ENCEPHALITIS CONFERENCE

Encephalitis 2022

THURSDAY
1ST DECEMBER 2022
09.00 - 18.15

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Poster Booklet

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Prof Dr Ajit Rayamajhi is a Consultant Paediatrician and works for the Government of Nepal. Besides clinical work, his research interest is to improve recognition and understanding of pathogenesis, diagnosis, management (including search of newer treatments) for children suffering from Acute Encephalitis Syndrome, especially Japanese encephalitis. He works with the Government, World Health Organization and other local and International Non- Government agencies for control of this dreadful disease which usually begins as a mild flu-like illness and quickly progresses to severe disability and death.

COMPARISON OF ALERT, RESPONSE TO VERBAL STIMULUS, RESPONSE TO PAIN, UNRESPONSIVE SCALE WITH PEDIATRIC GLASGOW COMA SCALE FOR ASSESSING LEVEL OF CONSCIOUSNESS IN CHILDREN

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Background

In pediatric population altered consciousness is a neurological emergency associated with high morbidity and mortality. Pediatric Glasgow Coma Scale (pGCS) is commonly used in the assessment of altered sensorium in children[1,2]. Alert, Verbal, Pain, Unresponsive (AVPU) scale being simple, easy to apply and not requiring sophisticated training can be alternative assessment tool[3]. Hence this study was conducted with the objective to compare accuracy of AVPU scale with pGCS for assessing level of consciousness in children.

Methodology

All children aged 2 months to 14 years with altered sensorium (GCS < 15), meeting inclusion criteria, in Emergency Department and Pediatric Intensive Care Unit of Kanti Children's Hospital, Kathmandu, Nepal from August 2021 to June 2022, were enrolled. Mean of pGCS for each component of AVPU scale was calculated and compared.

Results

Of the total 55 cases, 30 (55%) were male (male to female ratio1.2:1) and 33 (60%) below 5 years of age (mean 2.2 years) (Figure 1). Infectious etiology was in 35 (64%) and 20 (36%) non-infectious. Acute meningitis was 21 (38%), acute encephalitis 8 (14%), septicemia 6 (11%), acute gastroenteritis 3 (5%), hypertensive encephalopathy 3 (5%), hepatic encephalopathy 3 (5%), pediatric stroke 2 (4%) and other diagnosis 9 (16%). Verbal response observed in 47% was the most common AVPU scale (Table 1). Most common pGCS score was ≥ 8 seen in 90 % (Table 2). A/V/P/U of AVPU scale corresponded with mean pGCS score of 14, 12.5, 9.29 and 3.8 respectively (Table 3). One-way analysis of variance showed all components of AVPU had significantly different average pGCS scores (P < 0.001).

Conclusion

AVPU scale was comparable to pGCS in assessing level of consciousness in children with altered sensorium of both infectious and non-infectious etiology.

References

1. Borgialli DA, Mahajan P, Hoyle JD, Powell EC, Nadel FM, Tunik MG et al. Performance of the Pediatric Glasgow Coma Scale Score in the Evaluation of Children With Blunt Head Trauma. Acad Emerg Med, 2016 Aug;23(8):878-84. doi: 10.1111/acem.13014.
2. Reilly PL, Simpson DA, Sprod R, Thomas L. Assessing the conscious level in infants and young children: A paediatric version of the Glasgow Coma Scale. Childs Nerv Syst. 1988 Feb;4(1):30-3.
3. American College of Surgeons Committee on Trauma. Advanced Trauma Life Support for Doctors, 6th edn. Chicago: American College of Surgeons, 1997.

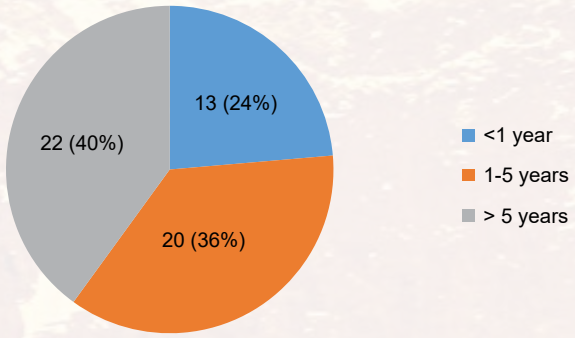

Figure 1: Shows distribution of recruited cases by age groups (n=55)

Table 1: Distribution of cases according to AVPU scale (n=55)

AVPU scale	Number (%)
Alert	7 (13%)
Verbal	26 (47%)
Pain	17 (31%)
Unresponsive	5 (9%)

Table 2: Distribution of cases according to pGCS score (n =55)

pGCS score	Number (%)
3	3 (5%)
5	2 (4%)
8	3 (5%)
9	7 (13%)
10	7 (13%)
11	3 (5%)
12	10 (18%)
13	9 (17%)
14	11 (20%)

Table 3: Comparison of pGCS score with of AVPU scale (n=55)

AVPU scale	pGCS Score		*p*- value
	Mean	Standard Deviation	
Alert	14	0.001	<0.001
Verbal	12.5	0.99	
Pain	9.3	0.85	
Unresponsive	3.8	1.09	

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Phenotyping cerebellar involvement as an immune-related adverse event in patients treated with immune checkpoint inhibitors: a systematic review.

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INTRODUCTION

The introduction of immune checkpoint inhibitors (ICI) has deeply reshaped the panorama of oncological therapies, however there is growing evidence that the use of these drugs is associated with the development of immune-related adverse events (iRAE). Among different clinical phenotypes that have been described, cerebellar involvement currently lacks a proper description.
The aim of this study is to characterize cerebellar iRAE through a systematic review of the literature.

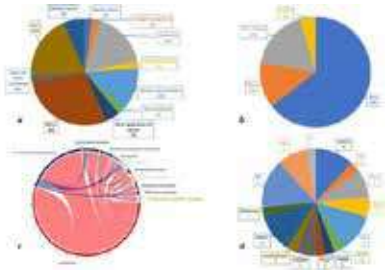
METHODS

A systematic review of the literature was performed according to PRISMA guidelines.
All cases were evaluated in a consensus of three neurologists.
Studies reporting patients with cerebellar involvement in association with iRAE were included and data from individual patients were extracted.
Cases in which another condition could alternatively explain cerebellar sings/symptoms were excluded.
Clinical, demographic and oncological data were collected by two authors and a comparison of patients with isolated cerebellitis versus multifocal involvement ("cerebellitis-plus") with seronegative and seropositive antibody status were performed.

RESULTS

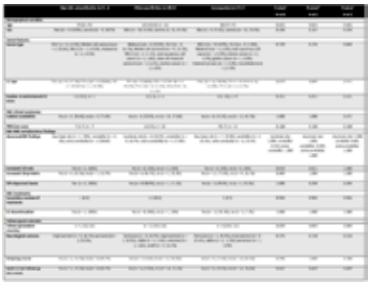
After screening 2765 records, 32 studies with 46 patients were included.
Median age was 63 (20-82), and most patients were male (n=29, 63.0%). Isolated cerebellitis was observed in 15 (32.6%) cases, while the remaining had "cerebellitis plus", mostly associated with encephalitis/encephalopathy.
Associated tumors included most frequently lung cancer, melanoma, and Merkel cell carcinoma. PD-1 inhibitor was the most commonly administered treatment (n=29, 64.4%), while exposure to CTLA-4 inhibitor was rare (n=2, 4.5%).
MRI was abnormal in 16 (43.2%) patients and inflammatory CSF findings were frequently observed.
Autoantibodies were detected in 26 (61.9%) patients and included novel reactivities. Among treatment strategies, the most common were steroids (n=36) and ICI discontinuation (n=28, 90.3%).
Relapses were reported in 5 (10%) patients.
Most patients showed improvement/remission (n=31, 73.8%), but, at last follow-up, 12 (26.1%)deceased.

The comparison of patients with isolated versus cerebellits-plus demonstrated a worse neurological outcome for the latter group (p=0.047), whereas patients with seronegative antibody status had more frequently non small cell lung cancer (p=0.004).
Finally, the comparison of patients according to the presence of high-risk, other autoantibodies and negative serostatus did not disclose any significant difference.



(a) oncological accompaniments of cerebellar immune-related adverse events (iRAE), (b) immune checkpoint inhibitors associated with the development of cerebellar iRAE, (c) chord diagram representing the association of clinical phenotypes among the included patients (R, circlize package), (d) antibody specificities in seropositive patients

Relevant demographic, clinical, paraclinical and radiological features of patients included in the systematic review.



Comparison of included patients according to the presence of high-risk antibodies, other specificites, and seronegative status

DISCUSSION

We higlighted, in our systematic review, some typical features of cerebellar involvement during treatment with ICIs, in particular that:

- cerebellitis may occur in isolation or in the context of a multifocal involvement;
- cerebellar imaging is frequently negative, but CSF usually shows inflammatory signs;
- PD-1 and PD-L1 inhibitors are the most frequent associated ICIs;
- Oncological accompainments differ from those usually associated with the paraneoplastic rapidly progressive cerebellar syndrome
- the majority of patients are seropositive for autoantibodies, including newly described reactivities
- the overall prognosis may be poor due to cancer progression, even though most of patients improve after immunotherapy.

CONCLUSION

We provide a systemic characterization of an unfrequent complication of cancer immunotherapy. The rapidly spreading of ICI as cancer therapy will likely cause an increase of IRAEs during the next years, and neurologist should be aware of these neurological complications to offer a prompt diagnosis and treatment.

For more informations
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Read more: 10.1111/ene.15624

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Dr Amy Quek is a Senior Consultant Neurologist at the National University Hospital and holds the academic rank of Assistant Professor at the Yong Loo Lim School of Medicine, National University of Singapore. She graduated from National University of Singapore and obtained her Membership of the Royal College of Physicians, UK. She completed Neurology Advanced Specialist Training at the National University Hospital, and Neuroimmunology Fellowship at the Mayo Clinic, USA. Dr Quek's clinical and research interests focus on the diagnosis and treatment of autoimmune and inflammatory neurological disorders, including autoimmune encephalitis, multiple sclerosis and neuromyelitis optica, as well as the interpretation of neural autoantibodies.

Meningoencephalitis following mRNA COVID Vaccination

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INTRODUCTION

Neurological events are dreaded but uncommon complications that can follow COVID-19 vaccination.[1] We describe 2 patients who developed meningoencephalitis following vaccination with SARS-CoV-2 mRNA BNT-162b2 (Pfizer-BioNTech).

METHODOLOGY

Medical records were reviewed to summarize key clinical, MRI and CSF findings.

CASE DESCRIPTION

Patient 1

Patient 1 is a 40-year-old man who presented with fever, headache, confusion and agitation 11 days after receiving his first dose of BNT-162b2 vaccine.

Cerebrospinal fluid evaluation demonstrated normal opening pressure (13 cmH20), lymphocytic pleocytosis (44 WBC/uL, 91% lymphoctyes), with elevated protein 0.69 g/L and normal glucose 3.3 mmol/L (serum glucose 6.7 mmolL). Electroencephalogram revealed generalized slowing in both hemispheres while MRI scan revealed normal brain structures. CSF and serum neural antibody screen was unremarkable, except for a low GAD antibody titer (0.14 nmol/L). Empirical antimicrobials (ceftriaxone, ampicillin and acyclovir) were ceased after infective investigations returned negative.

His symptoms spontaneously resolved 2 weeks later. Immunotherapy was not administered. He received his 2nd and 3rd doses of BNT-162b2 vaccines without symptom recurrence.

Patient 2

Patient 2 is a 63-year-old man with hypertension, hyperlipidaemia, diabetes mellitus, ischaemic heart disease and a remote history of tuberculosis. He presented with a 5-day history of fever that started 3 weeks after his first BNT-162b2 dose, was accompanied by confusion and drowsiness.

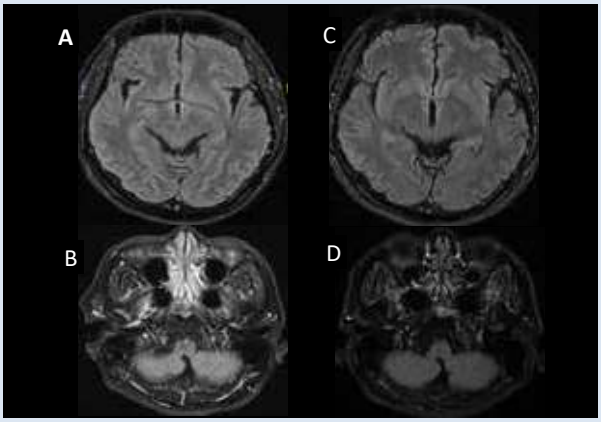
Neurologic examination revealed facial dyskinesia, dysmetria, myoclonus and gait unsteadiness. There were 23 WBC (82% lymphocytes), elevated protein (3.28 g/L) and normal glucose on CSF examination. Leptomeningeal enhancement was seen on MRI brain, and electroencephalogram demonstrated generalised slowing in both cerebral hemispheres (A) and (B). His serum and cerebrospinal fluid were negative for neural antibodies.

He was treated empirically for tuberculosis with anti-tuberculous medications, together with dexamethasone.

CASE DESCRIPTION (CONT)

He recovered within 2 months, and a repeat MRI brain showed resolution of the leptomeningeal enhancement (C) and (D). Cerebrospinal fluid cultures for tuberculosis later returned as negative from 3 separate lumbar puncture samples.

He received his 2nd and 3rd doses of BNT-162b2 vaccines without experiencing a neurological relapse.



MRI brain scans of Patient 2

MRI postcontrast axial fluid attenuated inversion recovery scans showed diffuse smooth leptomeningeal enhancement in the bilateral parieto-occipital lobes (A), around the brainstem and medial aspect of bilateral cerebellar hemispheres (B). 2 months after anti-tuberculous treatment and dexamethasone, there was resolution of the leptomeningeal enhancement (C) and (D).

CONCLUSION

Self-limiting meningoencephalitis was observed in 2 patients shortly following mRNA vaccination against SARS-CoV-2. No recurrences were observed on subsequent dosing of the mRNA vaccine, suggesting that such events may not preclude completion of the COVID vaccination schedules. Although temporally associated, a causal relationship with vaccine remains uncertain.[2] Future studies should examine the mechanistic link between vaccination and meningoencephalitis.

REFERENCES

1. Koh JS, Hoe RHM, Yong MH, et al. Hospital-based observational study of neurological disorders in patients recently vaccinated with COVID-19 mRNA vaccines. J Neurol Sci 2021;430:120030. DOI: 10.1016/j.jns.2021.120030.
2. Butler M, Tamborska A, Wood GK, et al. Considerations for causality assessment of neurological and neuropsychiatric complications of SARS-CoV-2 vaccines: from cerebral venous sinus thrombosis to functional neurological disorder. J Neurol Neurosurg Psychiatry 2021;92(11):1144-1151. DOI: 10.1136/jnnp-2021-326924.

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Andrea Gestsdottir is a medical student and did a one-year undergraduate research project under the supervision of Professor Morten Blaabjerg in Odense Autoimmune Encephalitis Research Group.

Assessment of CASE and NEOS scores in a Danish National NMDAR-encephalitis cohort

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BACKGROUND

The Clinical Assessment Scale in Autoimmune Encephalitis (CASE), is the first scale designed explicitly to evaluate the characteristic symptoms of AE and help assess the effectiveness of treatment and time of treatment escalation.
To predict neurological outcome 1-year after anti-NMDARE, the anti-NMDAR Encephalitis One-Year Functional status (NEOS) score, was developed.
As both CASE and NEOS are new tools, there is limited research on their performance in a real-life setting.
The aim of this study was to assess the function of the these scales in a national anti-NMDAR AE cohort.

METHODS

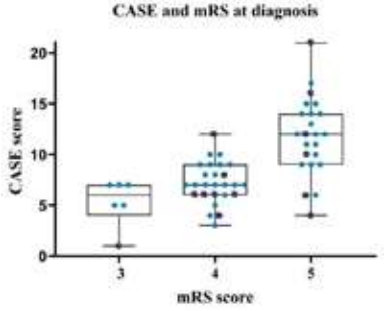
We retrospectively evaluated 55 patients from the Danish NMDARE cohort (2009-2019) according to CASE and 53 according to NEOS scores and mRS at one-year follow-up.
Patients were grouped based on underlying etiology into:
i) Idiopathic/teratoma associated
ii) Other (concomitant malignancy, demyelinating disease and post-herpes simplex).
Performance of CASE was assessed by internal consistency, reliability and comparison to mRS.
The association between the NEOS and one-year functional outcome was evaluated using a multivariate logistic regression model and Receiver-Operating Characteristic analysis.

