein (anti-GFAP) astrocytopathy has been recently described as the cause of a wide range of manifestations at the central nervous system, especially meningoencephalomyelitis that usually responds to glucocorticoids.

Our aim is to expand the phenotype that has been described to the date by reporting a case with new clinical findings.

MATERIAL/METHODS

- Case report.
- Review of literature.

RESULTS

A 20-year-old man with past medical history of severe depression consults to the emergency room after 1-week of progressive development of headache, fever, weakness and unsteady gait. His parents also remark that he has an **exaggerated startle response every time they touch him, or he hears a sound**. The patient undergoes a lumbar puncture (figure 1). He is admitted to the Infectious Diseases Department, but in few hours he is rapidly transferred to the Intensive Care Unit due to clinical deterioration with agitation and presentation of approximately 20 episodes of **sustained, conjugate and upward deviation of the eyes accompanied by cephalic hyperextension.** Figure 1 summarizes the clinical course.

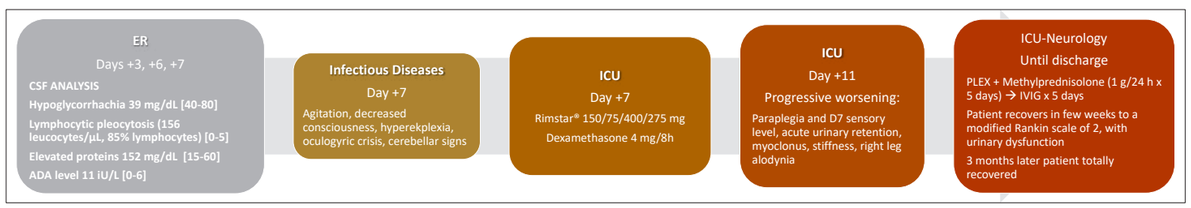

Figure 1. Clinical course after admission into the hospital

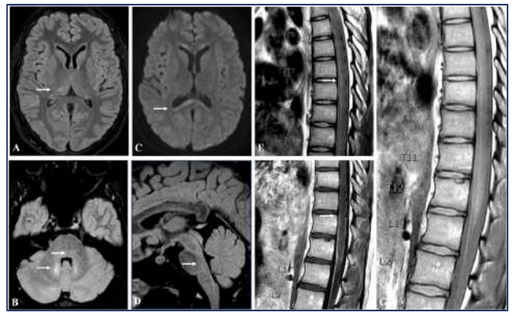

Figure 2. **MR image of brain and medulla.** Lesions at thalamus, corpus-callosum, dorsal pons and dentate nucleus with D7-D9 and D11-D12 myelitis.

Table 1 describes the full clinical phenotype. MRI of the brain and medulla is performed (Figure 2). After extending the analysis of a new CSF sample, testing for infectious diseases and onconeural and neuronal surface antibodies were negative. Indirect immunofluorescence assay revealed a characteristic pattern, indicative of a possible GFAP astrocytopathy (Figure 3).

Screening for a systemic tumor (blood tests, CT of cervical-thoracic-abdominal-pelvic regions and testicular echography) results negative.

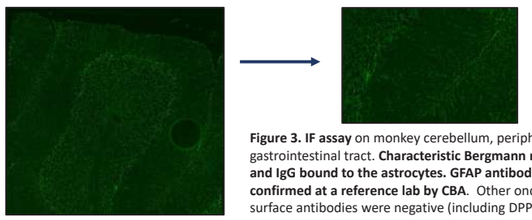

Figure 3. IF assay on monkey cerebellum, peripheral nerve and gastrointestinal tract. **Characteristic Bergmann radial pattern and IgG bound to the astrocytes. GFAP antibodies were confirmed at a reference lab by CBA**. Other onconeuronal or surface antibodies were negative (including DPPX and Gly-R).

DISCUSSION

To our knowledge, this is the first description of CNS **hyperexcitability with hyperekplexia, myoclonus and stiffness** as part of the clinical spectrum of autoimmune GFAP astrocytopathy. Other immune mediated syndromes, such as DPPX antibody-associated encephalitis and Antiglycine-receptor (Gly-R) encephalomyelitis include these clinical features, but many patients have a clinical picture compatible with PERM (progressive encephalomyelitis with rigidity and myoclonus), with typically subacute or slowly progressive course, not acute.

In our case, hyperekplexia was the main presenting feature that seriously progressed into an acute and severe meningoencephalomyelitis. The medial bulbopontine reticular formation (BPRF) of the lower brainstem has been implicated in its etiology. The lesion at the dorsal pons in our patient's MRI may explain these features, because of its proximity with the BPRF.

Another striking manifestation is the presence of **oculogyric crisis**, previously described in postinfectious encephalitis and focal lesions at basal ganglia or brainstem. Although the patient had normal EEG, it was obtained after the episodes and under antiepileptic drug. Whether this phenomenon is epileptic or secondary to brainstem/thalamic lesions remains unclear.

CONCLUSION

CNS hyperexcitability with hyperekplexia, myoclonus and stiffness, as well as oculogyric crisis, represent a new form of presentation to be included in the clinical spectrum of the autoimmune GFAP astrocitopathy. Immunotherapy with PLEX and IgIV is a treatment option for severely affected patients or non-responders to glucocorticoids.

ENCEPHALOPATHY	Fluctuating level of consciousness (GCS 11-13)
CEREBELLAR SIGNS	Moderate dysarthria Nistagmus in all the positions Bilateral finger to nose dysmetria
HYPEREXCITABILITY	Severe hiperekplexia Axial stiffness Spontaneous myoclonus
MOVEMENT DISORDERS	Oculogyric crisis
	Action tremor
SPINAL CORD (MYELITIS)	Flaccid paraplegia D7 sensory level, right leg alodynia Urologic dysfunction (spinal cord injury, dysautonomia?)

Table 1. Full description of the clinical phenotype of the patient.

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ODENSE AUTOIMMUNE ENCEPHALITIS RESEARCH GROUP

Neurodegenerative changes in human neurons exposed to anti-IgLON5 antibodies

SDU University of Southern Denmark

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BACKGROUND

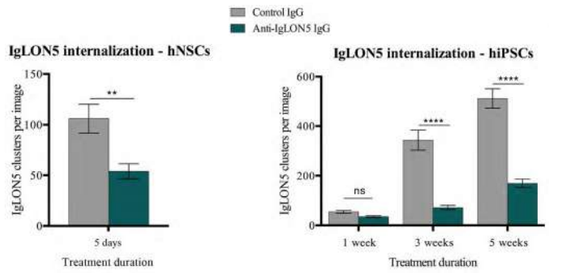
Anti-IgLON5 disease is a progressive neurological disorder, associated with autoantibodies against a neuronal cell adhesion molecule, IgLON5. In human post-mortem brain tissue neurodegeneration and accumulation of phosphorylated-Tau is found. Whether IgLON5 antibodies induce neurodegeneration or neurodegeneration provokes an immune response remains to be elucidated. To clarify this, we exposed human stem cell derived neurons to patient anti-IgLON5 antibodies.

METHODS

Human neural stem cells (hNSCs and hIPSCs) were differentiated for 14-48 days, and exposed from day 9-14, or day 13-48 to either i) IgG from a patient with confirmed anti-IgLON5 antibodies; ii) IgG from healthy controls or iii) left untreated. Electrical neuronal activity was quantified using a multi electrode array (MEA). Cultures were immunostained for β-tubulin III, phosphorylated-Tau and counterstained with DAPI. Other cultures were immunostained for synaptic proteins PSD95 and synaptophysin.

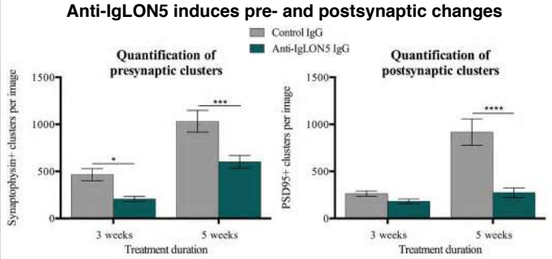
RESULTS

Patient antibodies reduce IgLON5 clusters in human neurons



Reduction of IgLON5 clusters in hNSCs when treated for 5 days with anti-IgLON5 IgG (n = 30) and hiPSCs after three and five weeks of exposure (n = 45)

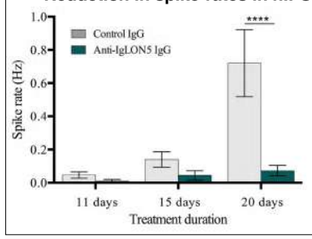
Anti-IgLON5 induces pre- and postsynaptic changes



Immunostaining for the synaptic proteins synaptophysin and PSD95 revealed a decrease in synaptophysin positive clusters after three weeks of exposure to anti-IgLON5, and in both synaptophysin and PSD95 clusters after five weeks of exposure (n = 15).

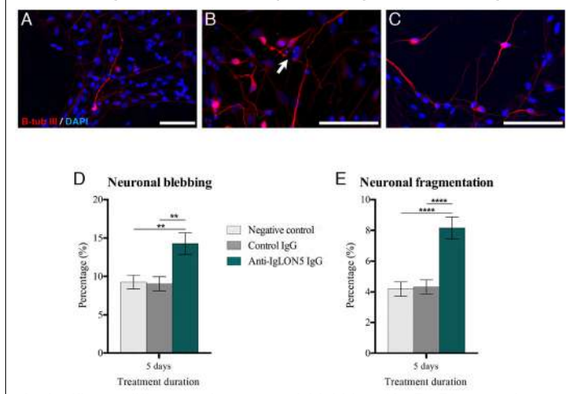
CONCLUSIONS:
Anti-IgLON5 antibodies induce synaptic changes and neurodegenerative features with early fragmentation, blobbing and p-Tau deposition,
These findings support the hypothesis that anti-IgLON5 antibodies lead to neurodegeneration and correlates with the neuropathological findings in patients postmortem.

Reduction in spike-rates in hIPSc exposed to anti-IgLON5



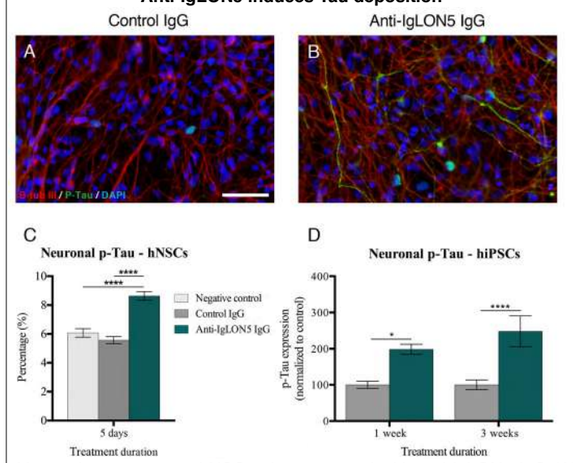
MEA analysis of hiPSC cultures showed the expected increase in neuronal activity as they matured, however, the spike rate of neurons treated with anti-IgLON5 IgG was significantly lower than that of untreated neurons (n = 5 wells)

Anti-IgLON5 induces early neurodegenerative changes



A significant difference in neuronal blebbing (A, B, D) was observed when comparing anti-IgLON5 IgG to controls (C). In addition, there was a significant difference in fragmented processes (B arrow, E) between anti-IgLON5 IgG, Control IgG and negative control.

Anti-IgLON5 induces Tau deposition



After 5 days exposure, hNSC cultures treated with anti-IgLON5 IgG (A) showed a drastic increase in percentage of neurons with p-Tau when compared to cultures exposed to control IgG (B) and negative control (C, n = 90-95). A similar increase in p-Tau in hiPSC cultures after one and three weeks of anti-IgLON5 IgG exposure was observed (D, n = 34-40)

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During my Clinical Lectureship, I am using functional genomics methods to understand neuroimmunological conditions in collaboration with Prof Irani. My particular focus is on applying recently developed single cell genomics approaches to immune-mediated diseases of the central nervous system, such as neuromyelitis optica, autoantibody-mediated encephalitis and multiple sclerosis. Single cell methods are ideally suited for studying the biology of extremely heterogeneous populations of cells, as exemplified by T-cells and B-cells in the case of autoimmunity these provide read-outs of cellular functions in individual cells rather than averaging over a large number of cells. This will enable me to identify novel mechanisms of disease.