RESULTS

Reliability of CASE

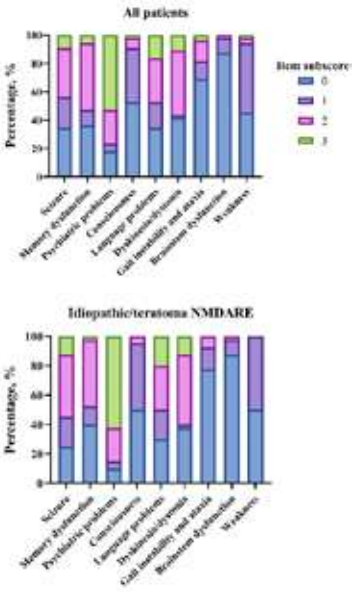
Inter- and intrarater reliability:
Intraclass correlation coefficient = 0.97/ 0.77
Internal consistency: Cronbach α = 0.54

Correlation of CASE and mRS



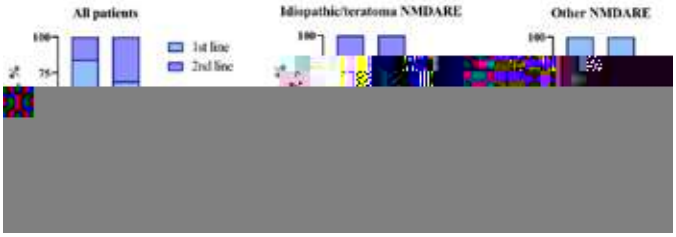
The total scores of the CASE compared to the mRS in the acute phase of disease. The values of mRS 0, 1, 2 and 6 are missing as no patient obtained those scores in the acute phase. Each box marks the interquartile range with a centre line representing the median.

Distribution of symptoms at disease onset



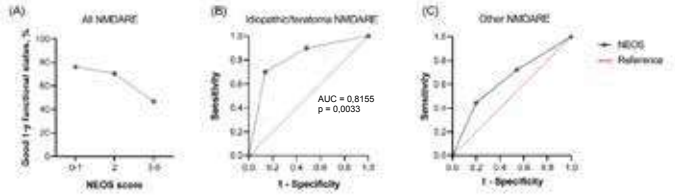
Distribution of symptoms and the CASE score at diagnosis for each item between all patients, idiopathic/teratoma patients and Other etiologies group.

CASE scores and treatment



The distribution of CASE scores below 10 or equal to or above 10 in relation to first- or second-line therapy can be seen for all patients (B) and the subgroups (C-D).

NEOS score and one-year functional outcome



NEOS Score and 1-year Functional Status. Probability of good functional status (mRS <2) at one year after disease onset according to the NEOS score for all NMDARE patients (A) and the receiver operator characteristic curve for prediction of 1-year prognosis of the NEOS score for the two subgroups (B-C).

CONCLUSIONS

CASE proved suitable for assessing severity of NMDARE and performed better than mRS and NEOS was a reliable tool to estimate one-year functional status in our national cohort.

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Dr Angel Miraclin has completed her speciality training in Neurology (DM Neurology) and currently works as an associate physician in the department of Neurosciences at Christian Medical College, Vellore, South India. Her core interests are in the field of neuro-infections and neuro-immunology, predominantly neuroinflammatory disorders occurring as a post or para-infectious phenomenon. She has publications in various national and international journals, predominantly focussing on infections and neuro-inflammatory disorders. She is a co-investigator in the encephalitis study, Brain Infections Global network, Liverpool.

Community acquired Cryptococcal choroid plexitis in an immunocompetant host – A case study with review of literature

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Clinical presentation

37 year old female patient from Assam presented with:

- ✔ Headache since 3 months
- ✔ Seizures since 1 month
- ✔ Altered behaviour since 15 days

On examination:

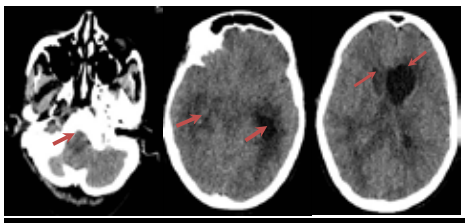
GCS - 12/15

Papilledema +

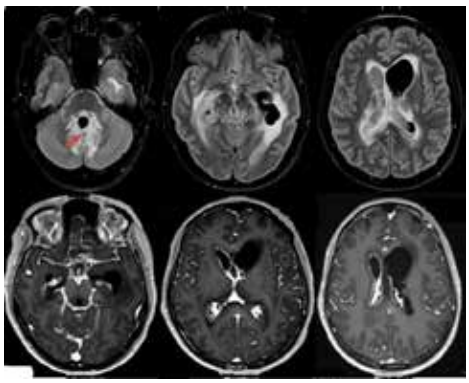
Bilateral VI nerve palsy

Meningeal signs++

CT Brain



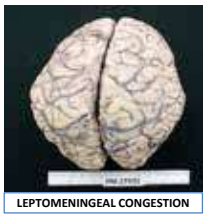
CT Brain: Tonsillar herniation, cerebral edema with obstructive hydrocephalus-'Trapped ventricle'



MRI Brain: Basal exudates, cerebral edema with obstructive hydrocephalus-'Trapped ventricle'

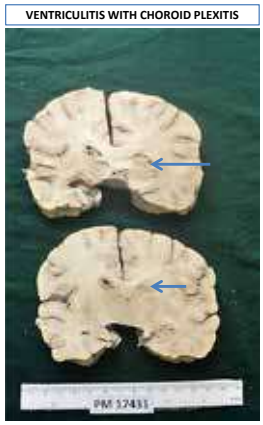
Course in hospital

- HIV status – negative.
- She was started on empirical ATT with steroids and antiedema measures.
- She had transient episode of decreased sensorium with anisocoria, in view of which EVD was placed and CSF analysis was sent.
- 120 Cells, poly – 93%; Ly – 7%
- CSF protein – 769 mg/dl, CSF glucose 65/232
- CSF Cultures (Bacterial and fungal) & Xpert TB- Negative
- CRAG CSF – Weak positive
- Started on Amphotericin B with flucytosine, in addition to ATT, Broad spectrum antibiotics.
- Progressed to develop hypothermia, DIC & succumbed to illness

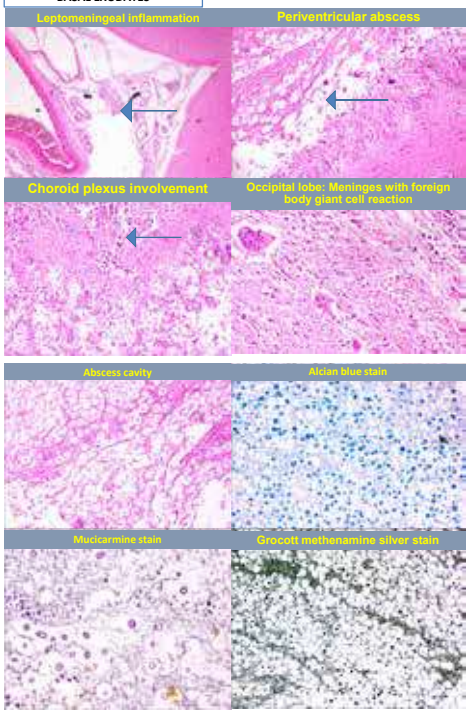


LEPTOMENINGEAL CONGESTION

BASAL EXUDATES

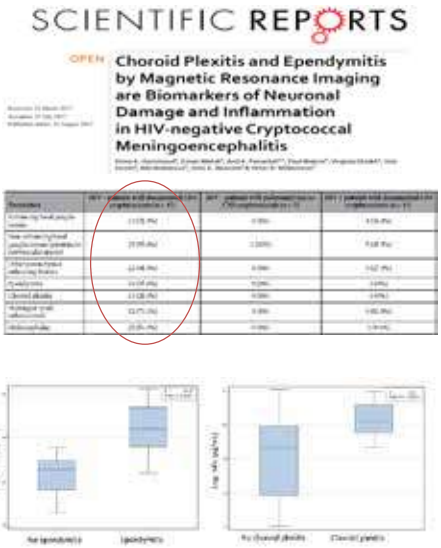


VENTRICULITIS WITH CHOROID PLEXITIS



Cryptococcal choroid plexitis

- CNS Cryptococcosis in previously healthy HIV− subjects accounts for almost a third of the cases in developed countries and is associated with significant (~30%) mortality despite optimal therapy.
- The **histologic makeup and strategic location** of the choroid plexus make it an important site of **initial dissemination.**
- Choroid inflammation can progress to ependymitis, intraventricular synechiae, loculation or enlargement, and entrapment of the temporal horn owing to the obstruction of flow by Cryptococci, as seen in our case.
- **Ependymal and choroid inflammatory changes could be used as disease biomarkers in HIV− patients** with clinical deterioration, of whom approximately 30% eventually succumb to the disease.



- A **post-infectious inflammatory response syndrome (PIIRS)** occurs which leads to CNS damage, with the majority of the patients having **negative fungal CSF cultures.**
- **sCD27 levels** have shown to best predict the presence of **intrathecal T-cell mediated inflammation.**
- **Ependymitis and hydrocephalus were the strongest predictors of high log(sCD27) levels** in the presence of symptomatic CM disease while hydrocephalus and a history of overt CM best predicted higher log(NFL) levels.

Learning Points

- Choroid plexitis and ventriculitis is a rare form of Cryptococcal meningoencephalitis in immunocompetant individuals with a fulminant course.
- ' **Trapped ventricle**' is an ominous sign suggesting high burden of organisms within the ventricular system – requires aggressive management.
- Role of steroids/intra-thecal therapy in such cases to be researched further.

References

1. Pagani-Estévez GL, Couillard P, Lanzino G, Wijdicks EFM, Rabinstein AA. Acutely Trapped Ventricle: Clinical Significance and Benefit from Surgical Decompression. Neurocrit Care. 2016 Feb;24(1):110–7.
2. Solár P, Zamani A, Kubíčková L, Dubový P, Joukal M. Choroid plexus and the blood-cerebrospinal fluid barrier in disease. Fluids Barriers CNS. 2020 May 6;17(1):35.
3. Qu J, Zhou T, Zhong C, Deng R, Lü X. Comparison of clinical features and prognostic factors in HIV-negative adults with cryptococcal meningitis and tuberculous meningitis: a retrospective study. BMC Infect Dis. 2017 Jan 10;17(1):51.
4. Kumari R, Raval M, Dhun A. Cryptococcal choroid plexitis: rare imaging findings of central nervous system cryptococcal infection in an immunocompetent individual. Br J Radiol. 2010 Jan;83(985):e014–7.
5. Lui G, Lee N, Ip M, Choi KW, Tso YK, Lam E, et al. Cryptococcosis in apparently immunocompetent patients. QJM Int J Med. 2006 Mar 1;99(3):143–51.
6. Tsai WC, Lien CY, Lee JJ, Lin WC, Hsu CW, Huang CR, et al. The prognostic factors of HIV-negative adult cryptococcal meningitis with a focus on cranial MRI-based neuroimaging findings. J Clin Neurosci Off J Neurosurg Soc Australas. 2018 Sep;55:57–61.
7. Dubbioso R, Pappatà S, Quarantelli M, D'Arco F, Manganelli F, Esposito M, et al. Atypical clinical and radiological presentation of cryptococcal choroid plexitis in an immunocompetent woman. J Neurol Sci. 2013 Nov 15;334(1–2):180–2.

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Opsoclonus Myoclonus Ataxia syndrome, Ovarian Teratoma and anti-NMDAR antibody An "Unresolved" Mystery

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Introduction

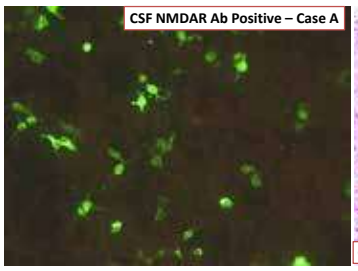
- Opsoclonus – myoclonus – ataxia syndrome (OMAS) is a unique presentation of neurological disorders characterized by:
  a) opsoclonus (chaotic, conjugate, rapid involuntary eye movements without inter-saccadic interval).
  b) myoclonus (sudden jerky movements involving the axial and limb musculature .
  c) ataxia (appendicular and axial of varying severity).
- In adults, majority are paraneoplastic secondary to solid organ tumours and could harbour antibodies against intracellular epitopes; however, certain proportions have detectable antibodies to various neuronal cell surface antigens.
- Anti- N-Methyl-D-Aspartate (NMDAR) antibodies and ovarian teratomas have been implicated in OMAS.
- Regarding the pathogenesis, there are two major observations;
  a) disinhibition of the fastigial nucleus, which is supported by the f-MRI studies on patients with OMAS in comparison to health subjects
  b) immune hypothesis, where a proportion of these patients have identifiable antibodies against neuronal cell surface antigens and neurofilament antigens.
- Overall, this entity could be considered in the **spectrum of autoimmune (brainstem) encephalitis**, with good response to immunotherapy and removal of neoplasm

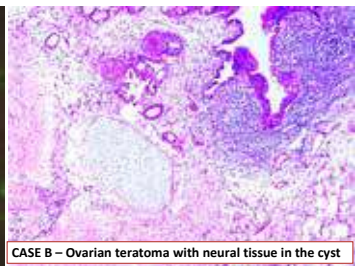
Methods

Report of two cases and review of literature

	Case - A	Case - B
History	• Sub-acute onset ataxia with involuntary jerky movements of the eyes and trunk. • Behavioural disturbances: increased fearfulness, anger outburst and violent behaviour towards her mother and husband	• Sub-acute onset gait ataxia with involuntary movements of the body, diplopia with oscillopsia and seizures. • Behavioural changes with decreased interaction with family members, decreased sleep and anhedonia.
Clinical examination	• Scanning staccato type of speech • Bilateral opsoclonus, action myoclonus with truncal and appendicular ataxia.	• Generalised tremors and action myoclonus. • Opsoclonus with decreased palatal movements and decreased gag reflex bilaterally. • Generalised dystonia with rigidity. • Bilateral cerebellar signs

Variable	Case A	Case B
Imaging		
MRI brain	Normal	Normal
Whole body PET – CT	Normal	Uptake In the right ovary
Cerebrospinal fluid analysis		
Cell counts(/cu mm)	4	2
Protein(mg/dl)	50	67
Glucose(mg/dl)	73	84
Investigations		
Autoimmune – encephalitis panel(Serum)	Neg	Neg
Autoimmune – encephalitis panel(CSF)	**1+ NMDAR**	Neg
Onconeural Antibodies	Neg	Neg
Management		
Medical	- Pulse steroids - Therapeutic plasma exchange - Bortezomib	- Pulse steroids - Therapeutic plasma exchange - Rituximab
Surgical	B/L oophorectomy No teratoma	B/L oophorectomy **Teratoma present**





Discussion

- Anti NMDAR encephalitis presenting as a brainstem cerebellar syndrome such as OMAS is a rarity.
- There are only few case reports reported in literature with antibody positivity and with clinical presentation as OMAS, among which 1 reported case is from the paediatric age group.
- In a large cohort of patients with teratoma associated encephalitis (211 patients), the novel presentation as brainstem – cerebellar syndrome with opsoclonus was seen in 58% of those who were negative for the anti NMDAR antibodies (22/38 patients), with none in the antibody positive group having the similar presentation.
- The mechanism of occurrence of this brainstem – cerebellar syndrome appears to be due to the dysfunction of omnipause neurons in the brainstem (para pontine reticular formation) and involvement of the fastigial nucleus.
- An unknown neuronal cell membrane-based antibody in conjunction with anti NMDAR antibody seems to be the most plausible explanation for this interesting observation.
- The outcomes of teratoma associated OMAS are remarkable with immunotherapy and almost 75% have complete recovery at a median follow up of 15 months
- We also report the good clinical improvement with bortezomib (BOR) in the OMAS associated with anti-NMDAR encephalitis.
- BOR targets the antibody secreting plasma cells, making it a potential second line therapy in those resistant to or in those with intolerance to RTX.
- Management in both cases was challenging in view of the progression and coexistent psychosis despite high doses of antipsychotic agents.
- The planning of surgical removal of teratoma is challenging, and often has to be prompt despite the severity of the illness

Learning points

- Our cases highlight this novel presentation of brainstem – cerebellar syndrome (OMAS) among patients with treatment responsive autoimmune encephalitis.
- Patients with teratoma associated OMAS and coexistent neuropsychiatric manifestations are negative for the anti-NMDAR antibody and those with the antibody and OMAS do not have a teratoma.
- A yet unidentified neuronal cell membrane directed antibody might be implicated in OMAS even in cases with anti NMDAR antibody.
- Judicious use of immunotherapy often translates into good clinical outcomes

References

1. Sahu JK, Prasad K. The opsoclonus–myoclonus syndrome. Pract Neurol. 2011 Jun 1;11(3):160–6.
2. Wong AM, Musallam S, Tomlinson RD, Shannon P, Sharpe JA. Opsoclonus in three dimensions: oculographic, neuropathologic and modelling correlates. J Neurol Sci. 2001 Aug 15;189(1–2):71–81.
3. Zee DS, Robinson DA. A hypothetical explanation of saccadic oscillations. Ann Neurol. 1979;5(5):405–14.
4. Sabater L, Xifró X, Saiz A, Alberch J, Graus F. Analysis of antibodies to neuronal surface antigens in adult opsoclonus-myoclonus. J Neuroimmunol. 2008 May 30;196(1–2):188–91.
5. Armangué T, Sabater L, Torres-Vega E, Martínez-Hernández E, Ariño H, Petit-Pedrol M, et al. Clinical and Immunological Features of Opsoclonus-Myoclonus Syndrome in the Era of Neuronal Cell Surface Antibodies. JAMA Neurol. 2016 Apr;73(4):417–24.
6. Pranzatelli MR, Travelstead AL, Tate ED, Allison TJ, Moticka EJ, Franz DN, et al. B- and T-cell markers in opsoclonus–myoclonus syndrome. Neurology. 2004 May 11;62(9):1526.
7. Pranzatelli MR, Tate ED, Swan JA, Travelstead AL, Colliver JA, Verhulst SJ, et al. B cell depletion therapy for new-onset opsoclonus-myoclonus. Mov Disord Off J Mov Disord Soc. 2010 Jan 30;25(2):238–42.
8. Player B, Harmelink M, Bordini B, Weisgerber M, Girolami M, Croix M. Pediatric Opsoclonus-Myoclonus-Ataxia Syndrome Associated With Anti-N-methyl-D-aspartate Receptor Encephalitis. Pediatr Neurol. 2015 Nov;53(5):456–8.
9. Armangue T, Titulaer MJ, Sabater L, Pardo-Moreno J, Gresa-Arribas N, Barbero-Bordallo N, et al. A novel treatment-responsive encephalitis with frequent opsoclonus and teratoma. Ann Neurol. 2014 Mar;75(3):435–41.
10. Carvajal-González A, Leite MI, Waters P, Woodhall M, Coutinho E, Balint B, et al. Glycine receptor antibodies in PERM and related syndromes: characteristics, clinical features and outcomes. Brain J Neurol. 2014 Aug;137(Pt 8):2178–92.

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Dr Philips is a conscientious doctor with a zeal for neurology. She trained in Internal Medicine in India, currently working as a registrar in a tertiary care hospital and wants to pursue a career as neurologist in the NHS

An Interesting case of Rapidly progressing paralysis.

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ENCEPHALITIS conference 2022, London

Introduction:

Progressive paralysis is a neurological emergency, as the patient often requires Intensive care management and respiratory support with invasive ventilation. Identifying aetiology can sometimes cause a clinical dilemma. Some of the cases seen in clinical practice include Guillain-Barre syndrome, Acute flaccid paralysis secondary to infections, encephalo-neuropathies etc, however, sometimes we tend to see lesser-known aetiologies like Rabies.

Rabies presents in two forms a) Furious form and b) Paralytic form or dumb rabies. In Furious form patients manifest hyperactivity, hyper-salivation, hydrophobia alternating levels of consciousness. This form consist of 80% of rabies manifestation and can be easily diagnosed. It's the paralytic form or dumb rabies which is not easily diagnosed and consist of 20% of overall cases as it is easily confused with GBS.

Case Report:

- A 28-year-old pre morbidly healthy female presented with a 12 days history of severe right lower limb pain along the toe to right hip, followed by multiple episodes of vomiting on the second day.
- On 5th day of her illness she developed bilateral lower limb weakness. She was found to have hyponatremia (Na 110mEq/L). She was treated with 3% Normal Saline. Her CSF examination was normal. Her sodium improved, however, her weakness has progressed now involving both upper limbs. She was referred to our hospital.
- On day 15 of her illness she was brought to our hospital, on examination she was confused, obeys simple commands, quadriparetic, complete external ophthalmoplegia, reacting pupil, areflexia, poor cough. She had no history of vaccination, dog bite, fever, seizure, recent travel. She had a pet cat which had died due to unknown illness few months before her presentation.
- Investigations:
  - MRI Brain showed hyper intense signals in caudal equine and right frontoparetial deep white matter.
  - MRI Spine showed hyper intense signals in caudal equina.
  - CSF- 25 cells/cumm, 80% Polymorphs, 20% Lymphocytes, Protein 158mg/dL, Glucose 87 mg/dL.
  - NCS- Pure motor demyelinating neuropathy in upper and lower limbs, absent F waves, conduction block, temporal dispersion with polyphasic waves.
- She was treated with IVIG considering Demyelinating neuropathy ?GBS.
- Pointers against GBS- Encephalopathy, Abnormal CSF pleocytosis, Abnormal MRI, History of leg pain and vomiting. Repeat MRI showed increase in hyper intensities and new hyper intensities in basal ganglia.
- Her CSF RT PCR for viruses was sent and was positive for Rabies virus.
- Nuchal skin biopsy was done- which was positive for Rabies virus.
- Patient further required mechanical ventilation and inotropic support and she had developed unreactive pupils and absent oculogyric reflexes and later died.
- Postmortem was not performed.
- No details of scratch or bite due to any other animal was known to relatives.

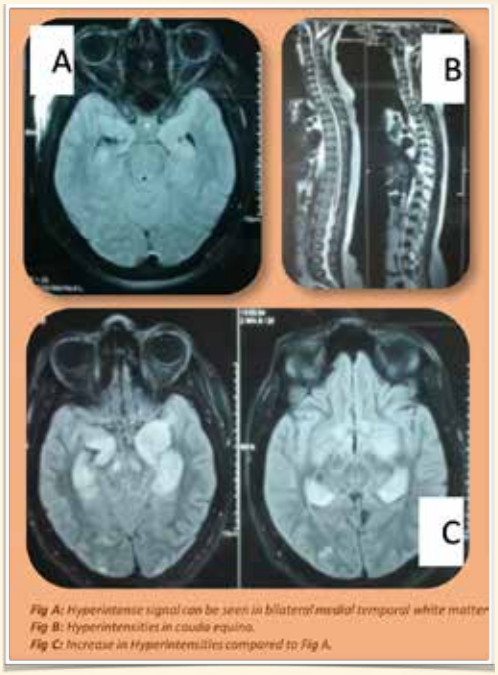

Fig A: Hyperintense signal can be seen in bilateral medial temporal white matter
Fig B: Hyperintensities in cauda equina.
Fig C: Increase in Hyperintensities compared to Fig A.

Summary:
- Ascending paralysis with encephalopathy, complete external ophthalmoplegia, areflexia and bulbar palsy.
- **Differentials:**
  - Gullian Barre syndrome
  - Bickerstaff encephalitis
  - Millard fisher syndrome
  - ADEM
  - Acute flaccid paralysis due to viral infections like- Enteroviruses, West-Nile virus, etc.
  - Paralytic type of Rabies.
- **Final Diagnosis:**

Paralytic type of Rabies (Dumb Rabies)

Discussion:

Rabies is neurotropic virus in the *Rhaboviridae* family, genus *Lyssavirus.*[1] It has an incubation period of 1-3 months & spreads from the site of inoculation to the CNS via the axons of peripheral nerves after attaching to N_M Ach receptors in muscles.[2] It presents in two forms a) Encephalitic b) Paralytic form. Encephalitic form of Rabies is common in humans accounting for 80% of cases which presents with a prodrome of fever, malaise, myalgias, headache, photophobia. Hydrophobia and aerophobia develop later as a result of involuntary pharyngeal spasms. And eventually, shock and respiratory failure. The paralytic form accounts for 20% of cases and manifests as ascending paralysis with involvement of bitten limb that then spreads to other limbs, the brainstem and the cerebrum. These patients eventually die as a result of respiratory & pharyngeal muscle paralysis. Rabies has the highest case fatality rate in humans and it is most commonly acquired through exposure to saliva from an animal bite. Rarely it can also occur due to contact with saliva over a skin break or mucous membrane, as well as organ transplantation. Dogs, Bats, foxes make up the majority of the animal reservoirs. However only a few cases of rabies transmission via domestic cats have been reported.[3] Treatment options include Rabies vaccine, Rabies immunoglobulin, Neutralising Monoclonal antibodies, Ribavirin, IFN-α, Ketamine, however with dismal benefit.[4] These were considered in this patient but she had advanced disease. The fatality rate in unvaccinated cases presenting with clinical features was reported to be close to 100%; however there are very few survivors who were treated with a combination of above therapies early in their disease course and were previously vaccinated against rabies.[5] Palliative care is critical in this deadly disease.

References:
1. Singh R, Singh KP, Cherian S, Saminathan M, Kapoor S, Manjunatha Reddy GB, et al. Rabies - epidemiology, pathogenesis, public health concerns and advances in diagnosis and control: a comprehensive review. Vet Q. 2017 Dec;37(1):212–51.
2. Lentz TL, Burrage TG, Smith AL, Crick J, Tignor GH. Is the acetylcholine receptor a rabies virus receptor? Science. 1982 Jan 8;215(4529):182–4.3.
3. Grobbelaar AA, Blumberg LH, Dermaux-Msimang V, le Roux CA, Moolla N, Paweska JT, et al. Human rabies associated with domestic cat exposures in South Africa, 1983–2018. J S Afr Vet Assoc. 2020 Jul 6;91:2036.
4. Jackson AC, Warrell MJ, Rupprecht CE, Ertl HCJ, Dietzschold B, O'Reilly M, et al. Management of Rabies in Humans. Clinical Infectious Diseases. 2003 Jan 1;36(1):60–3.
5. Willoughby RE, Tieves KS, Hoffman GM, Ghanayem NS, Amlie-Lefond CM, Schwabe MJ, et al. Survival after treatment of rabies with induction of coma. N Engl J Med. 2005 Jun 16;352(24):2508–14.

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Detection of neural autoantibodies in Denmark during 2019-2021

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INTRODUCTION

Detection of autoantibodies against neural antigens is the most important biomarker for the diagnosis of autoimmune encephalitis. In this study we investigated the real-life incidence of positive autoantibody tests during 2019 - 2021 in the national Danish test center for autoantibodies associated with neurological diseases.

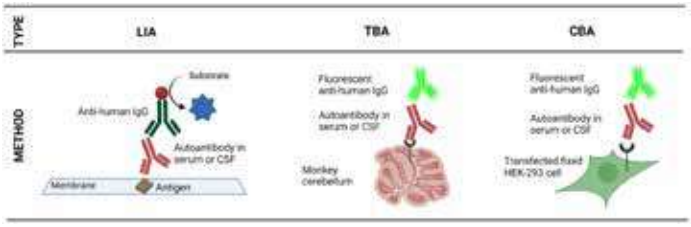
METHODOLOGY

Nationwide retrospective study, where test results were extracted from the laboratory information system at the national Danish ISO 15189 accredited test center for anti-neuronal antibody testing. All positive tests (serum and CSF) from January 2019 to December 2021 were included. Individual patients was only included once.

Autoantibodies against intracellular antigens were considered positive if detected by fixed tissue-based assay (TBA) using monkey tissue (cerebellum and enteric nervous system) and confirmed using recombinant line immunoassay (LIA) (Euroimmun AG, Lübeck, Germany). However anti-recoverin was only tested using LIA, and all anti-SOX1 positive LIA results was also reported. For autoantibodies targeting cell surface antigens, commercial cell-based assays (CBA) (Euroimmun AG, Lübeck, Germany) were used.

Annual incidence rate was calculated for autoantibodies against intracellular antigens and for autoantibodies targeting cell surface antigens overall, and for each subtype.

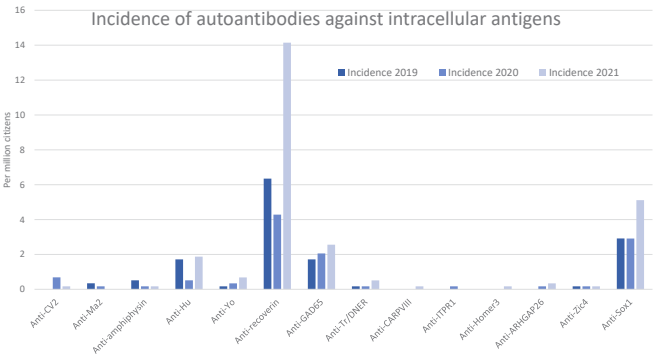
OVERVIEW OF ASSAYS USED



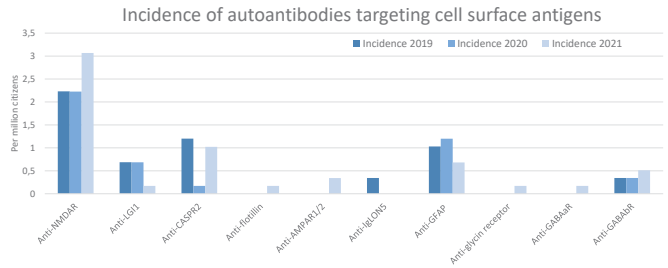
RESULTS

In total, 5288 tests for autoantibodies against intracellular antigens were performed (range 1520-1963 per year) and 5790 tests for autoantibodies targeting cell surface antigens were during the study period (range 1798-2016 per year). Of these, 697 samples (6,29 %) were found to be positive.

The overall yearly incidence of autoantibodies targeting intracellular antigens were 14.1 in 2019, 11.8 in 2020 and 26.1 in 2021. Incidence of subtypes are shown in the table below. Anti-recoverin and anti-SOX1 were found to be the most frequent autoantibodies in this group, suggesting a high number of false positives.



The overall yearly incidence of autoantibodies targeting cell surface antigens were 5.8 in 2019, 4.6 in 2020 and 6.3 in 2021. Incidence of subtypes are shown in the table below. In this group, anti-NMDAR antibodies were most frequent.



DISCUSSION and CONCLUSIONS

To provide highest sensitivity and specificity when testing for autoantibodies against intracellular antigens , it is recommended to combine a fixed TBA and a LIA. This approach was not possible for anti-recoverin antibodies and anti-SOX1, and our data suggest a high number of false positive tests for autoantibodies only tested on LIA. This leads to a risk of overdiagnosis and underlines the importance of the clinical diagnosis. Also, there is a need for reconsideration of cut-off values for positive tests. The incidence of positive autoantibody test results for autoantibodies targeting cell surface antigens in Denmark is similar to the estimated incidence of autoimmune encephalitis. As expected, the main antibodies detected was anti-NMDAR.

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REFERENCES

Ricken G, Schwaiger C, De Simoni D, Pichler V, Lang J, Glatter S, et al. Detection Methods for Autoantibodies in Suspected Autoimmune Encephalitis. Front Neurol. 20189:841.

Vogrig A, Gigli GL, Segatti S, Corazza E, Marini A, Bernardini A, et al. Epidemiology of paraneoplastic neurological syndromes: a population-based study. J Neurol. 2020267(1):26-35.

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Dr Ashwini M A, graduated MBBS from K S Hegde Medical Academy, Mangalore in 2008 and joined for post-graduation in Microbiology at JIPMER, Puducherry in 2010. After completing MD, Microbiology in April 2013, she worked as a senior resident in the Department of Neurovirology, NIMHANS for 3 years. She was responsible for the day functioning of the diagnostic section and was also actively involved in teaching, training, workshops, and CMEs conducted in the department. She worked as a consultant microbiologist and infection control officer in private hospitals until May 2020. Since then, she has been working as a senior scientific officer in the Department of Neurovirology, NIMHANS. She was part of the team that enhanced COVID-19 testing capacity in Karnataka state. She was also a part of the sero-surveillance study conducted at NIMHANS for all healthcare workers as well as state level to access the prevalence and population level infectivity respectively. She is the Co-Principal Investigator in the “Laboratory support for phase IV clinical trial Serum Institute of India” funded project and Co-Investigator in the ICMR-funded research project “Immune response to SARS-CoV-2 vaccine in a health care setting”.