POSTER PRESENTATION

Clinical features which predict neuronal surface autoantibodies in new-onset focal epilepsy: implications for immunotherapies

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Introduction

Neuronal surface-directed antibodies (NSAbs) are considered pathogenic in autoimmune encephalitis (AE). The same NSAbs are also described in the serum of people with more isolated forms of epilepsy but without frank encephalitis. The clinical relevance and therapeutic importance of these NSAb in patients with new-onset focal epilepsy is unclear. We undertook a prospective study to establish clinical features predictive of NSAb positivity, and asked whether detection of these NSAbs should alter patient management.

Materials and Methods

We recruited consecutive patients with new-onset focal epilepsy over four years. We collected information on clinical phenotype, investigations, Quality of Life in Epilepsy-31, Hospital Anxiety and Depression Score (HADS), Addenbrooke's Cognitive Examination (ACE), and modified Rankin Score (mRS). Serum samples were tested for the presence of known NSAbs. Analysis was undertaken in R using missForest imputation, Bayesian general linear modelling and multiple factor analysis.

Univariate analysis identified 11 features associated with NSAb status ($p<0.05$), six of which were highly predictive of NSAb positivity on multivariate analysis **(Figure 2).** We constructed a diagnostic score from these features: age ≥54 years=+1; self-reported mood disturbance=+1; limbic system lesions on MRI=+2; ictal piloerection=+2.5; ACE attention score ≥16=-1.5; and epilepsy risk factors=-1.5 (score ≥0: sensitivity=66.7%; specificity=84.9%). This score performed better than the previously reported APE2 score,[1] particularly in patients without AE (AUC 0.81 [regression model] *vs.* 0.56 [APE2 score]).

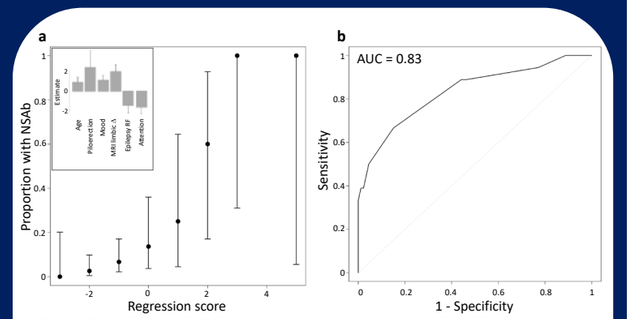

Figure 2 Prediction of NSAb positivity by clinical and paraclinical features
(**a**) The proportion of patients by total model score. Error bars show 95% confidence intervals. The inset shows the weighting and standard error of each factor within the regression model. (**b**) Receiver operator characteristic (ROC) curve of the total model score for predicting NSAb status across all patients.

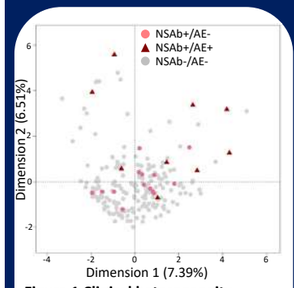

Figure 1 Clinical heterogeneity
Scatter plot of multiple factor analysis dimensionality reduction on clinical and paraclinical features in patients with new-onset focal epilepsy.

Results

23/219 (10.5%) of patients with new-onset focal epilepsy had detectable serum NSAbs. Patients were a clinically heterogeneous population but NSAb+ AE+ patients were a clearly distinct population (**Figure 1**).

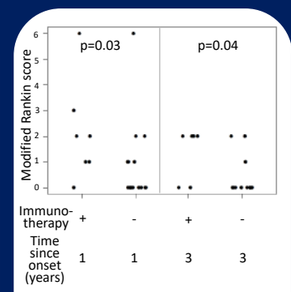

Figure 3 Long-term disability outcome
Jitter plot of modified Rankin score in NSAb+ patients at one and three years by immunotherapy status.

7/23 NSAb+ patients were treated with immunotherapy (all with AE). After one and three years, the untreated patients had lower disability ($p<0.05$, **Figure 3**). 11/16 of untreated patients were asymptomatic at three years.

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Summary

- 10.5% of patients had detectable serum NSAb
- Clinical features could predict NSAb positivity
- There were excellent immunotherapy-independent outcomes in NSAb+ patients without AE

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NEUROLOGICAL AND NEUROPSYCHIATRIC COMPLICATIONS OF COVID-19

FROM THE UK-WIDE CORONERVE STUDY OF 153 PATIENTS

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AIMS

- The aim of this study was to investigate the breadth of complications of COVID-19 across the UK that affected the nervous system.

BACKGROUND

- To our knowledge, this is the first nationwide, cross-specialty surveillance study of acute neurological and psychiatric complications of COVID-19.
- Concerns regarding potential neurological complications of COVID-19 are being increasingly reported.
- This data provides a snapshot of early research into this field.
- Characterization of clinical syndromes is crucial to allow rational selection and evaluation of potential therapies.

METHODS

- During the first phase of the pandemic, we developed a network of secure rapid-response case report notification portals across the spectrum of UK neuroscience bodies, including: Association of British Neurologists (ABN), British Association of Stroke Physicians (BASP), and Royal College of Psychiatrists (RCPsych).
- Broad clinical syndromes associated with COVID-19 were classified as a cerebrovascular event, altered mental status, peripheral neurology, or other.
- Physicians were encouraged to report cases prospectively and we permitted recent cases to be notified retrospectively.

RESULTS

- The ABN portal was launched on 2/4/20, BASP portal on 3/4/20, and RCPsych portal on 21/4/20. Data lock for this report was on 26/4/20.
- Cases were geographically dispersed across the UK with comparable distribution to the total laboratory-confirmed cases of patients with COVID-19 reported by Government Public Health bodies.
- There was an exponential growth in reported cases that was similar to overall COVID-19 data from UK Government public health bodies.
- Median patient age was 71 years (range 23–94; IQR 58–79) which broadly reflected the national data collected through Government Public Health bodies over the same timeframe.

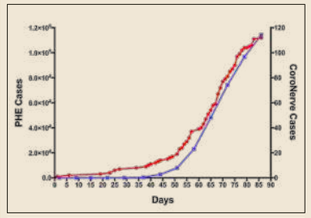

Figure 1: Temporal distribution of cases notified to the CoroNerve Study Group compared with those identified by UK Government public health bodies.

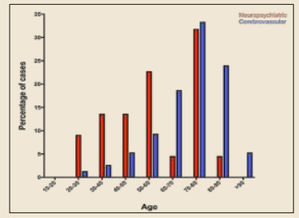

Figure 2: Age distribution of patients identified through the CoroNerve surveillance study meeting the clinical case definitions for cerebrovascular and neuropsychiatric events.

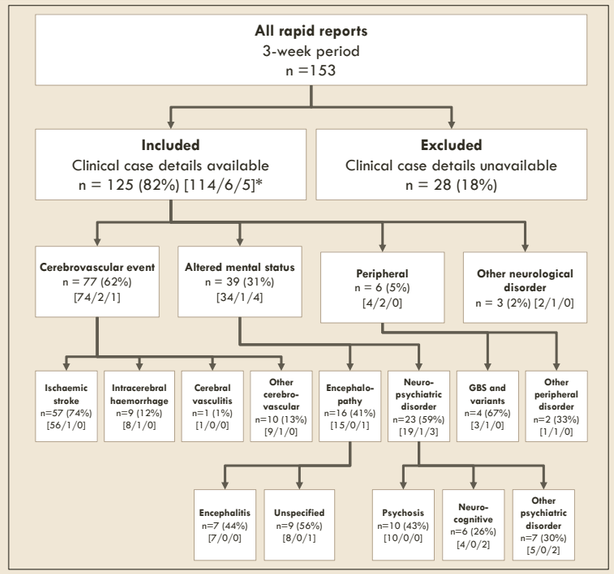

*Figure 3: Number of broad and specific clinical case definitions notified in the dataset, including evidence for severe acute respiratory syndrome coronavirus 2 within each grouping, according to the clinical case definition. *Figures in square brackets are numbers of [confirmed/probable/possible cases]*

CONCLUSION

- This study provides valuable and timely data that are urgently needed by clinicians, researchers, and funders to inform immediate steps in COVID-19 neuroscience research and health policy.
- Altered mental status was the second most common presentation, comprising encephalopathy or encephalitis and primary psychiatric diagnoses, often occurring in younger patients.
- Cerebrovascular events in patients with COVID-19 were identified as a major group within our cohort, predominating in the elderly population.
- Our rates of neurological and psychiatric complications of COVID-19 cannot be extrapolated to mildly affected patients or patients with asymptomatic infection, but instead gives a broad national perspective on complications severe enough to require hospitalisation.
- Future studies on neurological complications of COVID-19 would benefit from obtaining notification of all cases of infection admitted to every hospital as a denominator, or a cohort of COVID-19 patients without neurological or psychiatric complications as a control group.

Acknowledgements: All authors are indebted to the following professional bodies and their membership who contributed cases and form the CoroNerve Studies Group: Association of British Neurologists (ABN) (RoDAR team: Fardousa Musa & Joanne Lawrence), the British Association of Stroke Physicians (BASP) and the Royal College of Psychiatrists (RCPsych), the British Paediatric Neurology Association (BPNA), and the NeuroAnaesthesia and Critical Care Society (NACCS). The authors would further like to express their deepest gratitude to the patients who consented for their cases to contributed to the CoroNerve Studies group.

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Kelsey Martin received her Bachelor of Arts degree in Psychology from Princeton University. She currently is a second-year medical student at the Icahn School of Medicine at Mount Sinai in New York City, where she has spent the past year working on neurology research under the mentorship of Dr. Anusha Yeshokumar. Her current research interests are focused on the clinical symptomology of autoimmune encephalitis.

NATURAL LANGUAGE PROCESSING ANALYSES OF WRITTEN TEXT ACROSS STAGES OF ILLNESS IN ANTI-NMDA RECEPTOR ENCEPHALITIS

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Background

- **Anti-NMDA Receptor Encephalitis (anti-NMDARE)** is a subtype of autoimmune encephalitis characterized by psychosis, seizures and altered consciousness.
- **Natural language processing (NLP)** has predicted sympton onset in those at clinical high risk for psychosis (CHR).

Objective

This study aims to explore whether or not changes in language occur in patients with anti-NMDARE from the pre-illness phase to the acute illness phase and if these changes persist after recovery

Methods

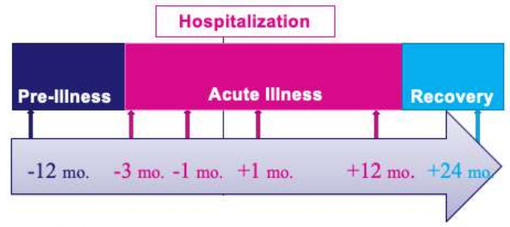
- Participants were asked to submit:
  - Six writing samples (from set times before, during, and after illness)
  - Demographic information
  - Self-reported symptom assessment
- Writing samples were de-identified; Data analysis was completed using an Information-Theoretic NLP model

Results

Table One: Demographic Features (n=7)

Median Age at Symptom Onset	22 years (Range: 17 to 31 years)
Number of Females	7 (100%)
Race and Ethnicity	6 White (86%); 1 (14%) Hispanic
Education Level at Time of Hosp	1 in HS; 2 in College; 1 Completed College; 1 in Grad School; 2 Completed Grad School

Figure One: Clinical Periods of Interest



- Aim 1: Figure 1 presents the results of various comparisons between time points, evaluated via NLP model, to identify which submissions should be classified as Pre-Illness, Acute Illness, and Recovery.
- Aim 2 & 3: Tables 2 & 3 show models with the highest degree of accuracy in classifying writing samples and the top language features driving these models

Table Two: Classifying Pre-Illness Compared to Acute Illness

	Pre-Illness Writing	Acute Illness Writing
Classified as Pre-Illness	4	3
Classified as Acute	9	22
Analysis		
Sensitivity	0.71	
Specificity	0.57	
Accuracy	68%	
ROC AUC (ability to discriminate)	0.66	

Driving Language Features:
(1) Determiners, (2) Adjectives, (3) Verb 3rd Person Singular, (4) Possessive Pronouns

Table Three: Classifying Pre-Illness Compared to Recovery

	Pre-Illness Writing	Recovery Writing
Classified as Pre-Illness	3	4
Classified as Recovery	2	3
Analysis		
Sensitivity	0.60	
Specificity	0.43	
Accuracy	58%	
ROC AUC (ability to discriminate)	0.71	

Driving Language Features:
(1) Existential "There", (2) Verb Base Form, (3) Pre-determiners, (4) Particles

Conclusions

- There appear to be changes in language from the pre-illness to acute illness periods in anti-NMDARE.
- While less prominent, there appear to also be language changes from pre-illness to recovery in anti-NMDARE.
  - Incomplete recovery? Long-term/permanent changes?
- Features associated with these changes were related to thought complexity, not semantics.
- **Future Directions:**
  - Examine how changes in language associate with symptamotology
  - Explore the role of early language assessment in diagnosis

Acknowledgements

No funding obtained for this study.