Antemortem diagnosis of rabies encephalitis: A laboratory audit in India

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Introduction

- Rabies is a **neglected tropical zoonotic disease and an acute fatal progressive encephalomyelitis** caused by viruses belonging to genus lyssavirus.[1]
- **Asia**, including the **Indian subcontinent**, represents more than half of the global burden of human rabies.[1]
- **Ante-mortem diagnosis of rabies** helps in differentiating from clinical mimics, initiating supportive care, infection control measures, and aids in disease surveillance.[2]
- **The department of Neurovirology, NIMHANS** is a **national referral centre** for laboratory diagnosis of rabies in India.
- We **retrospectively analysed the** laboratory confirmation of rabies on **antemortem samples** received from **January 2019 to December 2021** from the entire country.

Methods

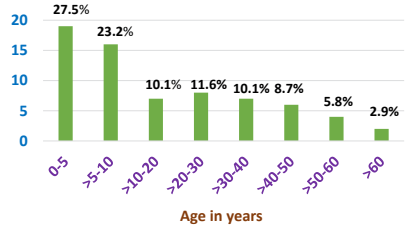
The following **diagnostic tests were performed** for the antemortem diagnosis of rabies:

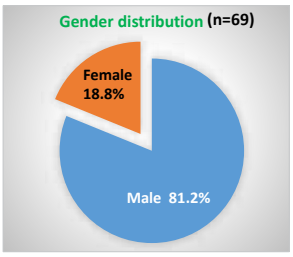
1. **Rabies real-time PCR for rabies viral RNA detection** in **CSF, saliva, and nuchal skin biopsy** samples performed by using a set of **primers and probe targeting the nucleoprotein (N) gene** described earlier. [3]
2. **Rapid fluorescent focus inhibition test (RFFIT)** for the estimation of **rabies virus neutralizing antibodies (RVNA)** in **CSF and serum samples**, performed according to the **World Health Organization (WHO)** recommended procedure [4] with some modifications.[5]

The **RVNA titres were diagnostic in CSF samples irrespective of rabies vaccination status** and in **serum samples of unvaccinated patients**. In **vaccinated patients**, **the significant rise of RVNA titres** were demonstrated in **paired sera** for the laboratory confirmation of rabies.

Results

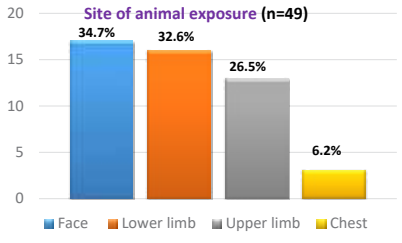
- A total of **448 clinical samples** from **187 suspected rabies cases** were received during the study period from **22 states and 1 union territory in India** and **59.4% from the public sector**. **Laboratory confirmed antemortem diagnosis of rabies** was obtained in **36.8%** (69/187).
- The **age** of laboratory-confirmed rabies patients ranged from **1 to 65 years (median - 10 years) 56.5% were from the paediatric age group (<15 years).**
- **Male preponderance (81.2%)** was observed.



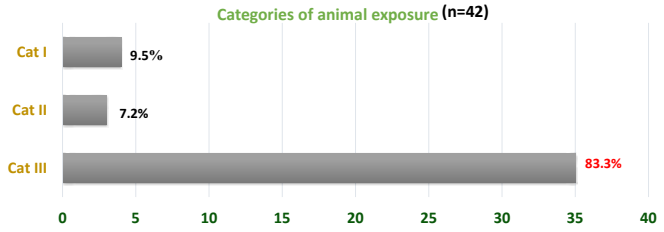


- **The dog is the most common animal causing** transmission of rabies (**92.4%**)
- The predominant site involved during animal exposure is **face (34.7%) and lower limb (32.6%) followed by upper limb (26.5%)**

Animal exposure (n=65)	No. (%)
Dog	60 (92.4%)
Mangoose	1 (1.5%)
Jackal	1 (1.5%)
No exposure	3 (4.6%)



- Majority of cases had **WHO classification category III (83.3%, 35/42)** of animal exposure.
- **Post-exposure prophylaxis** - Anti rabies vaccine (ARV) schedule was **completed (5 doses intramuscular or 4 doses intradermal) only in 22.6% (12/53);** partially vaccinated in 47.2% (25/53) and **did not receive the vaccine in 30.2% (16/53) of laboratory confirmed cases. Rabies immunoglobulin (RIG) was administrated in 41.9% (13/31) of category III wounds.**

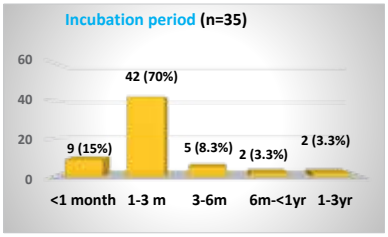


Clinical Form (n=62)	No (%)
Classical rabies	16 (25.8%)
Paralytic rabies	16 (25.8%)
Atypical rabies	**30 (48.4%)**

Incubation period - varied from 10 days to 3 years (median - 1 month)

Clinical features:

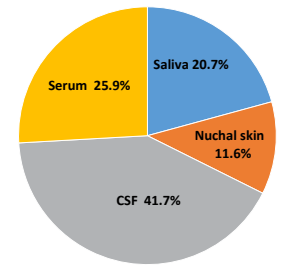
Fever is the predominant clinical finding **(68.2%) followed by altered sensorium (49.2%).**

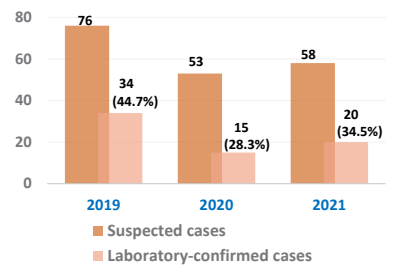


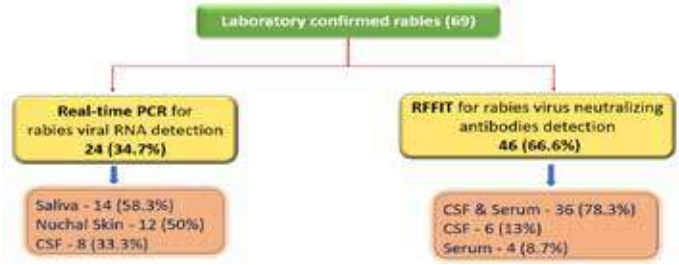
Clinical features (n=63)	No (%)
Fever	**43 (68.2%)**
Altered sensorium	**31 (49.2%)**
Hydrophobia	**17 (26.9%)**
Weakness of limbs	16 (25.4%)
Behavioural changes	13 (20.6%)
Aerophobia	9 (14.3%)
Seizures	8 (12.7%)
Vomiting	8 (12.7%)
Headache	8 (12.7%)

Laboratory findings:

The clinical samples received during the study period and year wise distribution of suspected and laboratory-confirmed cases are shown below.







- **Multiple/serial samples increase diagnostic sensitivity**

Conclusion

- Ante-mortem diagnostic tests include nucleic acid detection in various clinical specimens, and detection of specific viral antibodies in the CSF and serum.
- Several factors such as the duration of illness, clinical form of the disease, intermittent shedding of the virus in clinical samples such as saliva, sample integrity, rabies vaccination prior to disease onset and the immune status of the patient can influence the test results.
- Ante-mortem tests like **viral RNA detection tests** are more likely to be **positive during early phase of the illness, before neutralizing antibodies appear.**
- In contrast, serological diagnosis by **detection of viral antibodies in CSF and/or serum** are **valuable in establishing diagnosis in late phase of the illness (more than a week).**
- **Laboratory confirmation of rabies in antemortem samples is challenging.** If the test result is positive, it confirms the diagnosis of rabies but a negative test result does not rule out the diagnosis of rabies.
- **A combination of laboratory diagnostic tests of rabies such as real-time PCR on multiple/serial clinical samples and RFFIT in CSF and serum samples increases the sensitivity of antemortem laboratory diagnosis of rabies.**

References

1. World Health Organization. WHO Expert Consultation on Rabies: third report. World Health Organization Technical Report Series 1012. Geneva: WHO; 2018.
2. An overview of antemortem and postmortem tests for diagnosis of human rabies. Rupprecht CE, Fooks AR, Abela-Ridder B, eds. Laboratory techniques in rabies, 5th ed. Volume 1. Geneva: World Health Organization; 2018.43-54.
3. Nadin-Davis SA, Sheen M, Wandeler AI. 2009. Development of real-time reverse transcriptase polymerase chain reaction methods for human rabies diagnosis. J Med Virol 81:1484–1497.
4. Smith JS, Yager PA, Baer GM. A rapid fluorescent focus inhibition test (RFFIT) for determining rabies virus-neutralizing antibody. In: Meslin FX, Kaplan MM, Koprowski H, eds. Laboratory Techniques in Rabies. 4th edn. Geneva: World Health Organization, 1996, pp. 181–191. 13.
5. Ashwath Narayana DH, et al. Safety and immunogenicity study of a new purified chick embryo cell rabies vaccine Vaxirab-N (Pitman-Moore strain) manufactured in India. Human Vaccines and Immunotherapeutics 2014; 10: 120–125.

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Complex solutions for complex challenges: a Brain Infections Global systematic review of intervention packages to improve care of patients with encephalitis and other brain infections

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BACKGROUND

Encephalitis and other brain infections pose major global challenges, affecting low-resource settings disproportionately. Barriers to optimal diagnosis and management of patients with suspected brain infections cut across dynamic complex health systems, which could be addressed by intervention packages with multiple components. To inform the pragmatic hospital care improvement intervention in our "Brain Infections Global" study in Brazil, India and Malawi, we conducted a systematic review of the literature.

METHODS

Inclusion criteria for studies: Published reports of studies reporting effectiveness of intervention packages for diagnosis or management of patients with suspected/confirmed acute brain infections, vs. usual care. The interventions were deemed complex by meeting one or more core elements of the iCAT-SR tool (Lewin et al 2017). Designs included randomised trials, non-randomised head-to-head trials, before-vs.-after and stepped-wedge studies.

Exclusion criteria for studies: Reporting only neonatal, neurosurgical or nosocomial infections.

Search: Pubmed (MEDLINE) on 17 November 2021, using pre-defined search strategy.

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

Methodological quality: Assessed by two reviewers independently using Effective Public Health Practice Project tool for quantitative studies (EPHPP 2010).

Outcomes: Receipt of a microbiological diagnosis (primary); mortality; receipt of and time to lumbar puncture procedure; time to appropriate anti-infective therapy; length of hospital stay; neurological deficit; and quality of life.

Synthesis: Due to heterogeneity of study populations, designs and settings, meta-analysis was deemed inappropriate, and a narrative synthesis is presented.

RESULTS

Of 556 study reports screened, five studies met eligibility criteria (1570 participants in total; see **Figure**), published between 1998 and 2018. Study characteristics varied substantially, as outlines in **Table 1**. Two studies intervened in Malawi, Africa; three reported from Europe (two UK; one Italy). Three focused on adults; one included younger children; one included patients of all ages. Target syndromes comprised encephalitis (one study) and meningitis (three studies); one allowed any suspected central nervous system infection. Three studies focused on patient management; one introduced a pack for lumbar puncture procedures; one study's intervention targeted various aspects of care. Four studies compared patients cared for before vs. after introduction of the intervention; one randomised hospitals to either the intervention or no intervention. Overall quality was judged strong in one study, moderate in two studies, and weak in two.

Table 2 summarises results from the studies. One study reported an increase in microbiological diagnosis from 9% to 21% after introduction of a lumbar puncture pack, though this did not reach statistical significance. Two studies reported a mortality reduction after the intervention. Time to appropriate therapy was lower in one study. Remaining outcomes were similar with vs. without interventions. Quality of life was not reported.

TABLE 1: Characteristics of included studies

STUDY	COUNTRY	AGE GROUP	TOTAL PARTIC-IPANTS	TARGET SYNDROME	TARGET OF INTERVENTION	STUDY DESIGN	METHOD-OLOGICAL QUALITY
Cullinan et al 1998	Malawi	Infants & children under 6 years	160	Cerebral malaria or Meningitis	Management	Before vs. After	Weak
Michael et al 2013	United Kingdom	Adults	177	Central nervous system infection	Diagnosis	Before vs. After	Moderate
Viale et al 2015	Italy	Adults	181	Acute bacterial meningitis	Management	Before vs. After	Weak
Wall et al 2017	Malawi	Adults & adolescents over 14 years	563	Acute bacterial meningitis	Management	Before vs. After	Moderate
Backman et al 2018	United Kingdom	Any age	489	Encephalitis	Diagnosis & Management	Cluster-randomised trial	Strong

FIGURE: PRISMA flow diagram (simplified)

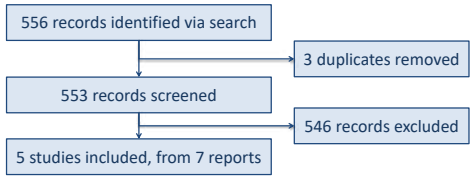

TABLE 2: Results reported by studies for the review's pre-defined outcomes

Abbreviations: d, days; h, hours; NA, not applicable; NR, not reported.

	Cullinan et al 1998		Michael et al 2013		Viale et al 2015		Wall et al 2017		Backman et al 2018	
OUTCOME	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	CONTROL	INTERVENTION
Participants	64	96	93	84	92	89	273	290	223	266
Receipt of a microbiological diagnosis	NR	NR	9%	21%	NR	NR	NR	NR	NR	NR
All-cause death	36%	22% (No P value)	NR	NR	14%	5% (P=0.04)	11%	15% (P=0.31)	NR	NR
Receipt of lumbar puncture	NR	NR	55%	48%	NA	NA	NR	NR	94%	88% (P=0.08)
Time to lumbar puncture	NR	NR	Median 8h	Median 8h (P=0.28)	NR	NR	NR	NR	Performed within 12h if no contraindication: 30%	Performed within 12h if no contraindication: 26% (P=0.73)
Length of stay in hospital	NR	NR	NR	NR	Median 15d	Median 13d (P=0.28)	NR	NR	NR	NR
Receipt of a syndromic diagnosis	NR	NR	NR	NR	NR	NR	NR	NR	Suspected: 9% Probable: 19%	Suspected: 14% Probable: 18% (No P value)
Time to appropriate therapy	NR	NR	NR	NR	NA	NA	Ceftriaxone within 1 hour: 7%	Ceftriaxone within 1 hour: 41% (P<0.001)	Aciclovir administered within 6h: 28%	Aciclovir administered within 6h: 30% (P=0.78)
Neurological deficit	NR	NR	NR	NR	Deficit at discharge: 19%	Deficit at discharge: 14% (P=0.40)	NR	NR	NR	NR

[1]University of Liverpool, UK; [2]National Institute of Mental Health and Neuro Sciences, India; [3]Malawi-Liverpool-Wellcome Trust Clinical Research Programme, Malawi; [4]Christian Medical College Vellore, India; [5]Oswaldo Cruz Foundation (Fiocruz), Brazil; [6]University of Birmingham.

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CONCLUSIONS

Studies of intervention packages for brain infections are limited and vary in setting, population and syndrome. Some interventions showed promise, although reporting of patient outcomes varied across studies, and reported outcomes often remained unchanged. Studies to investigate the impact of intervention packages for brain infections, especially in low-resource settings, are needed.

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FATAL PAROXYSMAL SYMPATHETIC HYPERACTIVITY IN PATIENTS WITH AUTOIMMUNE ENCEPHALITIS

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BACKGROUND

Paroxysmal sympathetic hyperactivity (PSH) is a potentially life-threatening neurological emergency due to dysregulation of the autonomic function. PSH is usually secondary to acute acquired brain injuries, but some cases have also shown an association to autoimmune encephalitis (AE). It is clinically characterized by the cyclic and simultaneous appearance of signs and symptoms secondary to exacerbated sympathetic discharge.