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Dr. Jennifer McCombe completed medical school at Queen's University in Kingston, Ontario and her neurology residency at the University of Alberta. Upon completion of her residency she was granted the Clinical Scholar Training Program Award which provided full funding to complete a Master's in Public Health at Johns Hopkins University in Baltimore. Her research during her term as a Clinical Scholar focused on the Neurologic complications of HIV infection and Neurologic Immune Reconstitution Inflammatory Syndrome. Dr. McCombe is currently an Associate Clinical Professor at the University of Alberta in Neurology. She has worked at the Northern Alberta Multiple Sclerosis clinic since 2013. She is a co-chair of the encephalitis working group at the University of Alberta Hospital, whose purpose is to develop diagnosis and treatment algorithms for the management of pediatric and adult patients with autoimmune encephalitis. Dr. McCombe is also actively involved in teaching and is the block coordinator for the Neurology block at the University of Alberta Medical School. She is the recipient of multiple local and national teaching awards.

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THE SUCCESSFUL TREATMENT OF FULMINANT ADEM IN AN ADULT PATIENT WITH HIGH DOSE CYCLOPHOSPHAMIDE

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BACKGROUND

Acute disseminated encephalomyelitis (ADEM) is an acute demyelinating syndrome typically diagnosed in children, with an incidence estimated at 0.3 to 0.6 per 100,000 per year (1). It is characterized by the development of multifocal neurological symptoms over a few days in addition to encephalopathy and often fever. It can rarely present in adulthood. The prognosis in adults is generally worse compared to children with an estimated mortality upwards of 25% in adult patients admitted to the ICU (2).

High-dose steroids are broadly accepted as a first line therapy for the treatment of ADEM. Intravenous immunoglobulin (IVIg) and plasma exchange are also often used. There are no consensus guidelines which outline in whom one should consider multimodal therapy nor when to consider additional therapies. The use of high dose intravenous steroids is based primarily on observational studies (3,4). The benefit of IVIg, similarly, is supported by observational studies (4) and case series (5). The effectiveness of plasma exchange is reported in case reports, small case series (6), and a small randomized trial (7).

METHODOLOGY

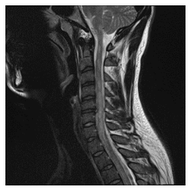
CASE REPORT

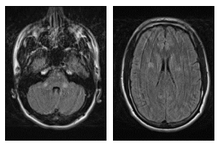
Herein, we discuss the case of an adult patient with ADEM treated with the Calgary MS Clinic high dose cyclophosphamide protocol (8,9). In addition, we review published reports of the outcome of patients with fulminant ADEM treated with cyclophosphamide.

Protocol Acknowledgement: Dr. Jodie Burton MD, MSc, FRCPC and Sharon Peters, RN

THE CASE

The patient is a 30 year old man who initially presented with a 3 day history of rapidly progressive flaccid quadriparesis and urinary retention, and a 1 day history of declining level of consciousness. He had a history of a preceding viral exanthem. Initial MRI revealed prominent lesions throughout the brain including around the periaqueductal region and hypothalamus, as well as a longitudinally extensive spinal cord lesion spanning the entire cord and conus.

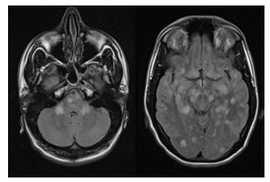


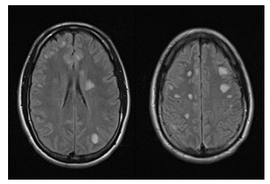


CSF revealed 104 white cells with 90% lymphocytes and 9% monocytes. The patient was initiated on high dose steroids shortly after admission. 3 days later he was started on a course of plasmapheresis. Despite this, his LOC continued to decline culminating quickly in coma. He developed autonomic instability as well as diaphoresis. He had reactive pupils but no other brain stem reflexes. Oligoclonal banding and CSF viral studies were negative. Serum and CSF antibodies were negative including MOG and aquaporin 4 antibodies.

THE CASE

Repeat MRI 5 days later, following the 5 day course of steroids and 3 runs of plasmapheresis, demonstrated an increase in lesion size and burden compared to the first. As such a decision was made, in discussion with the patient's family, to proceed with a high dose cyclophosphamide protocol involving 5 treatments administered over 8 days.





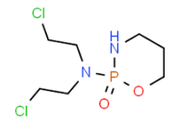
Within 5 days of the initiation of this protocol the patient became able to open his eyes and had conjugate, non-purposeful eye movements. Within 10 days he was able to track with his eyes. He ultimately improved such that his cognition returned to baseline, he developed full strength in the upper extremities, but regained only flicker movement in the lower extremities. He was able to return home requiring a wheelchair for mobilization.

CYCLOPHOSPHAMIDE IN ADEM

- Rothenberg *et al.*, 2015: Significant clinical improvement in a 22 year old man treated with 3 day course of cyclophosphamide 1000mg/m² (10).
- DeSena *et al.*, 2014: 5 children with ADEM accompanied by extensive transverse myelitis; 3 treated with a single dose of cyclophosphamide 1000mg/m with moderate response (11).
- Schwarz *et al.*, 2001: Follow-up study of 40 adult patients, 7 of whom received a cyclophosphamide 1000 mg/m², some repeatedly, with variable recovery, although largely good (3).
- Jaskowiak, 2016: Good radiologic response but minimal clinical response to low dose (180 mg daily) cyclophosphamide for 19 days in a 49 year old woman with hemorrhagic ADEM (12).
- Rodriguez-Porcel *et al.*,2014: 60 year old man with little improvement following a single dose of cyclophosphamide 750 mg/m² (13).
- Ayed *et al.*, 2017: Significant clinical improvement in a 3 year old boy treated with a single dose of cyclophosphamide 750 mg/m² (14).
- Ceronie & Cockerell, 2018: 69 year old man with minimal recovery after cyclophosphamide (dose not specified) (15).

OUR CYCLOPHOSPHAMIDE PROTOCOL

600 mg/m² for 5 doses on days 1,2,4,6, and 8 (9)



KEY POINTS

- ADEM has a worse prognosis in adults as compared to children.
- Fulminant ADEM is uncommon but has a mortality of 25% in adult patients.
- ADEM associated with extensive transverse myelitis also foretells a poor prognosis.
- In patients in whom treatment with steroids and IVIg/plasma exchange does not result in improvement, treatments with cyclophosphamide may result in improvement.
- Treatment guidelines are needed to standardize the treatment of adults with ADEM.
- Additional studies are required to determine the best course of action in patients with aggressive disease course.
- High dose cyclophosphamide can be used in patients with fulminant MS.
- High dose cyclophosphamide should be considered in patients with fulminant ADEM for whom steroids and IVIg/plasma exchange does not result in improvement and who remain critically ill.

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I am a clinical fellow, halfway through my Neurology training and currently completing my PhD within the Oxford Autoimmune Neurology Group at the University of Oxford, under Professors Sarosh Irani and Arjune Sen. My research is focused on autoimmune encephalitis, in particular, patients with LGI1- and CASPR2-autoantibodies and the cells which produce the autoantibodies. Greater understanding of these disease mechanisms may allow more targeted immunotherapies, with ultimate aim of improved patient outcomes. In parallel I am working with the Oxford Epilepsy Research Group, exploring the potential role of immunological dysfunction in a large cohort of patients with pharmacoresistant epilepsy.

Bone Marrow-Derived Antigen-Specific Long-Lived Plasma Cells in LGI1-Antibody Encephalitis: Novel Insights into Disease Mechanisms and Therapeutic Implications

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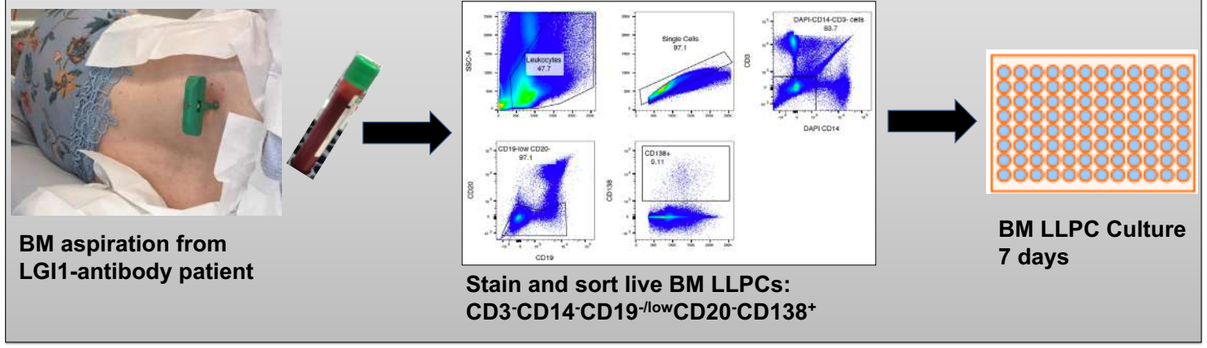
Background: Ongoing germinal centre (GC) reactions contribute to autoantibody production in LGI1-antibody and NMDA-receptor antibody-encephalitis (1,2). Yet, a proportion (~25%, Irani et al unpublished) of LGI1-autoantibody patients relapse or remain refractory despite adequate B cell-targeting immunotherapies.
These findings indicate that targeting GC B cells alone would not be a sufficient therapeutic target, and that other mechanisms of autoantibody production and disease perpetuation should be explored. Bone marrow (BM)-derived long-lived plasma cells (LLPCs) can produce autoantibodies for several decades (3).

Aims: to directly investigate the potential role of the bone marrow (BM) compartment in patients with LGI1-antibody encephalitis by asking whether BM-derived antigen-specific LLPCs contribute to LGI1-autoantibody production.

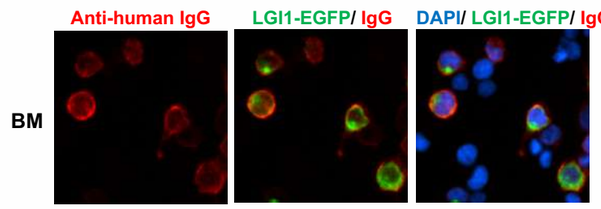
Methodology

LLPCs, defined by flow cytometry as live, $CD3^{-}CD14^{-}CD20^{-}CD19^{-/low}CD138^{+}$ cells, were purified from fresh BM aspirate from n=2 consenting patients with LGI1-antibody encephalitis. BM LLPC oligocultures were maintained in optimized culture conditions. After 7 days, culture supernatants were tested for LGI1-IgG by live cell-based assay.



Results

- LGI1-IgG autoantibodies were detected in the culture supernatant from one of the patients.
- The frequency of LGI1-specific IgG autoantibodies was 1:4920 of total cultured BM LLPCs.



Live CBA: specific LGI1-IgG

Conclusions

- We demonstrate, for the first time, the presence of LGI1-specific BM-derived LLPCs in a patient with autoimmune encephalitis by direct sampling of their BM.
- These proof-of-concept data demonstrate that the BM is a site for long-term autoantibody production and suggest a role for BM-derived LLPCs in autoimmune encephalitis.
- These findings provide novel insights into disease immunobiology and may inform use of more targeted immunotherapies (for instance, bortezomib) to improve clinical outcomes in these patients.

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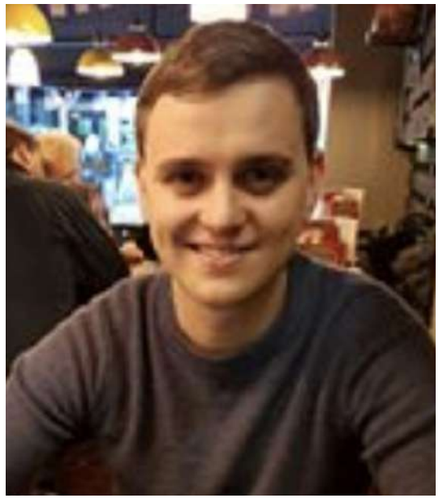

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James W Mitchell is an Association of British Neurologists (ABN) Fellow and neurology registrar based at the University of Liverpool and The Walton Centre NHS Foundation Trust. His primary research interests are in epilepsy, seizure disorders and outcome measurement in trials as well as clinical practice.

Autoimmune encephalitis as an increasingly recognised cause of non-convulsive status epilepticus (NCSE)

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Introduction and Objective

Status epilepticus (SE) is a severe condition of unrelenting seizures requiring urgent identification and treatment.

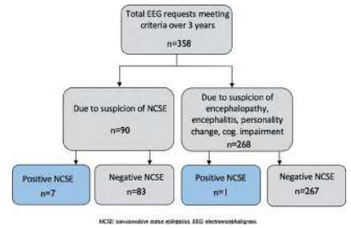
Whilst convulsive SE is readily identified, non-convulsive SE (NCSE) can be difficult to identify clinically, and electroencephalography (EEG) is required. Therefore, it is critical to identify the key clinical features associated with NCSE on EEG to inform future use of EEG.

This study aimed to evaluate clinical and aetiological factors in patients diagnosed with NCSE in a large neurophysiology department covering a regional neurology referral center as well as four secondary care facilities for general medical and surgical patients over a three-year period.

Methods and Case Grouping

All EEG requests between January 2015 and December 2018 screened. Cases selected if 18 years or older and reason for request:

1. NCSE OR
2. Encephalopathy, encephalitis, behavioural change, impaired consciousness, cognitive impairment.



Retrospective case note review performed for available cases. n=40 random cases selected from negative group where notes available to allow comparative analysis.

Results

In total, 358 EEGs were requested due to a clinical suspicion of NCSE, encephalopathy or encephalitis or due to behavioural change, impaired consciousness or cognitive impairment. Eight cases of patients in NCSE (in line with consensus EEG criteria) were identified from this cohort, 7 patients where the clinical suspicion was NCSE specifically and 1 patient where the request was due to a suspicion of metabolic encephalopathy in the context of hyperammonaemia. Where EEGs were performed on patients with clinical suspicion of NCSE, 7.8 % (95 %CI = 2.2 %–13.3 %) confirmed electrographic evidence of this diagnosis.

In patients with EEG confirmed NCSE, **alcohol excess** as a comorbidity was significantly more likely compared to the NCSE –ve cases (p=0.005). **Subtle motor signs** were observed in 50.0% of the cohort (95%CI = 15.4%-84.6%) and this discriminated from patients with a negative EEG recording (p=0.047). NCSE was attributed to presentation of previously diagnosed epilepsy in two patients, and secondary to autoimmune encephalitis another two patients.

Demographic Details	NCSE +ve group n=8	NCSE -ve group n=40	Test statistic
Age, median (IQR)	54 (45.3-64.5)	62.5 (49.5-75.5)	U=139, p=0.569
Male, % (95% CI)	37.5 (4.0-71.0)	45.0 (29.6-60.4)	FET, p=1.00
Comorbidity	**% (95% CI)**	**% (95% CI)**	
Epilepsy	37.5 (4.0–71.0)	10.0 (0.7–19.3)	FET, p = 0.080
Previous encephalitis	12.5 (0.0–35.4)	5.0 (0.0–11.8)	FET, p = 0.428
Previous meningitis	12.5 (0.0–35.4)	5.0 (0.0–11.8)	FET, p = 0.428
Alcohol excess	50.0 (15.4–84.6)	5.0 (0.0–11.8)	**FET, p = 0.005***
Previous stroke	12.5 (0.0–35.4)	5.0 (0.0–11.8)	FET, p = 1.00
Reason for EEG	**% (95% CI)**	**% (95% CI)**	
Impaired consciousness	75.0 (45.0–1.00)	47.5 (32.0–63.0)	FET, p = 0.248
Behavioural disturbance	37.5 (4.0–71.0)	57.5 (42.2–72.8)	FET, p = 0.441
Subtle motor signs	50.0 (15.4–84.6)	15.0 (3.9–26.1)	**FET, p = 0.047***

Cause of NCSE (diagnosis)	NCSE +ve group n=8		NCSE -ve group n=40		Test statistic
	Freq	% (95%CI)	Freq	% (95% CI)	
Epilepsy	2	25.0 (0.0–55.0)	4	10.0 (0.7–19.3)	FET, p = 0.571
Infective meningoencephalitis	0	-	1	2.5 (0.0–7.3)	
Autoimmune encephalitis	2	25.0 (0.0–55.0)	3	6.2 (0.0–15.7)	FET, p = 0.189
Tumour	0	-	3	6.2 (0.0–15.7)	
Neurodegenerative disease	0	-	1	2.5 (0.0–7.3)	
Other neuroinflammatory	1	12.5 (0.0–35.4)	2	5.0 (0.0–11.8)	FET, p = 0.428
Stroke / vascular pathology	1	12.5 (0.0–35.4)	4	10.0 (0.7–19.3)	FET, p = 1.00
Brain injury	2	25.0 (0.0–55.0)	2	5.0 (0.0–11.8)	FET, p = 0.124
FND / Psychiatric	0	-	3	6.2 (0.0–15.7)	
Neurosurgical complication	0	-	2	5.0 (0.0–11.8)	
Unclear diagnosis	0	-	15	37.5 (22.5–52.5)	

*Key – U, Mann-Whitney test statistic; FET, Fisher Exact Test; 95% CI, 95% confidence interval; *, statistically significant result at p<0.05*

Discussion

This study has demonstrated that **alcohol excess as a comorbidity** and **subtle motor signs on examination** (facial or perioral twitching, grimacing or subtle limb twitching) are associated with diagnosis of NCSE on EEG where clinically suspected.

In this population **autoimmune encephalitis (AIE) represented the cause of NCSE in a quarter of patients. AIE might be as common as known epilepsy as the cause of NCSE.**

Limitations:

- Retrospective data analysis – however this allowed for larger sample.
- Difference in recording of and access to clinical data between NHS Trusts.

Conclusion

Autoimmune encephalitis is an increasingly recognised cause of NCSE and should be considered in patients with suspected encephalitis with subtle motor signs. EEG should be requested on an urgent basis for such patients and managed with close involvement of neurological colleagues.
Furthermore, clinicians should take a careful alcohol history when suspecting NCSE since this may represent a risk factor.

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Associated Publication

Mitchell JW, Valdoleiros SR, Jefferson S, Hywel B, Solomon T, Marson AG, Michael BD. Autoimmune encephalitis as an increasingly recognised cause of non-convulsive status epilepticus: a retrospective, multicentre evaluation of patient characteristics and electroencephalography (EEG) results. Seizure. 2020 Jun 12. https://doi.org/10.1016/j.seizure.2020.06.020.

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Dr Netravathi, an Additional Professor in Neurology, NIMHANS has been involved on the care, evaluation and management of neuroinfection patients since 2011- HIV, HIV associated neurological disorders – PML, Cryptococcal meningitis, Toxoplasmosis, Tubercular meningitis, CNS infections: TB, Viral, bacterial and fungal infections. Initial Neuroinfection ward at NIMHANS was managed by Dr Netravathi M along with Dr Nalini and P Satishchandra since 2011. Dr Netravathi has also been involved in maintaining the HIV registry data of NIMHANS under NACO since 2011. Dr Netravathi was also involved in the thesis related to Neuroinfections. Dr Netravathi is an author to various Neuroinfections Chapters and publications.

SPECTRUM OF MOVEMENT DISORDERS IN PATIENTS WITH AUTOIMMUNE ENCEPHALITIS

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Introduction

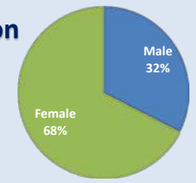
Movement disorders are a common clinical feature in Autoimmune Encephalitis (AIE). Objective of this study is to evaluate the spectrum of various movement disorders (MD) in AIE.

Methodology

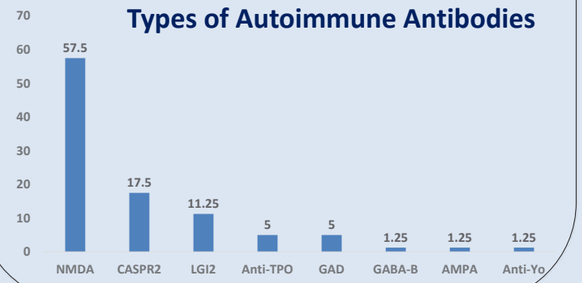
This is a chart review of patients with MD in various AIE from 2017-2020 (4 years).

Results

- **N = 80** patients of AIE
  - Among them 73 (91.3%) patients had MD.
- **Gender Distribution**



Types of Autoimmune Antibodies

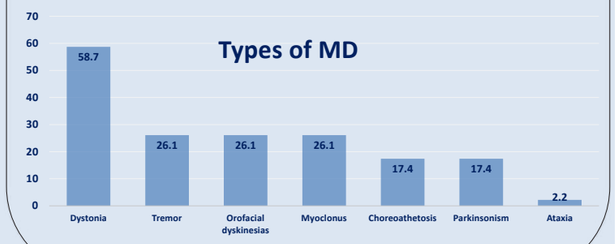


Hashimoto's Encephalitis

- N = 4; F:M-3:1
- Mean age: 47±13.4 years
- MD: Myoclonus – 100%

NMDAr Encephalitis

- N = 46; F:M-38:8
- Mean age: 16.5±13.7 yrs (Range:0.5-70yrs)
- Mixed MD: 58.7%; Single MD: 41.3%



CASPR2 antibody – Morvan's syndrome

- N = 14; F:M-4:10
- Mean age: 37.1±17.5 yrs
- MD: Myokymia (85.7%). All had Neuromyotonia.

Anti-GAD Encephalitis

- N = 4; F:M-3:1
- Mean age: 53.3±6.7 years
- MD: Stiffperson syndrome:50%, ataxia:25%, Tremor:25%

Others

- GABA-B encephalitis – Parkinsonism
- AMPA – Ataxia
- Anti-Yo - Ataxia

Conclusions

- **NMDAr encephalitis is the most common AIE with MD. The most common MD was dystonia followed by orofacial dyskinesias.**
- **Knowledge regarding type of MD & the age of predilection helps in antibody testing especially in resource-poor settings.**

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Being **aware** of autoimmune **encephalitis** is a turning point to **better diagnostics** for the neurological patient.

Anti-Hu encephalitis associated with an almost missed lung cancer - a clinical case.

Background

Autoimmune encephalitis is a syndrome caused by auto-antibodies to intra- or extracellular neuronal antigens. Clinical features include a wide range of symptoms and signs. Most often, patients have psychiatric symptoms and seizures, suggesting limbic system involvement, but there may be brainstem or peripheral nervous system involvement also. The course of the disease is subacute and progressive. The most important laboratory findings include cerebrospinal fluid pleocytosis, slow waves, epileptiform activity in the temporal region at EEG, and FLAIR temporal lobe hyperintensities at brain MRI. A tumor or infection may trigger the production of autoantibodies. If a tumor is implicated, "paraneoplastic syndrome", "onconeural antibodies" are used as terms for the related clinical manifestations and antibodies. One of the best known onconeural antibodies is the *anti-Hu* antibody, which is usually associated with small lung cell carcinoma.

Paraneoplastic symptoms precede the oncologic diagnosis in most of the cases.

Early diagnosis of the paraneoplastic syndrome and the underlying tumor is crucial. Antitumor treatment and immunotherapy can lower the mortality rate, can stop or even reverse the evolution of the neurological symptoms.

We present the case of a 52-year-old man with anti-Hu encephalitis and polyneuropathy. He had a six-month history of weight loss, depression, apathy, distal paresthesia in the legs, and walking difficulty. He took several neurological and psychiatric outpatient examinations and treatments; however, the symptoms had been progressing. Delirium complicated the clinical picture, so the family brought the patient to the emergency unit of our hospital.