METHODS

3 patients diagnosed with AE from our centre who died because of fatal PSH.

PATIENT 2

A 64 years-old man diagnosed with anti-amphiphysin encephalitis who was hospitalized due to pneumonia and presented unexplainable sweating, hypertension and ventricular tachycardia unresponsive to cardiopulmonary resuscitation maneuvers causing the death.

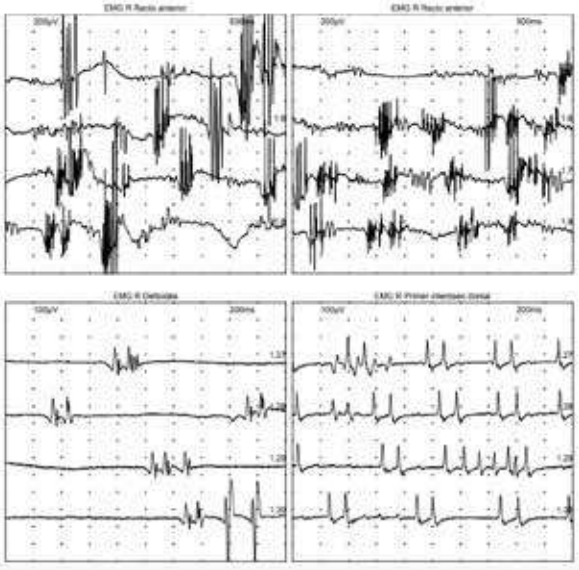
PATIENT 1

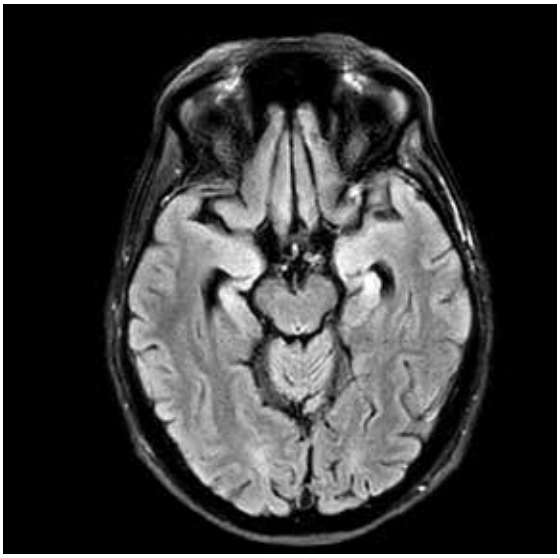
A 38 years-old man diagnosed with encephalitis anti-Caspr2 who suddenly developed tachycardia, hypertension, tachypnea, fever, sweating and painful cramps. He was transferred to ICU where he died because of multi-organic failure derived from the sympathetic storm.

All patients were men and had showed limbic encephalitis in the Brain MRI.

PATIENT 3

A 61 years-old man diagnosed with anti-Hu encephalitis who suddenly developed cycling episodes of hyperthermia, tachypnea, dystonic posturing and ventricular tachycardia. One episodi was refractor y to treatment for PSH and the patient died because of cardiac arrest.





CONCLUSIONS

According our case series fatal PSH is an unpredictable condition which is more frequent in men and is associated to limbic encephalitis caused by antibodies directed to neuronal surface receptors and onconeural antigens.

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Dr Ishant is a homoeopathic practitioner from India with a specialization in the field of Homoeopathic Pharmacy. With more than four years of clinical experience, he is presently engaged in research with Central Council for Research in Homoeopathy- an autonomous body under Ministry of Ayush, Govt. of India that undertakes basic, fundamental and clinical research in Homoeopathy both at a national and international level. Dr Ishant has a strong inclination towards clinical research and his endeavours in the field bagged him a scholarship for his MD Dissertation from CCRH, India. His expertise in combining Homoeopathic principles and pharmacy with clinical therapeutics is well appreciated. Moreover, he has also presented several research papers at various seminars held in the country and globally. His academic excellence and orating skills have an added extra advantage to his knowledge.

EFFECTIVENESS OF HOMOEOPATHIC PREPARATION OF BELLADONNA IN JAPANESE ENCEPHALITIS: A REVIEW

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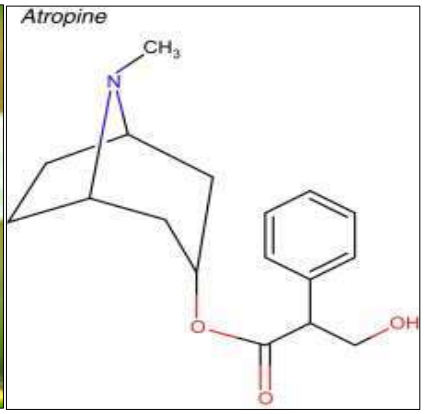
INTRODUCTION

- Encephalitis is a pathological condition involving ***inflammation of the brain parenchyma*** and it is an important cause of permanent neurological disability in both adults and children
- ***Japanese encephalitis (JE)*** is the most important cause of viral encephalitis in Eastern and Southeast Asia[1]
- The disease strikes ***1.9 to 14.3 people per 100,000 each year***, causing an average of 20,258 hospitalizations per year[2]
- Despite the availability of anti-viral therapies, most patients with encephalitis are left with some degree of ***neuropsychological impairment with high disability rates.***
- Homoeopathic medicine, ***Belladonna*** (Atropa Belladonna), is found to be effective in the treatment of encephalitis due to the similarity of its pharmacodynamics with the pathology of encephalitis.



Belladonna
Large, bushy, perennial herb with a thick, fleshy, juicy, branched and spreading root
Part used (in Homoeopathy): The whole plant[3]

Active principles: Tropane alkaloids (Atropine, Scopolamine, Hyoscyamine)[4]
Pharmacological action[4]: Anti-inflammatory, anti-viral, anti-oxidant etc.

AIM & OBJECTIVE

To conduct a ***literature review*** on the ***effectiveness*** of ***Belladonna*** in the treatment of ***Japanese Encephalitis***

METHODOLOGY

A comprehensive search for the articles published during the period 1990-2022 in different search engines (PubMed, Cochrane, Google Scholar, CORE-Hom database and other individual journal sites was performed.

RESULTS

- In vitro **(n=6)**
- In vivo **(n=2)**
- Clinical studies **(n=2)**

1. IN VITRO STUDIES

S.NO.	STUDY TITLE	RESULT
1	Sub-lethal Dose of ***Atropine*** Gives Protection from Japanese Encephalitis Virus Infection in Chick Embryo Model[5]	*Reduction in the viral load*, Up regulation of Interferon alpha and Toll like receptor
2	Changes in viral load in different organs of Japanese Encephalitis virus-infected chick embryo under the influence of ***Belladonna 200C***[6]	Belladonna 200C significantly *reduced the overall load in CAM and brain*
3	Effect of ***pure atropine*** and ***atropine sulphate*** on Japanese encephalitis virus infection in chick chorio allantoic membrane[7]	Atropine *upregulated type II interferon* and atropine sulphate *upregulated type I interferon* in CAM
4	Antiviral Activity of ***Belladonna*** During Japanese Encephalitis Virus Infection via Inhibition of Microglia Activation and Inflammation Leading to Neuronal Cell Survival[8]	B200 *reduced the pro-apoptotic and inflammatory* gene expression
5	Decreased intensity of Japanese encephalitis virus infection in chick chorioallantoic membrane under influence of ***ultradiluted belladonna extract***[9]	Ultra diluted Belladonna 3, 6, 30, 200 preparations used in this study showed *inhibition of viral growth on CAM*
6	Pre-treatment with ***Scopolamine*** Naturally Suppresses Japanese Encephalitis Viral Load in Embryonated Chick Through Regulation of Multiple Signaling Pathways[10]	Significant *upregulation of different TLRs interleukins as well as IFNs*

2. IN VIVO STUDIES

S.NO	STUDY TITLE	RESULT
1	Role of ***Ultra-diluted Belladonna*** Extract In the Immune-Mediated healing of JE Virus Infection in Mice[11]	*Decrease of JE viral load*, along with marked increase in relative mRNA expressions
2	Preventive and Curative Role of ***Belladonna 200*** Against Japanese Encephalitis Virus Infection in Adult Mice[12]	*Belladonna 200* acted as preventive and curative medicine in mice

3. CLINICAL STUDIES

S.NO	STUDY TITLE	RESULT
1	Evaluation of homoeopathic medicines as an ***add-on to institutional management protocol*** in ***Acute Encephalitis Syndrome***: An exploratory observational comparative study[13]	***Reduction of mortality and morbidity*** with add-on homoeopathic medicine (Belladonna 200C) in JE-affected patients
2	Effectiveness of Homeopathic Medicines as ***Add-on to Institutional Management Protocol for Acute Encephalitis Syndrome in Children***: An Open-Label Randomized Placebo-Controlled Trial[14]	Adjunctive homeopathic medicines (Belladonna) may ***improve clinical outcomes associated with AES***

CONCLUSION

The ***anti-viral properties*** of ***Belladonna*** against Japanese encephalitis have been **established** by a number of researchers. However, the exact ***mechanism of action*** of the ultra-high dilutions of Belladonna in Encephalitis needs to be ***explored***. ***More clinical trials*** must be undertaken to explore its potential fully in the treatment of Japanese Encephalitis.

References

1.Misra UK, Kalita J. Overview: japanese encephalitis. Progress in neurobiology. 2010 Jun 1;91(2):108-20
2. Wang H, Zhao S, Wang S, Zheng Y, Wang S, Chen H, Pang J, Ma J, Yang X, Chen Y. Global magnitude of encephalitis burden and its evolving pattern over the past 30 years. Journal of Infection. 2022 Jun 1;84(6):777-87.
3. Homoeopathic Pharmacopoeia of India; 1st vol;1971;Government of India, Ministry of Health
4. Maurya VK, Kumar S, Kabir R, Shrivastava G, Shanker K, Nayak D, Khurana A, Manchanda RK, Gadugu S, Kar SK, Verma AK. Dark classics in chemical neuroscience: an evidence-based systematic review of belladonna. ACS Chemical Neuroscience. 2020 Jul 14;11(23):3937-54.
5. Chakraborty U, Sinha M, Bhattacharjee A, Nayak D, Khurana A, Manchanda RK, Sarkar D, Das S. Sub-lethal dose of atropine gives protection from Japanese encephalitis virus infection in chick embryo model. InProceedings of the Zoological Society 2020 Sep (Vol. 73, No. 3, pp. 235-242). Springer India.
6. Chakraborty U, Katoch S, Sinha M, Nayak D, Khurana A, Manchanda RK, Sarkar D, Das S. Changes in viral load in different organs of Japanese Encephalitis virus-infected chick embryo under the influence of Belladonna 200C.
7. Chakraborty U, Sinha M, Bhattacharjee A, Banerjee S, Bandyopadhyay S, Khurana Dn, Manchanda Rk, Sarkar D, Das S. Effect Of Pure Atropine And Atropine Sulfate On Japanese Encephalitis Virus Infection In Chick Chorio Allantoic Membrane. Asian Jr Of Microbiol Biotech Env Sci. 2019;21:512-8.
8. Kumar S, Maurya VK, Kabir R, Nayak D, Khurana A, Manchanda RK, Gadugu S, Shanker K, Saxena SK. Antiviral activity of belladonna during Japanese encephalitis virus infection via inhibition of microglia activation and inflammation leading to neuronal cell survival. ACS chemical neuroscience. 2020 Oct 15;11(21):3683-96.
9. Bandyopadhyay B, Das S, Sengupta M, Saha C, Das KC, Sarkar D, Nayak C. Decreased intensity of Japanese encephalitis virus infection in chick chorioallantoic membrane under influence of ultradiluted Belladonna extract. Am J Infect Dis. 2010;6(2):24-8.10. Bhattacharjee A, Chaudhuri R, Dash JJ, Saha M,
10. Choudhury L, Roy S. Pre-treatment with Scopolamine Naturally Suppresses Japanese Encephalitis Viral Load in Embryonated Chick Through Regulation of Multiple Signaling Pathways. Applied Biochemistry and Biotechnology. 2021 Jun;193(6):1654-74.
11. Bandyopadhyay B, Banerjee A, Das S, Sengupta M, Chakravarty R, Ray K. Role Of Ultra-diluted Belladonna Extract In The Immune Mediated Healing Of Je Virus Infection In Mice. World Journal Pharmaceutical Research. 2016 Jan 17;5:1615-27.
12. Sengupta M, Bandyopadhyay B, Das S. Preventive and Curative Role of Belladonna 200 against Japanese Encephalitis Virus Infection in Adult Mice. Int. J. Curr. Microbiol. App. Sci. 2014;3(1):160-6.
13. Manchanda RK, Oberai P, Varanasi R, Singh S, Singh N, Khan T, Prasad R, Singh JR. Evaluation of homoeopathic medicines as add-on to institutional management protocol in Acute Encephalitis Syndrome: An exploratory observational comparative study.
14. Oberai P, Varanasi R, Padmanabhan M, Upadhyaya A, Singh S, Singh SP, Vikram D, Khan T, Prasad R, Gupta AK, Singh JR. Effectiveness of homeopathic medicines as add-on to institutional management protocol for acute encephalitis syndrome in children: an open-label randomized placebo-controlled trial. Homoeopathy. 2018 Aug;107(03):161-71.

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Qualitative and quantitative analysis of sleep/wake changes in a LGI1-Ab mediated rodent seizure model

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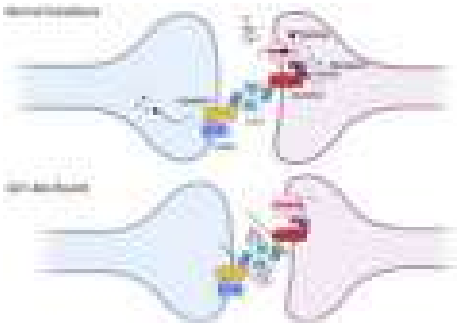
Background and Methods



Why interictal EEG?

Much of the work done to establish our understanding of symptom progression in epilepsies and autoantibody-associated seizure disorders (e.g., **LGI1-encephalitis**) has focused on examining ictal spikes and seizure properties.

Seizures are often difficult to capture in patients due to their varying frequency, duration, and location of origin. Here, we evidence the potential in examining **interictal EEG** more thoroughly as a source of insight for **tracking disease progression**.

Methods

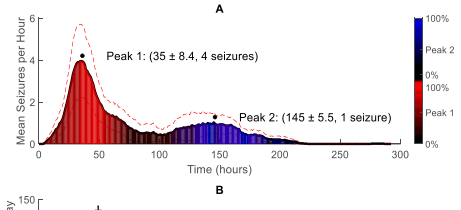
Video-EEG data from Wistar rats (**5 controls, and 5 treated with human-derived monoclonal LGI1-antibodies**) was extracted and the arousal state of each rat was visually classified.

The **Fast Fourier Transform** data from **23185 eight-second epochs** of EEG were normalised (**z-scored**) to visually-labelled awake data from each rat within the first 48 hours of recording and condensed into six frequency bands.

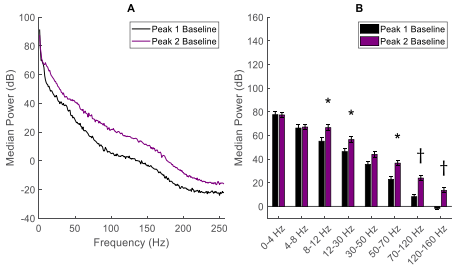
For our **supervised classification model** (support vector machine), normalised control data was used to create a **normal range of brain states against which the LGI1-Ab-treated rats were tested**. Epochs which fell outside of the normal range were considered outliers, and potentially novel, putatively pathological brain states.

Results

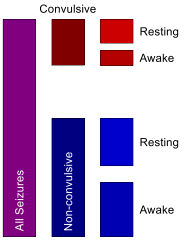
The semiology of seizures across two peaks in a rodent model of LGI1-encephalitis is qualitatively linked to pre-seizure arousal state. Interictal spectral properties are affected by the progression from the first to second peak.