Methods

We clinically examined the patient and did the following tests and imaging:

1. general blood tests
2. renal, liver, and thyroid tests
3. serum B1 and B12 vitamin levels
4. anti-HIV serology and syphilis screening tests
5. cerebrospinal fluid analysis
6. chest X-ray
7. electromyography and nerve conduction studies (EMG+NCS)
8. cerebral CT and contrast-enhanced MRI
9. a panel of serum onconeuronal antibodies
10. finally, contrast-enhanced chest CT

Results

The physical examination was unremarkable; the patient was non-febrile and cardiopulmonary stable. The neurological assessment revealed confusion, memory and attention deficit. He had bilateral cerebellar syndrome, a polyneuropathic syndrome, and walking difficulty, so we admitted him to our clinic. In the hospital, he developed focal aware myoclonic seizures at the level of the face and both arms. CSF analysis showed normal protein levels and normal white blood cell count. EEG revealed bilateral theta rhythm and rare sharp waves, polyspikes in the right hemisphere. The brain CT had no changes, but MRI revealed FLAIR cortico-subcortical hyperintensity in the left insula, without restriction or enhancement (Fig.1,2).

There were not described any nodules or masses at the initial screening chest X-ray (Fig.3).

EMG and NCS confirmed sensory neuropathy.

We ordered a panel of serum onconeural antibodies. The patient was positive for anti-Hu antibodies, we put him on immunomodulatory corticosteroid treatment, and the first next step was ordering contrast-enhanced pulmonary CT (Fig.4). A mass in the left inferior lobe was described. We referred the patient to an oncology unit.

The evolution was rapidly progressive; he could not undergo surgery or biopsy. The oncology specialist initiated salvage chemotherapy (etoposide). The treatment slowed down the progression of the disease, so that bronchoscopy with transbronchial biopsy was done five months later, which confirmed small cell lung cancer.

Despite all the effort that was done, the patient succumbed eight months after the initial hospitalization.

Discussion

Paraneoplastic syndromes are rare, being difficult to keep a high level of suspicion to diagnose such patients. In our case, the clinical and laboratory findings were suggestive for autoimmune encephalitis with polyneuropathy. Positive anti-Hu antibodies lead us to the possibility of a paraneoplastic syndrome, so we diagnosed the triggering lung cancer despite an initial false-negative screening chest X-ray.

A timely diagnosis of paraneoplastic encephalitis is a U-turn point – it leads to adequate treatment, can stop the neurological regression, and save the patient's life.

Regardless of the negative outcome in our patient, the initial good clinical response to treatment supports the mentioned above statement and is encouraging us to offer better diagnosis and treatment to patients with autoimmune encephalitis.

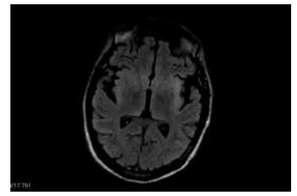

Fig.1: FLAIR band hyperintensity in the left insula.

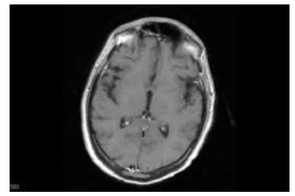

Fig.2: T1 weighted image with contrast shows no enhancement in the left insula.

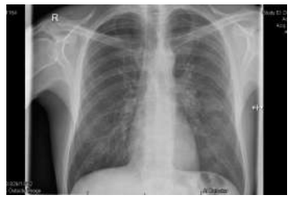

Fig.3: The initial chest X-ray was described as showing enhancement of the interstitium in the basal area of both lungs, but no nodule or mass was mentioned.

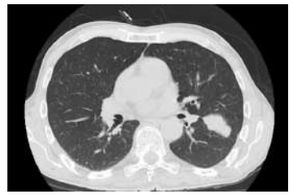

Fig.4: Pulmonary CT reveals a mass in the left lung with associated adenopathy.

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First report of neuroinvasive endemic West Nile Myelitis in Belarus

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BACKGROUND

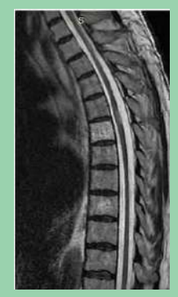
According to ECDC since the beginning of the 2019 transmission season more than 460 WNV human infections with 50 deaths were reported. Previously WNV in Belarus was recognized only as influenza-like illness and aseptic meningitis.

CLINICAL CASE

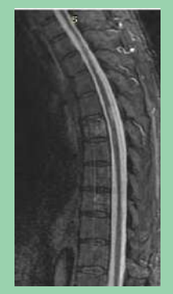
We present a case of 64 years old man who was admitted to Minsk City Infectious Diseases Hospital in July 2019 with weakness in the legs, loss of sensation up to Th10 level, bladder and bowel dysfunction, spinal pain, headache and fever. Before the first clinical signs of illness the patient lived in rural area where he indicated multiple mosquitoes bites. History of travel abroad was absent.

Investigation of the cerebrospinal fluid revealed pleocytosis 116/mm3 with lymphocytic predominance (84%), increased level of protein (1,2 g/l) and normal glucose. MRI of the thoracic and lumbar spine showed abnormalities in spinal cord compatible with myelitis (Picture 1). The patient was treated by intravenous human immunoglobulin (IVIG) 0,4 g/kg every 24 hours for 5 days with improvement in legs function, resolution of spinal pain and fever but subsequently died due to progressive chronic heart failure.

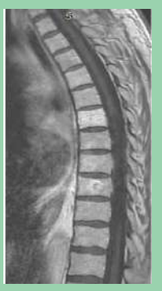
Serum and CSF of the patient was taken twice with difference in 20 days (8th and 28th days of the fever) and tested by real-time PCR and/or serology for the presence of multiple pathogens including herpes simplex virus, varicella zoster virus, cytomegalovirus, Epstein-Barr virus, enteroviruses, tick-borne encephalitis virus, Borrelia burgdorferi sensu lato, human immunodeficiency virus and WNV. For the IgM and IgG to WNV detection Anti-WNV ELISA (IgG / IgM) (Euroimmun, Germany) kits were used.



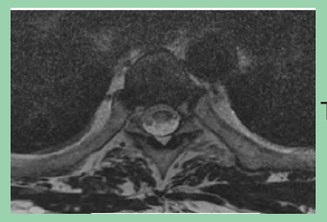
T2W saggital



T2W STIR



T1W +Gd



T2W axial

Picture 1. Intramedullary at the level of the posterior horns in the Th4-Th5 segments of the spinal cord focus of MR hyperintensity in T2W saggital, T2W axial, T2W STIR saggital. This focus is oval in shape with clear borders. There were no signs of contrast enhancement in post-gadolinium T1W.

RESULTS

The diagnosis of WNV meningomyelitis was confirmed by detection of IgM to WNV in the first serum sample with subsequent appearance of IgG to WNV in the second serum sample. PCR of the first serum for WNV was negative. Other potential causes of infectious myelitis were excluded using PCR of the CSF and/or serology.

CONCLUSION

It is important to be aware of potential neuroinvasive forms of WNV infection in Belarus especially in elderly patients even without history of travel outside the country. IVIG may be promising drug for the complimentary treatment of neuroinvasive WNV infection.

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After a master degree in biomedical sciences, in 2018 I started a PhD in the 'Serine Proteases, Inflammation and Glial cells (SPrInG)' group, led by Dr Fabian Docagne in the Physiopathology and Imaging of Neurological Disorders (PhIND) unit led by Pr Denis Vivien at the French Institute for Health and Medical Research (INSERM) in Caen, France. The team focuses on neuroimmunology and neuroinflammation and has developed a new, immune-driven model of anti-N-Methyl-D-Aspartate receptor (NMDAR) autoimmune encephalitis, recently published in Brain. To complete this work, my main scientific project is the analysis of human and murine CD4 T cell response against NMDAR involved in the help of humoral response, in the context of anti-NMDAR autoimmune encephalitis.

Analysis of **T cell response** against N-Methyl-D-Aspartate receptor (**NMDAR**) and implication for immunotherapy development targeting **neurological and psychiatric disorders**

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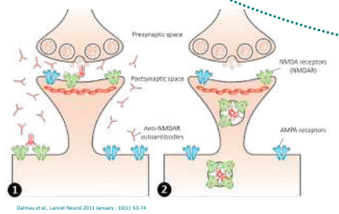
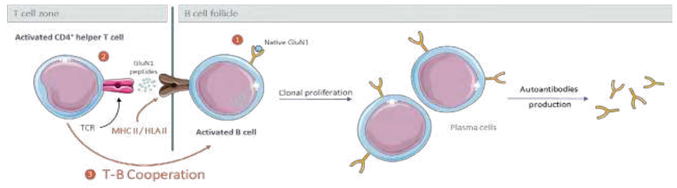
Background



Autoantibodies against GluN1 subunit of N-Methyl-D-Aspartate receptor (NMDAR) have been highlighted in many central nervous system disorders such as stroke and multiple sclerosis. Their role are well described in schizophrenia and autoimmune anti-NMDAR encephalitis. In these disorders, autoantibodies induce the internalization and delocalization of NMDAR in postsynaptic neurons (*cf* left schema) leading to various symptoms, such as psychotic and neurologic dysfunctions.

Aim

Autoimmune anti-NMDAR encephalitis is mediated by B cells. So, why are we looking for CD4⁺ T epitopes?

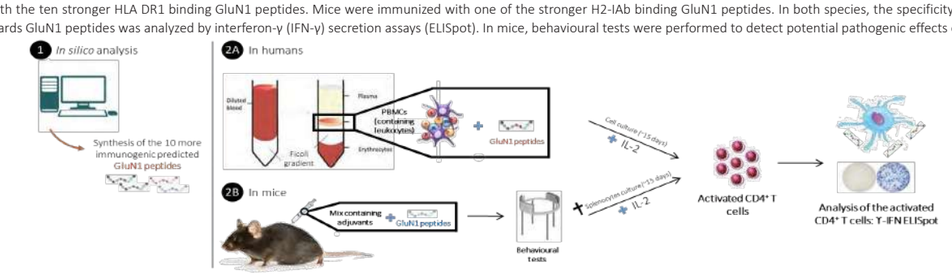


1. B cell response is initiated by the recognition of the native antigen (NMDAR GluN1).
2. B cells endocyte and process the antigen and display peptides *via* a Major Histocompatibility Complex II (MHCII) molecule (= Human Leukocyte Antigen [HLA] in humans) to T cells.
3. In turn, activated T cells help B cells to produce (auto)antibodies: **there is a strong T-B cooperation.**

Our goal is to characterize GluN1 CD4⁺ T epitopes *in vitro* in the human (HLA DR1) context and *in vivo/ex vivo* in C57Bl/6 mice (H2-IAb).
Characterization of epitopes may be useful to determine diagnostic and/or prognostic markers; and develop immunotherapy strategies.

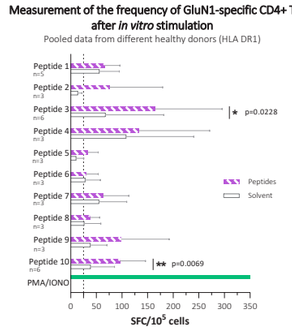
Materials and methods

Binding of GluN1 epitopes to MHCII has been predicted *in silico via* IEDB, NetMHCIIpan & TEPITOPE softwares. In humans, Peripheral Blood Mononuclear Cells (PBMCs) of healthy donors were stimulated with the ten stronger HLA DR1 binding GluN1 peptides. Mice were immunized with one of the stronger H2-IAb binding GluN1 peptides. In both species, the specificity of activated CD4⁺ effectors towards GluN1 peptides was analyzed by interferon-γ (IFN-γ) secretion assays (ELISpot). In mice, behavioural tests were performed to detect potential pathogenic effects of autoantibodies.



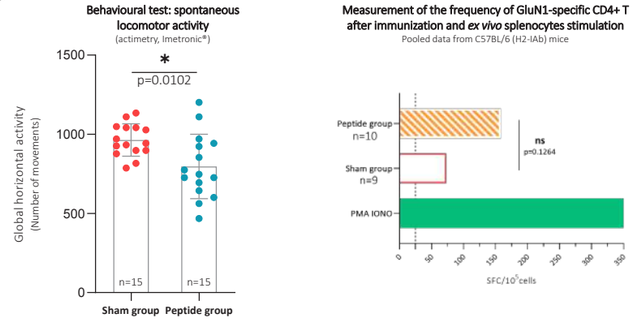
Results

2A In humans



Our study showed that, the stimulation with 2/10 GluN1 peptides induced a T-cell response in six healthy donors HLA DR1.

2B In mice



In mice, the most immunogenic predicted peptide caused locomotion disturbances after immunization but there is no difference in anxiety (O-maze), medium-term memorization (Y-maze) and depression-like (forced swim) behavioural tests. Nevertheless, today, T-cell response against the murine GluN1 peptide used to stimulate mice splenocytes *ex vivo,* is not detectable with the IFN-γ ELISpot technique.

Discussion

We identified two immunogenic peptides from GluN1 in the HLA DR1 human context: the peptide 3 and peptide 10.
Further studies are currently performed to determine whether peptides arise from the processing of the native GluN1 protein.
In mice, the most immunogenic predicted GluN1 peptide induced locomotion disturbances.
However, *ex vivo/in vitro* analysis must be completed to correlate immune response with behavioural tests; and must be performed with other GluN1 peptides.
Identifying CD4⁺ T epitopes will be helpful to understand the immunopathological mechanisms involved in neurological and psychiatric disorders and could be exploited to develop tolerogenic strategies such as a vaccinal approach with peptides or an adoptive cell therapy with specific regulatory T cell.

Dr Bhagteshwar Singh

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I am the coordinating clinical research fellow of the NIHR Global Health Research Group on Brain Infections ("Brain Infections Global"), based out of the University of Liverpool, and a senior trainee in infectious diseases & general internal medicine. I am currently based in India at the Christian Medical College, Vellore, and providing emergency COVID-19 support to the WHO Southeast Asia Region Office as a clinical consultant.

Pathogens causing brain infections in Brazil, India & Malawi: a Brain Infections Global systematic review and meta-analysis

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BACKGROUND

Encephalitis and other brain infections are a major cause of death and disability globally. Identifying responsible pathogens can be difficult, particularly with limited resources. This analysis was conducted to inform diagnostic testing approaches in our "Brain Infections Global" study, which aims to improve the diagnosis of patients with possible brain infections in Brazil, India and Malawi, using a pragmatic hospital intervention. It should also be of wider use to clinicians and policymakers who are seeking to ensure the right pathogens are prioritised for testing in each setting.

QUESTIONS

1. Which pathogens are responsible for acute brain infections in Brazil, India & Malawi?
2. Which tests & testing strategies have been used to identify pathogens?

METHODS

Inclusion criteria for studies: Published reports of causes of acute (onset <4 weeks before presentation) brain infections, including encephalitis, meningitis and brain abscess, in Brazil, India and Malawi.

Exclusion criteria for studies: Published before 1999; reporting only neonatal, neurosurgical or nosocomial infections; reporting < 100 patients.

Search: Pubmed and Scopus on 15 February 2019, using pre-defined search strategy; manual review of reference lists of included articles.

Screening & data extraction: By two reviewers independently using Rayyan (web-based systematic review software) and Excel.

Risk of bias: Assessed by two reviewers independently using a bespoke tool, modified from JBI prevalence study quality assessment tool.

Meta-analysis: Proportions of patients found to have each pathogen pooled across studies in each country; presented with 95% confidence intervals. Performed using *meta* package in *R*, employing a random-effects DerSimonian and Laird model with Freeman-Tukey transformation. Variation in pathogen mix explored in pre-defined clinical subgroups. Statistical heterogeneity tested using I^2.

FIGURE 1: PRISMA flow diagram (simplified)

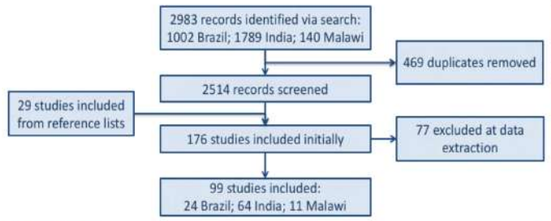
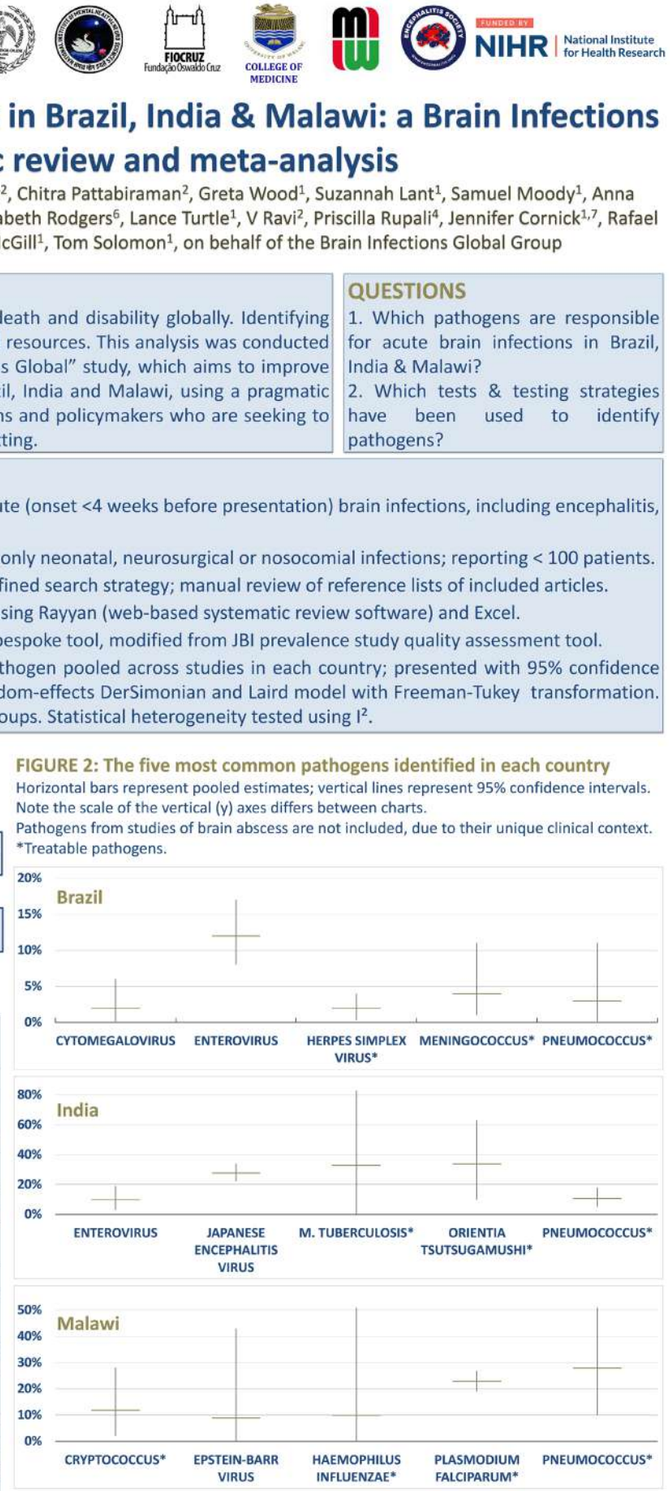


FIGURE 2: The five most common pathogens identified in each country

Horizontal bars represent pooled estimates; vertical lines represent 95% confidence intervals.
Note the scale of the vertical (y) axes differs between charts.
Pathogens from studies of brain abscess are not included, due to their unique clinical context.
*Treatable pathogens.



RESULTS

Of 2983 studies screened, 99 met eligibility criteria (Figure 1). 69/99 were prospective; 12 included adults only, 36 children, and 51 both; and 29/99 started recruitment after 2010.

Risk of bias varied, with fewer than half (44/99) achieving a score of 4/6 or above (*higher* score = *lower* risk of bias).

While 38/64 Indian studies reported causes of suspected/confirmed encephalitis, only 3/24 from Brazil and none of the 11 Malawian studies focused on encephalitis.

Due to wide variations in testing approach, the denominator used in the primary analysis was the number of participants tested for each pathogen.

The five most commonly reported pathogens for each country are reported in Figure 2. Three of the five in both Brazil and India, and four of the five in Malawi, are treatable.

Estimates were not precise (note wide confidence intervals in Figure 2), due to proportions varying significantly between studies (statistical heterogeneity), and several pathogens being tested for in smaller numbers of studies.

There were considerable differences in pathogen mix by age group, syndrome (e.g. encephalitis vs. meningitis) and the type and location (within each country) of study hospitals.

CONCLUSIONS

Causes of brain infections vary between the three countries, but the literature is mostly dated. Encephalitis is under-studied in Brazil and Malawi. At least three of the top five pathogens in each country are treatable, but often with very different drugs. The results highlight the need for large systematic studies to describe the causes of brain infections and the value of tailoring diagnostics to priority pathogens in low- and middle-income countries, both of which are core aims of the Brain Infections Global programme.

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Dr Suma R, a graduate in dental surgery is currently pursuing Masters in Public Health from Department of Epidemiology at NIMHANS. Her areas of interest are paediatric preventive dentistry, public health dentistry, infectious disease epidemiology with emphasis on neuroinfections and mental health promotion through life course approach.

Profile of patients with Acute Encephalitis Syndrome attending a tertiary care hospital in south India

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[1]MPH Scholar, Epidemiology, NIMHANS; [2]Additional Professor, Neurology, NIMHANS; [3]Professor, Epidemiology, NIMHANS; [4]Director of NIMHANS and Senior Professor, Epidemiology, NIMHANS; [5]Associate Professor, Psychiatric social work, NIMHANS; [6]Clinical Research Fellow, Brain Infections Global; [7]Professor, Neurovirology, NIMHANS; [8]Senior Professor, Neurovirology, NIMHANS

Introduction

- Encephalitis is of major public health importance worldwide as it causes huge emotional and economic loss to many lives(1).
- Aetiologies of Encephalitis vary worldwide and change constantly challenging the management(2,3).
- India is witnessing the classical spread of viruses causing neuro infections as in other tropical countries.
- Thus, an epidemiological understanding of this devastating disease is essential to develop better prevention, intervention, and control strategies.

Objective

- To describe the sociodemographic, clinical, etiological and neuroimaging profile of Acute Encephalitis Syndrome case patients visiting a tertiary neurospeciality care hospital in India.

Methodology

- Record review of all patients attending Neurology emergency and Out patient services, diagnosed with AES during 2019 was conducted.
- The records under the codes G02*, G02.0*, G04, G04.0, G04.8, G04.9, G05*, G05.0*, G05.1* of ICD 10 classification between January 1st 2019 to December 31st 2019 were retrieved.
- Data was collected using specifically developed Clinical case proforma for this study.

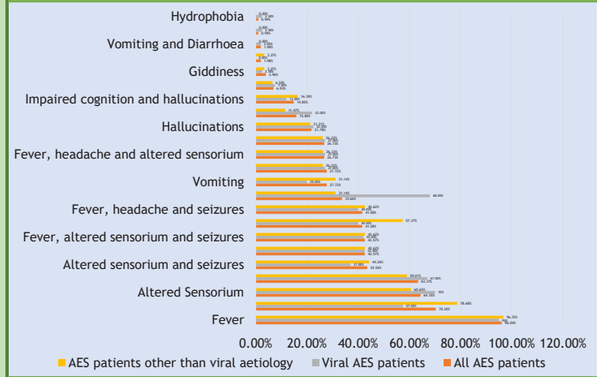
Sampling framework

*AIE = Autoimmune Encephalitis, MRD = Medical records department
Other diagnosis were Neuromyelitis optica spectrum disorder, Neuritis , Nystagmus, Spinal dysmorphism, Radiculopathy , Subacute sclerosing panencephalitis

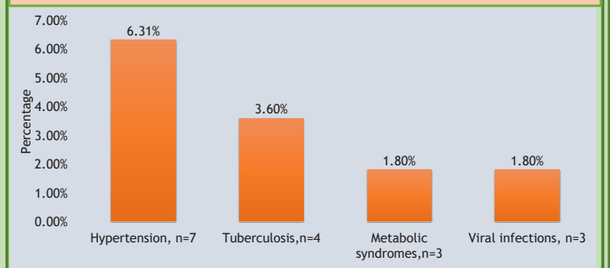
Results

- Most patients were adults (61.38%) and waged workers (46.53%).
- CSF pleocytosis was present in about 44% of the subjects and increased CSF protein was seen in 40 (39.6%) patients.
- Abnormal CT Brain and MRI findings were found among 44.55% and 41.58% of AES patients respectively.
- Recovery/improvement was seen for the treatment in 70% of Viral AES patients while for AES patients other than viral aetiology it was only in 42.62%.