- **LGI1-Ab-treatment causes seizures in bimodal distributions with peaks at 35±8.4 and 145±5.5 hours post infusion**

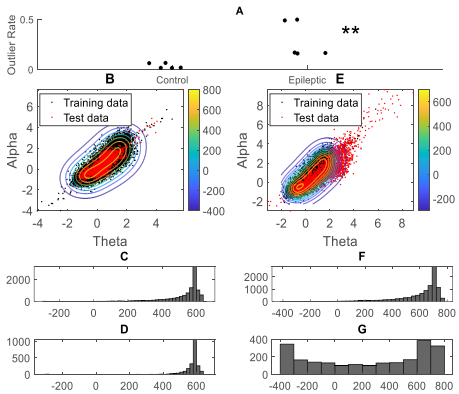


- **Interictal EEG spectra differ between early and late seizure periods**



- **402 seizures were examined**
- **Non-convulsive seizures tended to be preceded by wakefulness (n = 219, OR: 1.14)**
- **Convulsive seizures were more often preceded by restfulness (n = 85, OR: 1.57)**

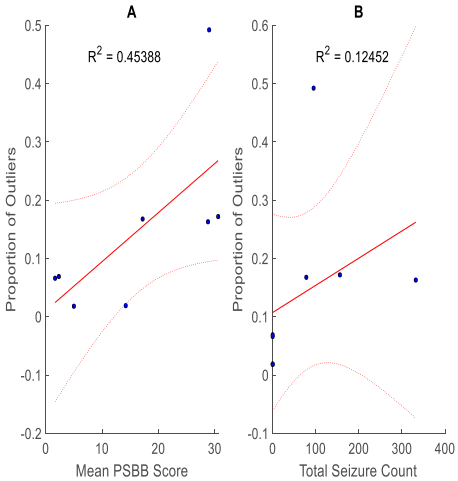
LGI1-Abs cause the development and novel pathological interictal brain states in supervised classification model.



- **Supervised classification (SVD) can be used to learn normal ranges of EEG spectra from controls (n=5)**
- **Interictal EEG in LGI1-Ab-treated rats (n=5) falls in the abnormal range in 29.9% (16.3-50%) of epochs compared to 3.9% (1.9-6.9%) among controls**

- **Previously-seen changes in interictal EEG spectra are not solely due to a change in the time spent in normal behavioural sates, but also due to the development and occupation of novel, putatively pathological brain states which become progressively abnormal as the disease advances**

Proportions of abnormal interictal brain dynamics are associated with worse disease outcome measurements.



- **Rates of abnormal interictal EEG are positively associated with worsening measures of disease outcome among controls (n=4) and LGI1-Ab-treated rats (n=4)**
- **OR vs PSBB (r = 0.6737)**
- **OR vs Total seizure count (r = 0.3529)**

Discussion

Our supervised classification model has shown that rats treated with human-derived LGI1-antibodies occupy novel, putatively pathological, brain states as their disease progresses that are not found in control Wistar rats. Hence the changes in median frequency band powers seen in interictal data are principally the result of altered brain dynamics rather than a change in the time spent in a given normal behavioural or brain state. Future work will aim to identify any antibody-dependent deviations from this normal range as such information would allow us to infer why different autoimmune-associated encephalopathies present symptoms differently.

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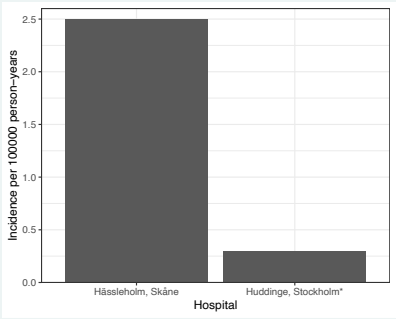
Dr Jakob Theorell conducted his PhD studies on human immunodeficiency syndromes affecting lymphocyte cytotoxicity in the group of Professor Yenan Bryceson at the Department of Medicine, Huddinge from 2010 to 2017, in parallel with his clinical training. After obtaining his medical license and PhD in 2017, he started working as a clinical resident at Psychiatry Southwest. In 2018, he took up a postdoctoral researcher position in the Oxford Autoimmune Neurology Group led by Professor Sarosh Irani. There, he primarily studied lymphocyte function and clonality in the context of autoimmune neurological syndromes, specifically NMDA-R, LGI1 and CASPR2 autoantibody encephalitis as well as Neuromyelitis Optica. He came back to Sweden in 2020 and took up his clinical duties at Psychiatry Southwest and a postdoctoral position in Professor Fredrik Piehl's group, where he focused on immune cell phenotyping in Myasthenia gravis. Since April 2022 he is a team leader in Jenny Mjösberg's group, Center for Infectious Medicine, Department of Medicine Huddinge.

Where are the LGI1 and CASPR2 encephalitis patients in Stockholm, Sweden?

Jakob Theorell, MD/PhD, Alexandra Gardner, MD student

LGI1 and CASPR2 encephalitides are underdiagnosed in Stockholm. It is likely that patients with these disorders instead are diagnosed with dementia. Using databases as well as biobanks from the centralized dementia diagnostic service in Stockholm, subgroups of patients with an increased likelihood of encephalitis will be tested using live-cell based assays.



Incidence of LGI1 encephalitis in two hospital catchment areas in Sweden 2016-2021. Left: Hässleholm Hospital, with a catchment area of 60 000 individuals (data from M. Esbjörnsson).. Right Huddinge with a catchment of ~400 000 individuals. *Conservative approximation.

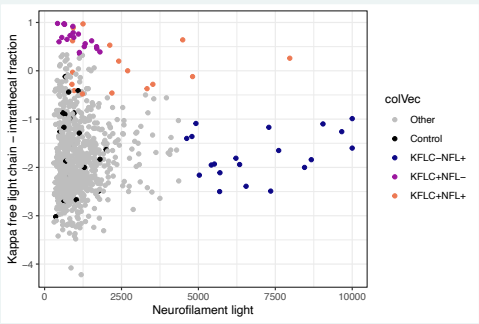
Introduction

Encephalitis with autoantibodies to the LGI1 and CASPR2 autoantigen mainly affect individuals above 50 years of age[1]. They are associated with memory loss and personality changes, in addition to often subtle forms of epilepsy, such as the LGI1-pathognomonic faciobrachial dystonic seizures[1]. LGI1 is internationally the second most common encephalitis autoantigen, yet in Stockholm, the patients are underrepresented, and no cases with FBDS are known to the authors.

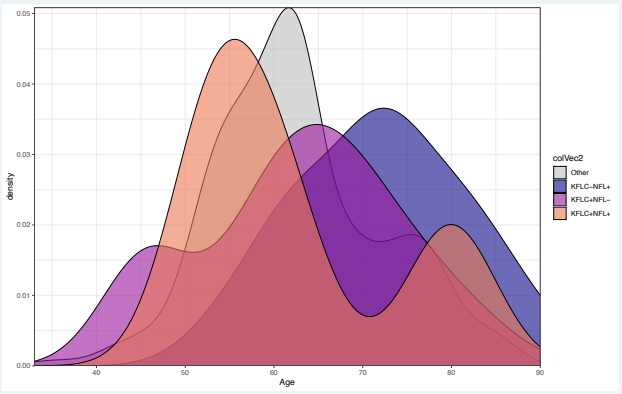
Materials

Utilising a unique collection of 11 000 samples from patients under investigations for dementia, we aim at screening for autoantibodies to LGI1 and CASPR2 as well as NMDA-R and GABA-B, which are the other two encephalitis autoantibodies that are over-represented in the subgroup of encephalitis patients that are erroneously initially diagnosed with neurodegenerative dementia[2].

We hypothesise that a combination of Neurofilament light (NFL, a neuronal damage marker) and Kappa free light chain-intrathecal fraction (KFLC-IF, indicator of intrathecal antibody production) will identify high-risk individuals for encephalitis among these patients.



Distribution of NFL and KFLC-IF among 759 patients undergoing dementia investigations. Highlighted populations will be prioritised for testing but eventually all will be included



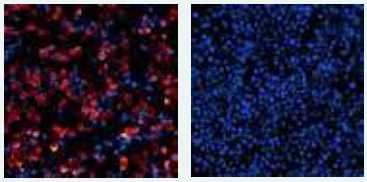
Density plot of clusters of dementia patients defined by NFL and KFLC-IF levels.

Results

When clustering the patients based on NFL and KFLC-IF, the populations with differing combinations of increases in neuronal damage and intrathecal antibody production separate. The median age of the NFL+KFLC-IF+ group, 58, is significantly lower than the NFL+KFLC-IF- group, 72.5 (Benjamini-Hochberg-corrected Mann-Whitney p-value 0.03).

Discussion

The experimental side of this project has just commenced, and results are yet incomplete. However, as the NFL/KFLC-IF finding above might indicate, it is likely that the dense clinical database associated to material at hand will, if cases are identified among the patients, make it possible to identify screening parameters that can forego direct testing for autoantibodies, thus hopefully increasing the number of identified and treated autoimmune encephalitis patients in Stockholm.



Example of live Cell-based assay for CASPR2 autoantibody detection. Left panel: HEK 293 cells transiently transfected with CASPR2 and subsequently incubated with serum from a known CASPR2 patient. Right panel: serum from the same individual incubated with HEJ 293 cells transiently transfected with LGI1. Red color: anti-human IgG. Blue color DAPI.

References

Jakob Theorell, MD/PhD is a team leader at the Center for Infectious Medicine focusing on epidemiological as well as immunocellular aspects of autoimmune neurological research. He is also a registrar in adult Psychiatry

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Dr James Badenoch is an Academic Foundation Doctor at Barts Health NHS Trust and Queen Mary University of London, FY1 at Newham University Hospital and FY2 at St Bartholomew's and The Royal London hospitals. His research interest is in neuropsychiatry and the nervous system associations of infectious diseases. He has contributed to several projects evaluating neuropsychiatric features of COVID-19 and recently monkeypox infection. He is starting a research job at Barts with the Preventative Neurology Unit.

Neurological and psychiatric presentations associated with human monkeypox virus infection: a systematic review and meta-analysis

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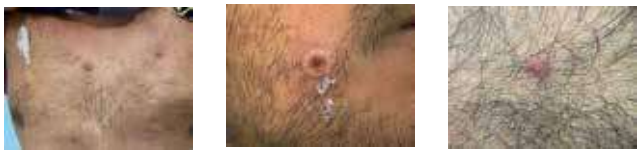
Introduction

- Monkeypox infection is mostly associated with dermatological lesions and influenza-like symptoms
- There is evidence of nervous system involvement with the related Orthopoxviruses: smallpox infection (variola virus) and smallpox vaccination (vaccinia virus).
- Potential nervous system associations of monkeypox infection are important to recognise and have implications for the current outbreak

Figure 1: monkeypox dermatological lesions



Taken from https://dermnetnz.org/topics/monkeypox

Aims and method

Aims

1. Summarise the prevalences of neurological and psychiatric presentations of human monkeypox infection
2. Describe the spectrum of such presentations

Method

- Searched MEDLINE, EMBASE, PsycINFO, AMED & MedRxiv up to 31/05/2022
- Included any study design which reported neuropsychiatric features
- Minimum of 10 individuals per study for inclusion in the meta-analysis

Results

Figure 2: PRISMA flow diagram

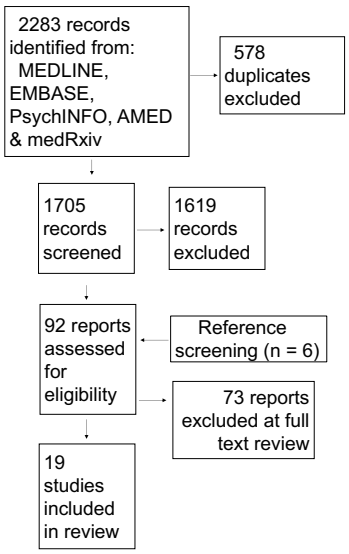


Table 1: Design of included studies

Cohort	12
Cross-sectional	2
Case series	4
Case report	1

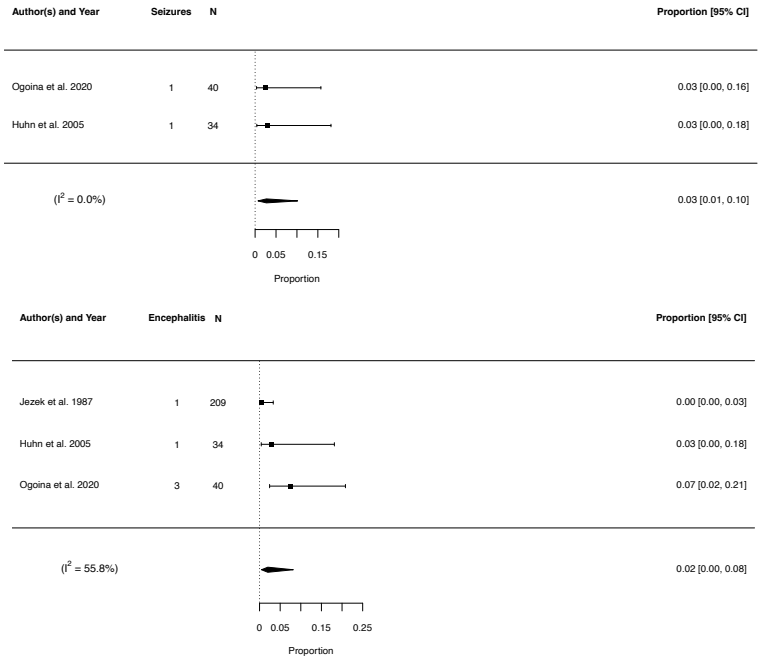
Table 2: Quality of cross-sectional & cohort studies

Low	6
Medium	8
High	0

Table 3: Origin of studies

USA	6
Nigeria	5
Democratic Republic Congo	5
Republic of Congo	2
UK	1

Figure 3: pooled prevalence of seizure and encephalitis



Interpretation

- There is preliminary evidence for a range of neuropsychiatric presentations associated with monkeypox infection prior to the current outbreak, based on a small number of studies of moderate quality without controlled populations.
- **Serious neurological complications (encephalitis and seizure) were present in 2-3%** and nonspecific neuropsychiatric symptoms (**headache, myalgia and fatigue**) were frequently reported.
- There is **less evidence regarding the psychiatric presentations** or sequelae of monkeypox infection. However, the effect of stigma surrounding monkeypox infection and disfiguring skin lesions could contribute to psychological distress.
- There are knowledge gaps surrounding putative factors which influence the risk of neurological and psychiatric presentations including overall monkeypox infection severity and viral clade. Further gaps concerning the severity and duration of neuropsychiatric symptoms exist.

Future directions

- Monkeypox-related nervous system presentations may warrant surveillance within the current monkeypox outbreak, with prospective longitudinal studies evaluating the mid- to long-term sequelae of the virus.
- Robust methods to evaluate the potential causality of monkeypox with these clinical features are required at an individual and epidemiological level.

Funding

The study was funded by UKRI/MRC (MR/V03605X/1), MRC-CSF (MR/V007181/1), MRC/AMED (MR/T028750/1) and the Wellcome Trust (102186/B/13/Z) and (102186/B/13/Z) and UCLH BRC. The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

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Dr Paber graduated medical degree - Cebu Doctors University College of Medicine Internal Medicine Neurology. Currently, he is pursuing Fellowship in Clinical Neurophysiology – electro diagnostics, nerve sonography and evoked potential.

CLINICAL MANIFESTATIONS AND OUTCOMES OF TOXOPLASMA ENCEPHALITIS AS THE ONLY PRESENTATION OF PATIENTS WITH ACQUIRED IMMUNE DEFICIENCY SYNDROME: A COHORT STUDY

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BACKGROUND AND OBJECTIVES

The aim of the study is to profile, evaluate and describe the clinical manifestations and outcomes of toxoplasma encephalitis as initial manifestation of Acquired Immune Deficiency Syndrome.

METHODS

This is a prospective cohort study that profiled patients with toxoplasma encephalitis at presentation and are newly diagnosed with Acquired immune Deficiency syndrome between January 2019 – December 2020.

CRITERIA FOR THE STUDY GROUP FOR THIS STUDY ARE THE FOLLOWING:

ADMITTED PATIENTS PRESENTED WITH:

A. CLINICAL SYMPTOMS (SUCH AS FEVER, HEADACHE, FOCAL NEUROLOGIC DEFICIT)

B. COMPUTED TOMOGRAPHY (CT), MRI FINDINGS COMPATIBLE WITH TOXOPLASMOSIS

C. POSITIVE SERUM TOXOPLASMA IGG

D. NOT DIAGNOSED AS HIV INFECTED OR AIDS AT THE TIME OF ADMISSION

2. AGE AT LEAST 18 YEARS AT STUDY ENTRY.

DESIGN

WE USED A COHORT STUDY TO DETERMINE PATIENTS WITH TOXOPLASMA ENCEPHALITIS AT PRESENTATION AND ARE NEWLY DIAGNOSED WITH ACQUIRED IMMUNE DEFICIENCY SYNDROME AND THEIR OUTCOME. THE REPORTED ACUTE TOXOPLASMOSIS CASES ARE LABORATORY CONFIRMED WITH SEROLOGIC ASSAYS USING TOXOPLASMA IGG. QUANTITATIVE MEASUREMENT IS NOT NECESSARY TO DETERMINE PRESENCE OF TOXOPLASMA INFECTION. ADDITIONAL SEROLOGIC TESTING FOR CD4 COUNT WAS ALSO TESTED.

THE STUDY GATHERED DATA REGARDING THE PROFILE, CLINICAL MANIFESTATION, RISK FACTORS AND THEIR OUTCOME FOR TOXOPLASMA ENCEPHALITIS. THE MODIFIED RANKIN SCORE WAS USED TO DETERMINE FUNCTIONAL OUTCOMES AT TWO WEEKS AFTER DISCHARGE AND AT 6 MONTHS AFTER DISCHARGE. THE DATA WAS ANALYZED USING DESCRIPTIVE STATISTICS. TABLES WERE USED TO PRESENT THE DATA.

RESULTS

There were 45 patients who presented with central nervous system infection and 11 patients were seen to satisfy the inclusion criteria and were not excluded in the study.

TABLE 1: DEMOGRAPHIC DATA

	Mean	SD	N = 11	Percentage
Age	29.8	±6.1	-	-
Sex	-	-	Male - 10 Female - 1	90% 10%
Sexual Orientation	-	-	Homosexual- 6 Heterosexual- 5	54% 46%
Civil Status	-	-	Single – 10 Married -1	90% 10%
Work	-	-	Unemployed - 6 Student -2 Employed- 2 OFW -1	54% 18% 18% 10%

Table 3 Modified Rankin Scale Outcomes

Outcome MRS	Admission N = 11	%	Discharge N = 11	%	Ffup 2 weeks N = 9	%	Ffup 6 months N = 9	%
0	-	-	2	18%	3	33.33%	4	44.44%
1	5	45%	4	36%	3	33.33%	2	22.22%
2	2	18%	1	9.3%	1	11.11%	1	11.11%
3	0	-	0	-	0	-	1	11.11%
4	2	18%	1	9.3%	1	11.11%	0	-
5	2	18%	1	9.3%	1	11.11%	0	-
6	0		2	18%	0		1	11.11%

Table 2 : Neurologic Manifestations of Patients with Toxoplasma Encephalitis as initial presentation of AIDS

Neurologic Manifestation	Count	SD
GCS	12	±2
Non focal		Percentage
Headache	10	90%
Confusion/psychosis	7	64%
Seizure/Convulsion	6	54%
Nausea/Vomiting	4	36%
Fever	4	36%
Coma	2	18%
Focal		
Hemiparesis	8	72%
Visual Alteration	5	46%
CN deficit	4	36%
Sensory Deficit	2	18%
Meningism	1	10%
Ataxia	0	-
Involuntary movement	0	-

DISCUSSION

Toxoplasma encephalitis should be considered as a sentinel event to diagnose AIDS. They usually manifests with patients with very low CD4 count and a high titer of serum toxoplasma IgG. They can have no other co – infection and can be the only AIDS defining infection. Treatment with Cotrimoxazole and steroids were seen to have good outcomes to patients with more than 2 weeks treatment and hospitalization within 3 weeks. Those with poor MRS on admission and discharge had poorer outcome. Those who completed Cotrimoxazole treatment and started on antiretroviral therapy were seen to have improvement in MRS within 6 months.

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Dr Kerstens is a clinical neurologist with experience in autoimmune neurology as junior associated neurologist at the neuroimmunology unit of the Academic Hospital of Antwerp, Belgium. In addition, he is a clinical research fellow at Erasmus MC University Medical Center in Rotterdam, the Netherlands, as part of a six-month European Joint Programme on Rare Diseases (EJP-RD) grant. In 2016, he obtained his medical degree with great distinction at the University of Antwerp. Thereafter, he was trained in neurology at Antwerp and Rotterdam, completing his five-year residency in August 2021.

Epidemiology of paraneoplastic neurological syndromes and antibody-positive autoimmune encephalitis in the Netherlands

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Jeroen Kerstens [1], MD, Marco Schreurs [2], Juna de Vries [1], MD PhD, Rinze Neuteboom [1], MD PhD, Daniëlle Bastiaansen [1], MD, Yvette Crijnen [1], MD, Juliette Brenner [1], MD, Robin van Steenhoven [1], MD, Marienke de Bruijn [1], MD PhD, Agnes Van Sonderen [1], MD PhD, Marie Vermeiren [1], MD, Peter Sillevis Smitt [1], MD PhD, Maarten Titulaer [1], MD PhD.

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Introduction

The number of epidemiologic studies in patients with paraneoplastic neurological syndromes (PNS) and autoimmune encephalitis (AIE) is limited. However, these studies are critical to enable the development of health care strategies and planning of clinical trials.

Methodology

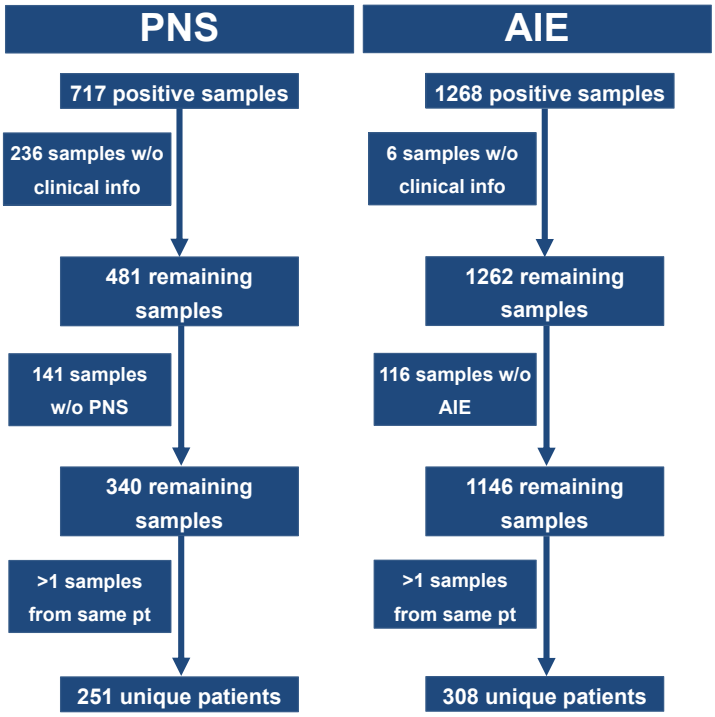
Nationwide retrospective Dutch cohort study. We identified all patients who tested positive for antibodies against cell-surface (AIE: NMDAR, LGI1, Caspr2, AMPAR, GABABR, GABAAR, DPPX, GlyR, IgLON5, mGluR1) or intracellular antigens (PNS: Hu, Yo, Ri, Tr, CV2, Ma1, Ma2, amphiphysin, KLHL11, GFAP) at our national referral center between 2016 and 2021. Clinical information was collected through chart review and/or contact with referring physicians.

Conclusions

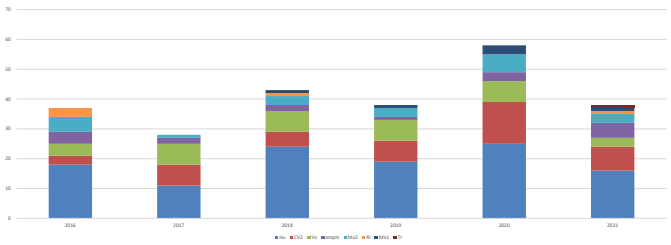
- Incidence rates of AIE and PNS are higher in the Netherlands than those previously reported for France, and are increasing over the years, probably in part due to improved recognition and diagnostics.
- While 20 different antibodies are tested, just three of them (NMDAR, LGI1, Hu) make up over 60% of positive results.
- No clear effect of the COVID-19 pandemic on incidence rates was observed.

Results

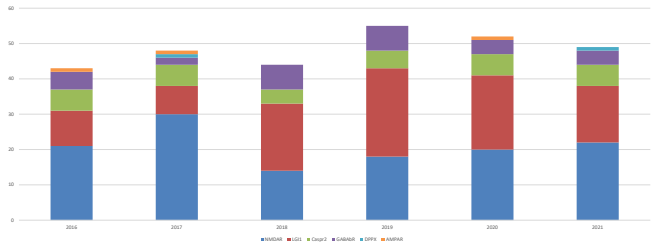
Sample flowchart



Temporal trends

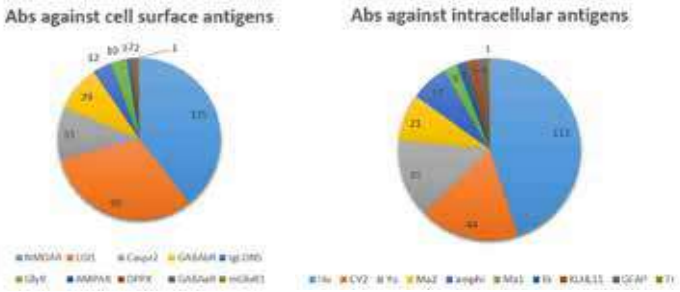


Graph 1: Absolute numbers of new Ab-positive patients per year for the 8 classical PNS-Abs.



Graph 2: Absolute numbers of new Ab-positive patients per year for the 6 classical AIE-Abs.

Antibody distribution

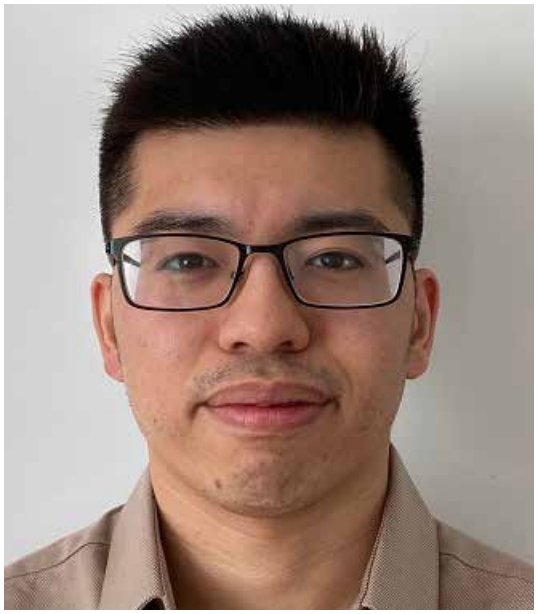


Incidence rates

- Crude minimal incidence rate for the total observation period was 4.6 (95% confidence interval 4.2-5.0) per million person-years for both groups combined: 3.0 (2.7-3.3) per million person-years for AIE and 1.6 (1.4-1.8) per million person-years for PNS.
- We observed a global increase in incidence rates over the years, ranging from 3.9 (3.1-5.0) in 2016 to 5.6 (4.4-6.4) per million person-years in 2021 for AIE and PNS combined.

Reference

Hébert J, Riche B, Vogrig A, Muñiz-Castrillo S, Joubert B, Picard G, Rogemond V, Psimaras D, Alentorn A, Berzero G, Desestret V, Rabilloud M, Honnorat J. Epidemiology of paraneoplastic neurologic syndromes and autoimmune encephalitides in France. Neurol Neuroimmunol Neuroinflamm. 2020 Aug 26;7(6):e883. doi: 10.1212/NXI.0000000000000883. PMID: 32847939; PMCID: PMC7455315



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Dr Chen is a junior doctor currently working as a neurology clinical fellow at Queens Square Hospital in London. He has an interest in encephalitis and is hoping to apply for neurology specialist training in the near future. He completed his MBBS at Imperial college London and a BSc in Neuroscience with the Brain Sciences division at Hammersmith Hospital.

Risk of seizure activity in patients with encephalitis; regional and volumetric analysis of cerebral oedema and development of a multivariable prediction model.

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Background

Seizures may occur in up to 67% of patients with encephalitis and are associated with increased morbidity and mortality (1-4). Identifying factors associated with seizures in these patients can help in recognising those at high risk to aid clinical management. The presence of observable changes on neuroimaging have been associated with occurrence of seizures in encephalitis, although it is currently unclear which brain regions and by which degrees of oedema are most predictive (2,5).

Aims

To identify the regions and quantity of brain oedema on the MRIs of patients with encephalitis relative to the presence of seizures. To combine neuroimaging findings with clinical variables to develop and validate a prediction model for seizure risk in patients with encephalitis.

Methods

The patients in our first cohort were recruited through the Aetiological Study of Encephalitis led by the UK Health Protection Agency (6). The second cohort of patients recruited through the Understanding and Improving the Outcome of Encephalitis (ENCEPH-UK) cohort study (7). To be included in this study, each patient required a 2D T2-weighted and/or T2-weighted fluid attenuated inversion recovery (FLAIR) MRI of the brain. The outcome we studied was case files indicating occurrence of a seizure on admission or as an inpatient. Volumetric analysis on the first cohort was conducted by two independent blinded investigators using the Cavalieri method of stereology with point counting (8). Stereological analysis was performed using *EasyMeasure* software.

	First cohort N=69	Second cohort N=195
Mean age (±SD)	**31.8 (±22.9)**	**49.3 (±19.0)**
Female (%)	**37 (53.6%)**	**101 (50.2%)**
Median GCS on admission (IQR)	**13 (8 – 15)**	**14 (11 – 15)**
Median Duration of symptoms In days (IQR)	**7 (4 – 16)**	**5 (2 – 13)**
Aetiology (%)		
Unknown	**29 (42.0%)**	**77 (39.5%)**
HSV	**12 (17.4%)**	**51 (26.2%)**
Other infective cause	**11 (15.9%)**	**30 (15.4%)**
Auto-immune mediated	**17 (24.6%)**	**37 (19.0%)**
Seizures (%)	**41 (59.4%)**	**72 (36.9%)**
Visible oedema on MRI (%)	**44 (63.8%)**	**108 (55.4%)**

Table 1: Comparison of demographics and characteristics of first cohort (UKHPA study) and second cohort (ENCEPH UK study).

Results

Overall, 44 (63.8%) patients had visible oedema on their admission MRI and this was associated with an increased risk of having an inpatient seizure (OR 4.74 [95% CI] [1.66 – 13.6], p<0.01). Greater volumes of oedema in cortical structures and the temporal lobe were also associated with an increased risk of seizures (OR 1.79 [1.13 – 2.82], p<0.01 and OR 1.77 [1.06-2.95], p=0.03 respectively).

When studying clinical variables, a Glasgow coma scale (GCS) score of <10 on admission increased the risk of future seizure activity (OR 10.80 [2.54-45.87], p<0.01). A multivariate model combining these variables had an AUROC of 0.86 (95% CI 0.76 – 0.97, p<0.001) with good calibration in the first cohort. The second cohort differed in age, symptom duration and seizure occurrence compared to the first. Despite this, validation of the model on this cohort showed an AUROC of 0.69 (95% CI 0.61 – 0.76, p<0.001) and good calibration.