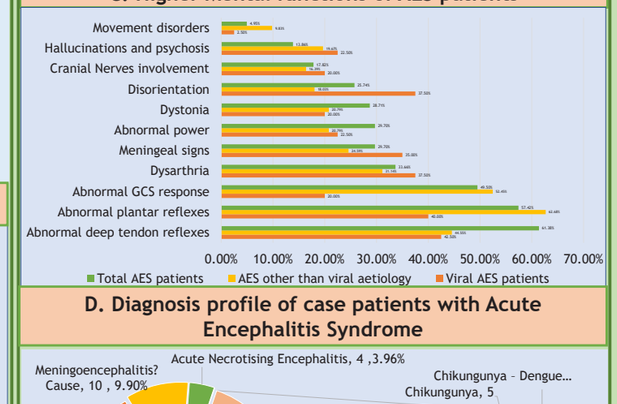
A. Clinical Features of AES patients



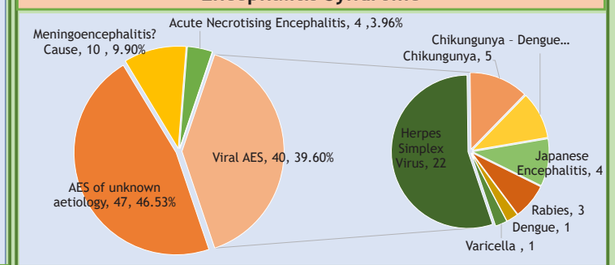
B. Comorbidities among AES patients



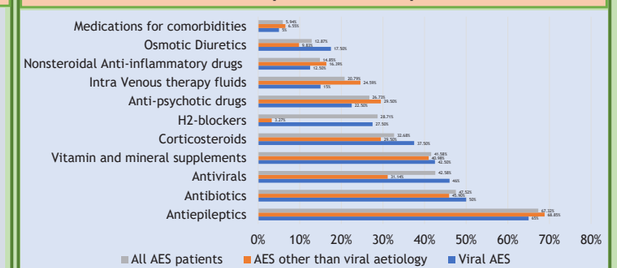
C. Higher Mental functions of AES patients



D. Diagnosis profile of case patients with Acute Encephalitis Syndrome



E. Treatment profile of AES patients



Conclusions

- The study provides a detailed sociodemographic, clinical and etiological profile of Acute Encephalitis Syndrome based on record review in a tertiary care hospital in India.
- Being a record review and a cross sectional assessment of AES patients during the hospital stay, the sequalae of such patients post discharge is not available.
- Based on the findings of the study, syndromic approach to diagnosis, laboratory investigations and management could be planned.

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Acknowledgements

- Centre for Public Health, Department of Epidemiology, NIMHANS, Departments of Neurology, Neurovirology, Medical records, Neuromicrobiology, Neuropathology, Neuroimaging and interventional radiology and the data centre of NIMHANS and Brain Infections Global project groups - Bengaluru and UK teams.

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I'm currently an Internal Medicine Trainee in East Yorkshire. I have recently completed a year long teaching post with Hull York Medical School, during which time I have studied a for a Postgraduate Certificate in Medical Education. Prior to this, I was working under the supervision of Dr Benedict Michael and Professor Tom Solomon during my Academic Foundation Programme, where I worked on several projects in relation to encephalitis. I graduated from the University of Manchester with my primary medical qualification and a Masters of Research in medical sciences.

UNIVERSITY OF LIVERPOOL

NHS The Walton Centre NHS Foundation Trust

How should we define a 'good' outcome from encephalitis?

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Introduction

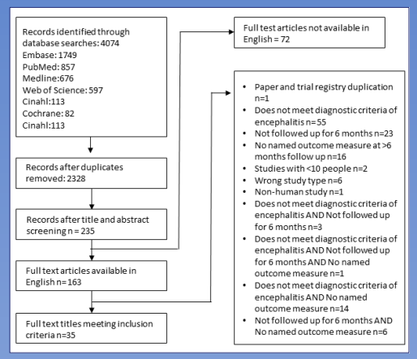
Encephalitis is inflammation of the brain caused by infection or autoimmunity. The majority of survivors suffer neurological sequelae (1). Standardised outcome measures which assess quantitative and qualitative data, which are applicable across a range of settings and aetiologies, and crucially are important for patients and their family, are needed for accurate interpretation of both observational studies and clinical trials (2,3,4). The first step in developing this process is a better understanding of the strength and weaknesses of those measures which have been used in observational studies and clinical trials.

Methods

A systematic literature review has been performed using Cochrane Library, Web of Science, EMBASE, PubMed, MEDLINE and CINAHL in June 2019. The search strategy included 45 variants of the phrase "long term sequelae" and 7 terms related to "encephalitis" which were separated with the Boolean operator "OR", with the two groups combined using the Boolean operator "AND". One Reviewer screened titles, abstracts and two Reviewers determined if shortlisted full-text articles met the inclusion criteria. Key data was extracted from these papers and presented as a narrative summary composed in close collaboration with encephalitis patient and public input with third sector partners throughout.
Inclusion criteria:

- Human
- Diagnosis of encephalitis meeting one of the following criteria:
  - Identified aetiology identified with clinical correlation
  - Clinical diagnosis meets consensus statement of the international encephalitis consortium (5), or the case definition for autoimmune encephalitis (6), or the International Pediatric Multiple Sclerosis Study Group criteria for the diagnosis of ADEM (7).
- A named outcome measure used to follow up the patient
- Minimum follow up time of 6 months
- Published after 1990
- Full text available in English after reasonable efforts to translate
- Case series including more than 10 patients, case-control studies, cohort studies, controlled trials.

Prisma Flow Chart



Results

A total of 35 papers were included, in which 37 named outcome measures were used on a total of 3,133 patients. These broadly fall into five categories: physical, cognitive, mood, quality of life, and functional outcomes. The outcome measures used for most patients were Modified Rankin Score, Glasgow Outcome Score, Barthel index, and Euro-QoL-5D, which were all used on over 1,000 patients each. GOS used in 46%, mRS in 33%, Barthel in 37% . In 14 papers, complex neurological, psychiatric, psychological outcomes were expressed as one of these 5-6 point scales, which tested a total of 601 (19%) of patients.

Physical Outcome Measures	Number of Studies	Number of patients
Modified Rankin Scale	18	1034
Glasgow Outcome Score	6	1436
Barthel Index	5	1173
Expanded Disability Status Scale	3	147
Adapted Modified Rankin Scale	2	112
Rankin Scale	1	26
Glasgow Outcome Score-Extended	1	Protocol only
Glasgow Outcome Score-Extended Paeds	1	Protocol only
Gross Motor Function Classification System	1	Protocol only
National Hospital Seizure Severity Scale	1	109
Total	39	4037

Mood Outcome Measures	Number of Studies	Number of patients included
Beck Depression Inventory	3	72
Beck Anxiety Inventory (BIA)	2	Protocols only
Strengths and Difficulties Questionnaire (SDQ)	1	Protocol only
WHO-5 Wellbeing Index	1	26
Hamilton Depression Scale	1	33
Zung Depression Scale	1	96
Zung Anxiety Scale	1	96
Total	10	323

Functional Outcome Measures	Number of Studies	Number of patients
Liverpool Outcome Score	6	370

Cognitive Outcome Measures	Number of Studies	Number of patients
Mini Mental State Examination	3	210
Wechsler Memory Scale IV (WMS-IV)	3	Protocols only
Wechsler Adult Intelligence Scale IV (WAIS-IV)	2	Protocols only
Trail Making Test parts A&B	2	Protocols only
Addenbrookes Cognitive Examination	2	33
Kognitive Probleme bei Kindern und Jugendlichen (KOPKIJ)	1	12
Hamburg-Wechsler intelligenztest fur Kinder-III(HAWIK-II)/Hannover-Wechsler-Intelligenztest für das Vorschulalte- III (HAWIVA - III)	1	12
Kaufman Assessment Battery for Children (K-ABC)/testing battery for attentional performance (KiTAP)	1	12
Adaptive Behaviour Assessment	1	Protocol only
Bayley Scales of Infant and Toddler Development III (BSID-III)	1	Protocol only
Wechsler Preschool and Primary Scale of Intelligence III (WPPSI-III)	1	Protocol only
Wechsler intelligence scale for children IV	1	Protocol only
Language module in neuropsychological assessment battery (NAB)	1	Protocol only
Informant Questionnaire on Cognitive Decline in the Elderly	1	253
Telephone Interview for Cognitive Status (TICS-M)	1	72
Total	22	582

QoL Outcome Measures	Number of Studies	Number of patients
Euro-QoL-5D	3	1107
Short Form-36	2	Protocol only
Short Form-12	1	26
Lancashire Quality of Life Profile	1	72
Paediatric Quality of Life Inventory	1	49
Total	9	1254

Discussion

Many outcome measures have been applied to presenting outcome data for patients with encephalitis.

Most of these outcome measures assess only a single category of post-encephalitic sequelae.

Excluding the Liverpool Outcome Score, the outcome measures used are not validated in encephalitis.

Areas for future research:

- Validating the outcome measures used in encephalitis research
- Working with patient and public groups to develop a composite outcome measure using both existing and potentially novel core datasets that assesses the outcome domains of importance to both clinicians and patients.
- Development of a core outcome set to enable data comparison between research studies

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Dr Volonghi is a medical doctor who studied at the University of Brescia and got her degree in 2007. In 2012 she worked with Prof. Rothwell and his team in the OXVASC study and in 2013 she finished the residency in Neurology with a thesis about stroke in young people. From 2013 up to now, she has been working in the Neurology Unit of Spedali Civili di Brescia, her main interests being cerebrovascular disease in the first period and thereafter neurologic infectious diseases and neuroimmunological disorders, including myasthenia gravis, autoimmune and paraneoplastic

PARANEOPLASTIC LIMBIC ENCEPHALITIS ASSOCIATED WITH SIADH AND TRIPLE ANTIBODY-POSITIVITY

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INTRODUCTION

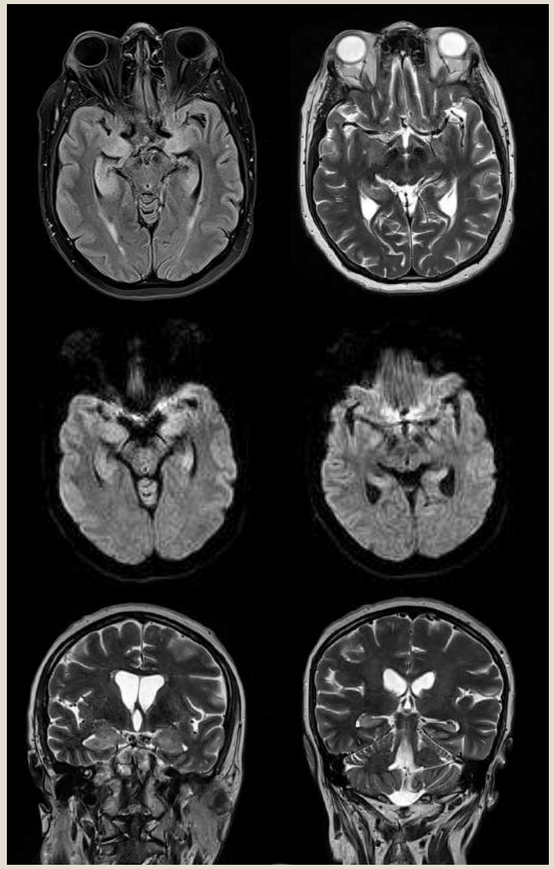
Limbic encephalitis is a rare neurological condition characterized by memory loss, confusion, sleep disturbances and seizures. It could be paraneoplastic or not and associated with different autoantibodies, the most frequent being LGI1, CASPR, AMPAR, GABA-b R, Hu, Ma2 and GAD antibodies.

METHODOLOGY

We describe a 58-year-old woman who was admitted to our hospital because of focal temporal seizures, memory loss and hyponatremia.

FINDINGS

Her medical history was notable for hypertension, schizophrenia and bipolar disorder. Medications included Aripiprazole, Vortioxetine, Bisoprolol, Ramipril and Hydrochlorothiazide. Computed tomography (CT) of the head was unremarkable, whereas electroencephalogram revealed focal temporal epileptic activity. Brain MRI showed bilateral temporal hyperintensities on T2 and FLAIR sequences with mild diffusion restriction on DWI.



A lumbar puncture revealed moderate protein increase with 6 cells and oligoclonal bands.
In the hypothesis of LGI1 encephalitis, we started intravenous methylprednisolone for 3 days followed by oral prednisone tapering, with rapid improvement of both confusion and seizures. For the hyponatremia, fluid restriction and hypertonic salin were applied at first and when the blood sodium increased, furosemide and sodium chloride tablets were prescribed. The patient underwent imaging of the chest, abdomen and pelvis to look for evidence of occult cancer, but no specific findings were detected. She went home and after few weeks we received the results of the autoantibody panel, which surprisingly did not show the presence of LGI1 antibodies, but revealed a positivity for GABA-b receptor (serum and CSF), anti-Hu and GAD (serum) antibodies. FDG-PET was then prescribed, revealing the presence of lung cancer with bone metastasis. Histological examination was conclusive for a small cell lung cancer (SCLC). During the subsequent chemotherapy the patient had a further clinical improvement without any other neurological disturbances. After the chemotherapy conclusion however, memory loss got worse as well as hyponatremia. In the attempt to improve the quality of life of the patient, we then tried prednisone again, together with cyclophosphamide and plasma exchange, but, unfortunately, no further improvement was seen.

DISCUSSION/CONCLUSIONS

Limbic encephalitis and hyponatremia are not pathognomonic of LGI1 encephalitis and could represent different paraneoplastic syndromes in SCLC. In the contrast to LGI1 encephalitis, in which the antibodies are proposed to affect hypothalamic release of antidiuretic hormone (ADH) or directly act on receptors in the kidneys, in SCLC, hyponatremia is linked to a syndrome of inappropriate ADH secretion (SIADH) secondary to the ectopic production of ADH. Our patient is exceedingly peculiar because of the presence of triple antibody-positivity, a condition that strongly recommend searching for a tumor.

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After attending the Neurological Intensive Care Unit and the Stroke Unit of the Hospital in Verona in 2014, I began the formal training as a resident in Neurology at the University of Verona in 2016. In those years of regular and continuous attendance, I completed my education as a neurologist and I was introduced to the field of Neuroimmunology and basic sciences thanks to the continuous attendance at the Neuropathology Laboratory. From September 2019 to March 2020 I worked as a Research Fellow at the Neuroimmunology Laboratory of the Mayo Clinic (Rochester, MN, USA), under the direct supervision of Professor Andrew McKeon. There, I focused on many research projects including the identification of new autoantibodies. I am still working on those projects as a research collaborator. I consolidated my interest and expertise into the clinical and pathological manifestations of neurological autoimmune diseases and in performing different diagnostic techniques/assays that can be applied to both Clinical and Research/Development settings.

SARS-CoV-2 infection: a potential trigger of inflammatory neurological disorders

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INTRODUCTION

Autoimmune encephalitis can be triggered by viral infections, as described in patients with antibodies to neuronal cells surface proteins or myelin oligodendrocyte glycoprotein (MOG). Few cases associated with acute SARS-CoV-2 infection have been reported. However, the possible occurrence of parainfectious/postinfectious encephalopathies has not been extensively examined, yet.

METHODS

We retrospectively identified patients referred for antibody testing (i.e. MOG or neuronal cell surface antigens) to the Laboratory of Neuropathology, University Hospital of Verona, Italy, between March 1st, 2020 and August 31st, 2020. Among the 339 included cases, 107 were referred for suspected autoimmune encephalitis (encephalitis cohort) and 232 cases presenting with myelitis, isolated optic neuritis, or ADEM had suspected MOG-associated disease (MOGAD cohort).

SARS-COV-2 IgA and IgG were analysed in all sera with an FDA approved ELISA kit (Euroimmun, Luebeck, Germany) according to manufacturer's instruction. Available CSF of seropositive patients were also tested, as previously described (at 1:10 dilution).[1] To evaluate the test used, 453 pre-COVID-19 pandemic samples were also analysed and the test showed a high specificity (97.4% for IgA and 99.8% for IgG).

We collected demographic, clinical, and paraclinical information including brain/spinal cord MRI, electroencephalogram and CSF data of all IgG/IgA seropositive cases and of a group of 75 seronegative subjects, for comparison. Disability at discharge was graded according to the Modified Ranking Scale (mRS) and was taken as the primary outcome measure considering mRS≤2 as consistent with a good outcome. All patients consented to diagnostic procedures and biological sample storage at the referring laboratory.

RESULTS

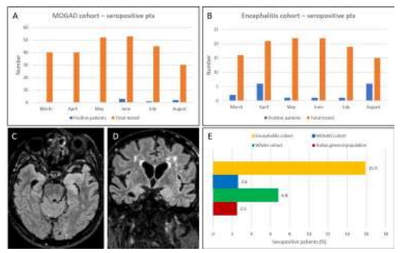
We identified 23 patients seropositive for SARS-CoV-2 IgA and/or IgG (IgA and IgG n=13, IgA only n=9, IgG only n=1). Among these, 6 patients belonged to the "MOGAD cohort" and 17 to the "encephalitis cohort". The temporal distribution of seropositivity in the two cohorts is reported in Fig. A and B. Among 21 paired CSF samples available, 3 resulted positive for SARS-CoV-2 IgG and 1 for both IgA and IgG. Patients with CSF positive SARS-CoV-2 antibodies had a diagnosis of ADEM with known SARS-CoV-2 infection (n=1), SARS-CoV-2 para-infectious limbic encephalitis (n=1), and idiopathic transverse myelitis (n=2). A well-known SARS-CoV-2 infection was reported by treating physicians in only 10 cases, diagnosed with positive SARS-CoV-2 PCR on nasopharyngeal swab (n=9) or CSF (n=1). In 1 case with interstitial pneumonia the infection was highly suspected but not confirmed by several molecular analyses. Interestingly, only 6 patients had symptoms consistent with SARS-CoV-2 infection. In particular, 2 patients had fever and cough, 1 case had exclusively anosmia and ageusia, and 3 patients had interstitial pneumonia, resolved before neurological symptoms' onset. Autoimmune testing revealed the presence of MOG-IgG in 1 pediatric case with ADEM, titin-IgG in 1 patient with post-infectious encephalitis, and amphiphysin-IgG in 1 case with limbic encephalitis (Fig C-D). Demographic, clinical, laboratory, and radiological information of seropositive cases are reported in Table 1. Detailed comparison between the seropositive and the seronegative group is reported in Table 2.

Pt no. age, gender	Known SARS-CoV-2 infection	COVID systemic symptoms	Abnormal MRI	CSF cells, protein (mg/dL)	Diagnosis	Cohort	Specific Ab	Serum SARS-CoV-2 IgG	Serum SARS-CoV-2 IgA	CSF SARS-CoV-2 IgG	CSF SARS-CoV-2 IgA
1. 53, M	No	No	Yes	2, 43	Optic neuritis	MOG	0	+	+		
2. 68, F	No	No	No	0, 22	Axonal polyneuropathy	ENC	0		+		
3. 83, M	No	No	Yes	1, 36	Limbic encephalitis	ENC	Amphiphysin		+		
4. 58, F	No	No	NA	NA	Optic neuritis	MOG	0	+	+		
5. 75, M	Yes	No	No	3, 40	Encephalopathy	ENC	0	+	+		
6. 78, F	Yes	Yes	Yes	57, 113	Encephalitis	ENC	0		+		
7. 70, F	Yes	Yes	Yes	2, 27	Encephalitis	ENC	0	+	+		
8. 27, F	No	No	NA	10, 25	Myelitis	MOG	0	+		+	
9. 67, F	No	No	Yes	10, 72	3rd cranial nerve palsy	ENC	0		+		
10. 73, F	Yes	No	Yes	4, 58	Encephalitis	ENC	Titin	+	+		
11. 36, F	No	No	No	19, 48	Focal epilepsy	ENC	0		+		
12. 70, F	No	No	Yes	1, 33	Encephalopathy	ENC	0	+	+		
13. 69, M	Yes	Yes	Yes	1, 77	Limbic encephalitis	ENC	0	+	+	+	+
14. 77, M	Yes	No	No	1, 50	Encephalitis	ENC	0	+	+		
15. 61, M	No	No	Yes	20, 35	Myelitis	MOG	0	+	+	+	
16. 20, F	No	No	No	0,40	Status epilepticus	ENC	0	+	+		
17. 5, F	No	No	Yes	33, 30	ADEM	MOG	MOG		+		
18. 60, F	Yes	No	No	0, 21	Encephalitis	ENC	0	+	+		
19. 64, F	Yes	Yes	Yes	22, 45	ADEM	MOG	0	+	+	+	
20. 71, F	Yes	Yes	No	NA	Encephalopathy	ENC	0	+	+		
21. 58, M	No	No	NA	NA	Encephalitis	ENC	0		+		
22. 71, M	No	No	Yes	9, 59	Status epilepticus	ENC	0		+		
23. 73, F	Yes	Yes	Yes	16, 23	Limbic encephalitis	ENC	0	+	+		

Table 1

	Seropositive (n=23)	Seronegative (n=75)	*P* value
Age, mean (median, range)	60.3 (68, 5-83)	45.3 (42, 18-85)	0.001
Female gender (%)	15/23 (65)	45/75 (60)	0.653
Significant comorbidities (%)	9/23 (39)	23/75 (31)	0.449
Seizures (%)	8/23 (35)	8/75 (11)	0.006
Myelitis (%)	3/23 (13)	17/75 (23)	0.316
Optic neuritis (%)	3/23 (13)	21/75 (28)	0.145
Encephalopathy (%)	17/23 (74)	24/75 (34)	0.001
Positive MRI (%)	13/20 (65)	60/73 (82)	0.097
Abnormal EEG (%)	11/13 (85)	19/23 (83)	0.877
CSF pleocytosis (%)	9/20 (45)	49/72 (68)	0.059
CSF protein content increased (%)	8/20 (40)	36/72 (50)	0.428
CSF restricted oligoclonal bands (%)	0/10	31/63 (49)	0.003
Autoantibodies positivity (%)	3/23 (13)	5/75 (7)	0.329
Outcome at discharge (mRS), mean	2.8	1.4	0.004

Table 2



DISCUSSION

We herein describe a cohort of patients with neurological symptoms and concomitant SARS-CoV-2 antibodies. The design of this examination, which is different from previous studies aiming to assess neurological symptoms in patients with well-known COVID-19, allowed us to describe in detail the neurological conditions associated with antibody positivity and to report patients with neurological symptoms in the context of an asymptomatic or pauci-symptomatic infection.

The frequency of SARS-CoV-2 seropositivity was higher in our study group (6.9%) than in the Italian population (2.5%). When considering the two included cohorts separately, it becomes clear that this difference was mainly due to patients with suspected encephalitis (15.9% of seropositivity), while in patients with suspected MOGAD the frequency of seropositivity (2.6%) was broadly in line with that reported in the general population (Fig. E).

Interestingly, in the encephalitis cohort the "peaks" of seropositivity followed the trend of the infection among the general population (first peak between March and April and a second one in mid-August, Fig. A), thus supporting a para-infectious rather than post-infectious etiology. On the other hand, the few seropositive cases with suspected MOGAD have been registered 2-4 months after the first peak of SARS-CoV-2 infection (Fig. B), thus suggesting a possible post-infectious origin of the disease.

Among our findings, the observation that seropositive cases were significantly older than seronegative patients was not unexpected, since SARS-CoV-2 infection in more common in older subjects.

Interestingly we also noted a significantly higher frequency of encephalopathy/encephalitis in the seropositive subgroup. These data further reinforce our observation on the high incidence of encephalitis/encephalopathy among seropositive cases and expand previous observations on the high frequency of encephalopathy in patients with COVID-19, providing evidence of the occurrence of this syndrome also in patients without a severe systemic infection.[2]

Finally, the concomitant CSF SARS-CoV-2 positivity in 4 seropositive cases (in 2 patients in absence of respiratory symptoms) gives further strength to our findings. The prevalence of myelitis in this cohort might suggest that spinal cord involvement is a peculiar feature of paired serum and CSF positivity, but this hypothesis has to be confirmed in larger studies.

CONCLUSION

An antecedent/concomitant SARS-CoV-2 infection occurs in a significant percentage of patients with encephalitis/encephalopathy, usually in absence of well-known neuronal antibodies and also in cases without systemic symptoms. Future larger multicenter and prospective studies will expand our observations and clarify the pathological nature of these conditions.

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