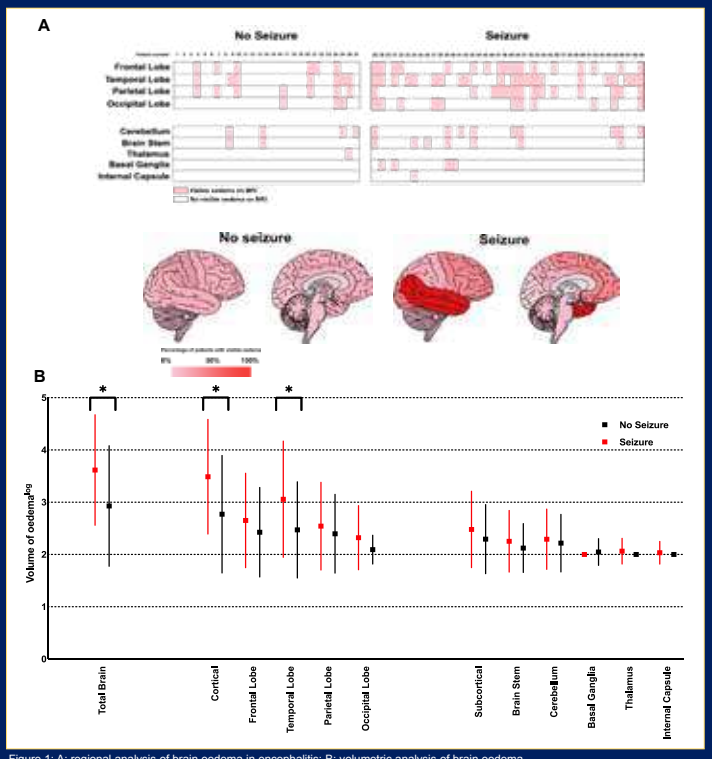

Figure 1: A: regional analysis of brain oedema in encephalitis; B: volumetric analysis of brain oedema.

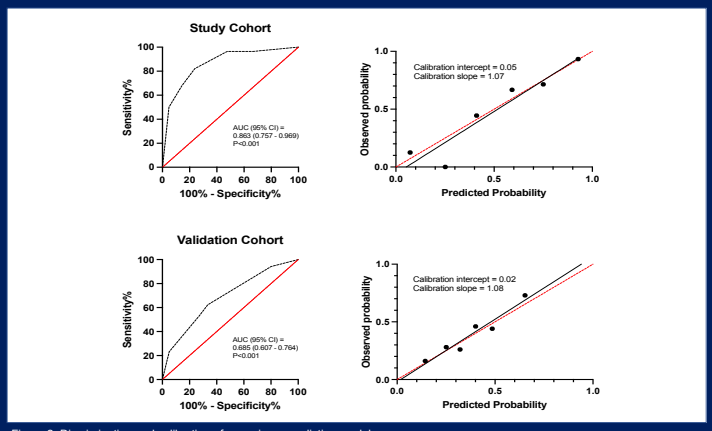

Figure 2: Discrimination and calibration of our seizure prediction model

Discussion

Several pro-inflammatory cytokines play a key role in lowering the seizure threshold through excitatory neurotransmitter release and the generation of vasogenic oedema (9-10). This is particularly seen when inflammation involves epileptogenic areas of brain parenchyma (3). More extensive inflammation in encephalitis reflected in greater volumes of observable brain oedema may further lower this seizure threshold. Visualisation of oedema in neuroimaging could provide an in-vivo assessment of the pathological excitatory activity, allowing it to act as a useful indicator for seizure risk.

Conclusion

We identified regions in which brain oedema is common in patients with encephalitis. We developed a novel practical prognostic instrument to predict the risk of seizures in patients with encephalitis. Our score showed satisfactory validation in our second cohort and showed good discrimination and calibration.

References

1. Misra UK, Kalita J. Seizures in encephalitis: predictors and outcome. Seizure 2009;18:583-587.
2. Misra UK, Tan CT, Kalita J. Viral encephalitis and epilepsy. Epilepsia 2008;49 Suppl 8:13-18.
3. Spatola M, Dalmau J. Seizures and risk of epilepsy in autoimmune and other inflammatory encephalitis. Curr Opin Neurol 2017;30:345-353.
4. Yeshokumar AK, Coughlin A, Fastman J, et al. Seizures in autoimmune encephalitis-A systematic review and quantitative synthesis. Epilepsia 2021;62:397-407.
5. Defres S, Keller SS, Das K, et al. A Feasibility Study of Quantifying Longitudinal Brain Changes in Herpes Simplex Virus (HSV) Encephalitis Using Magnetic Resonance Imaging (MRI) and Stereology. PLoS One 2017;12:e0170215.
6. Granerod J, Ambrose HE, Davies NW, et al. Causes of encephalitis and differencesrepresentations in England: a multicentre, population-based prospective study. Lancet Infect Dis 2010;10:835-844.
7. Defres ST, K.; Michael, B.; Ellul, M. Solomon, T, et al. Clinical Predictors of Encephalitis in UK Adults – A Multi-Centre Prospective Observational Cohort Study. http://dx.doi.org/10.2139/ssrn.3859285202l.
8. Pudelphelt M. Computer interface for convenient application of stereological methods for unbiased estimation of volume and surface area: studies using MRI with particular reference to the human brain.: University of Liverpool, 1999.
9. Vezzani A, Fujinami RS, White HS, et al. Infections, inflammation and epilepsy. Acta Neuropathol 2016;131:211-234.
10. Vezzani A, Granata T. Brain inflammation in epilepsy: experimental and clinical evidence. Epilepsia 2005;46:1724-1743.

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Dr Jing Zhou is a senior postdoc in Neurology department of UCSF. Her goal in research is to understand pathophysiology of neurological diseases and find out effective treatment for these diseases. She has been studying the pathophysiology of paediatric anti-NMDA receptor encephalitis by generating mouse models for six years. She has well examined these mouse models across anatomical and behavioural levels. She has a series of interesting findings. Most importantly, she demonstrates that brain circuit deficits caused by patient-derived autoantibodies during development, cause subsequent behaviour deficits in adulthood. This is relevant to the effects of this syndrome in paediatric and newborn patients and may also shed light on the protracted neurocognitive deficits experienced by anti-NMDA receptor encephalitis patients even after resolution of the acute phase of the illness.

Transient, developmental exposure to patient-derived anti-NMDA receptor autoantibodies causes long-term axonal and behavioral defects

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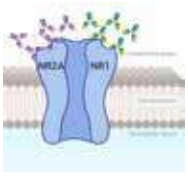
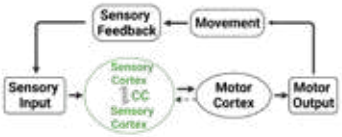
INTRODUCTION



Anti-NMDA receptor (NMDAR) encephalitis is associated with functional blocking autoantibodies against NMDAR, with a predilection for children and young adults. Despite initial responsiveness to immunotherapy, these patients are often left with residual cognitive deficits and behavioral abnormalities that can last from months to years. It remains enigmatic why effective immunotherapy cannot sustain patients' recovery, provided that anti-NMDAR antibodies selective, dose-dependent, and reversible decrease in NMDAR surface density and synaptic localization. Thus, we reason that *additional* ***long-lasting pathophysiologic changes may contribute to anti-NMDAR encephalitis pathogenesis.***

MODEL

Model of Bilateral Sensory-Motor Integration

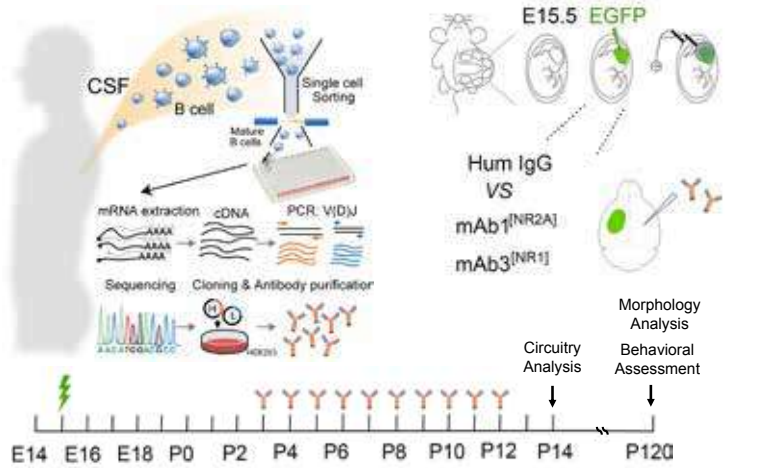


Persistent sensory-motor deficits are seen in children, indicating that ***sensory-motor circuits may be disrupted in these patients.*** Sensory-motor coordination relies on the callosal connections in somatosensory cortex.

Corpus Callosum (CC): The largest interhemispheric commissural circuit in mammals. The connectivity of the CC is essential for coordinated sensory-motor function and for many higher cognitive processes.

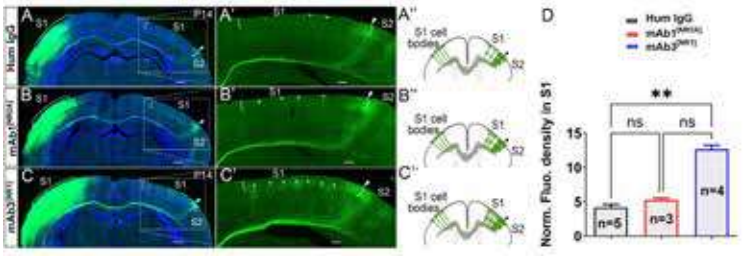
METHODS

Generated anti-NR1 and anti-NR2A human monoclonal antibodies (mAbs); injected into mouse brain; examined axonal morphology, callosal circuity, and behavior.

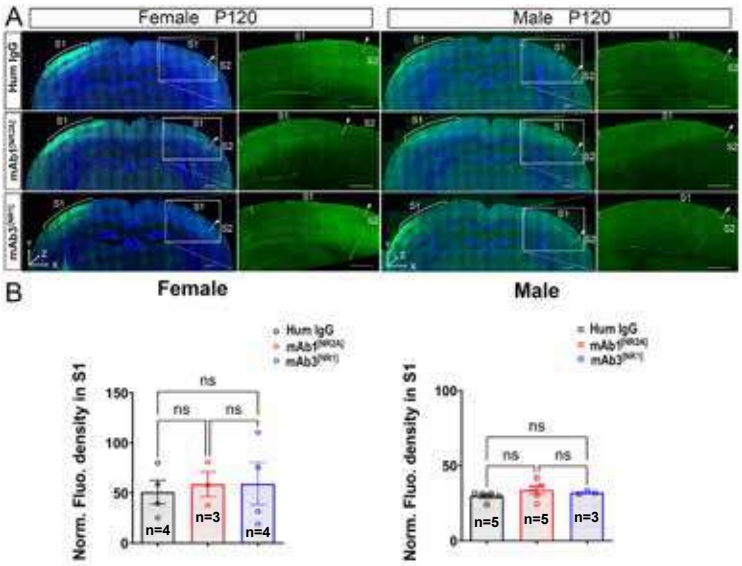


RESULTS

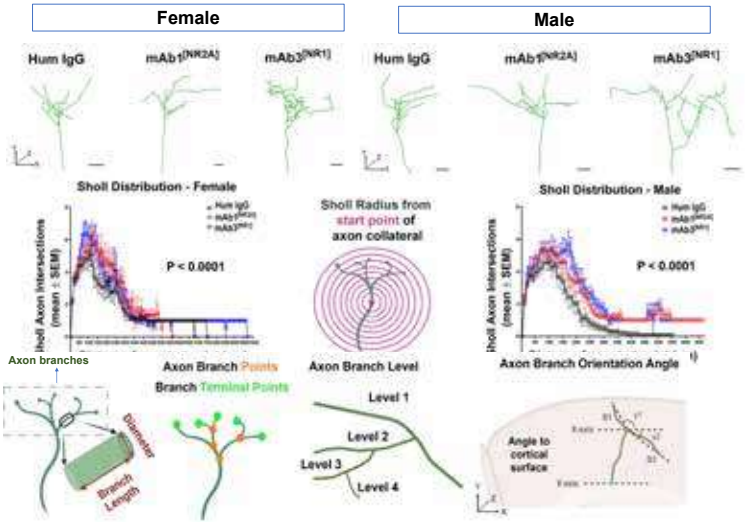
Disrupted callosal innervation in primary somatosensory cortex (S1) at P14



Disrupted callosal innervation in S1 was recovered when mice at P120



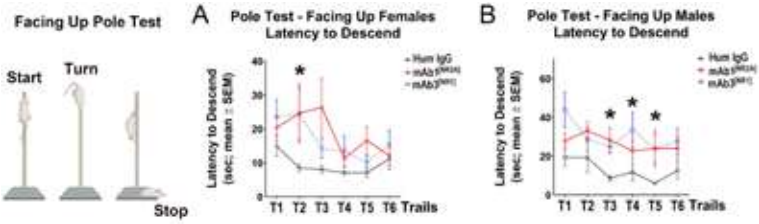
Permanent morphology alteration of S1 callosal neurons at P120



Treatment	Gender	Branch Dimeter	Branch Numbers	Branch Levels	Branch Angle	Branch ORIEN	Total Branch Length	Terminal Field Area
mAb1[NR2A]	**Female**	–	–	–	–	–	–	↑
mAb3[NR1]	**Female**	–	↑	–	–	–	↑	–
mAb1[NR2A]	**Male**	↓	–	–	–	–	–	↑
mAb3[NR1]	**Male**	↓	↑	↑	↑	←→	↑	↑

–: No Change; ↓: Reduced; ↑: Increased; ←→: Opposite Direction

Persistent impaired fine movement in mAbs treated mice



Treatment	Gender	Locomotor Activity	Muscle Strength	Muscle Coordination	Nest Building	Balance Check	Latency of Facing Up Pole
mAb1[NR2A]	**Female**	–	↑	–	–	–	–
mAb3[NR1]	**Female**	–	–	–	–	↑	↑
mAb1[NR2A]	**Male**	–	–	–	–	↑	↑
mAb3[NR1]	**Male**	–	–	–	✖	–	↑

–: No Change; ↑: Increased; X: Impaired

SUMMARY

Reduced diameter, increased branch complexity in S1 callosal axon terminals increase the signal propagation failures

1, Transient, developmental exposure to patient-derived anti-NMDAR autoantibodies results in long-lasting morphometric and physiologic axonal defects in mice.
2, These cellular and physiologic perturbations are read out as persistent functional deficits in fine sensory-motor tasks.
3, These findings explained the cellular basis of the prolonged neurological deficits of this disease and set an example on the role of autoantibodies in defective building of brain structure for other autoimmune neurological diseases.
4, Our findings are relevant to the effects of this syndrome in pediatric and newborn patients and may also shed light on the protracted neurocognitive deficits experienced by anti-NMDAR encephalitis patients even after resolution of the acute phase of the illness.

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Acute Cerebellitis with Scrub Typhus Infection – Case series from South India

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Background

- **Scrub typhus** is a mite-borne Rickettsial disease caused by *Orientia tsutsugamushi,* a gram-negative cocco-bacilli transmitted through the bite of chigger mite.
- Neurological involvement manifests as:
  a) Meningoencephalitis
  b) Cranial neuropathies
  c) Cerebral infarcts
  d) Acute disseminated meningoencephalitis
  e) Transient extrapyramidal syndromes
  f) Opsoclonus–myoclonus
  g) Guillain-Barre syndrome.
- The neurological damage as evidenced by autopsy studies occurs due **focal vasculitis and lymphocytic infiltration of blood vessels** caused by the bacteria.
- **Acute Cerebellitis (AC)** has been reported with Murine typhus (endemic typhus),caused by *Rickettsia typhi* as a part of the meningoencephalitis syndrome, however similar occurrence with Scrub Typhus infection has been scarcely reported.

Aims and Objectives

- To study the incidence, management and outcomes of acute cerebellitis among patients with scrub typhus infection.

Methods

- Retrospective observational cohort study
- Period : 2015 – 2019
- **Inclusion criteria:**
- Patients with febrile illness diagnosed as ST based on the presence of eschar and/or positive scrub IgM Elisa
- Clinical features of cerebellitis
- **Outcomes:**
- Incidence of acute cerebellitis in ST infection
- Proportion with favourable outcome at discharge as defined by disability as measured by Modified Rankin's score≤2.

Results

Patients with Acute febrile illness (2015 – 2019) n = 2600

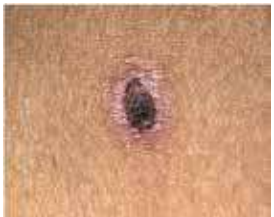
↓

Patients with Scrub typhus n = 1091 (42%)

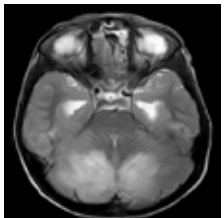
↓

Scrub typhus with Neurological Involvement n = 91 (8%)

Incidence of Acute Cerebellitis – 7 %



ESCHAR – pathognomonic of 'Scrub typhus'



T2 FLAIR hyper-intensities involving bilateral cerebellar hemispheres

Variable	Value, n-7
Age(years± SD)	52±18
Clinical characteristics	
Altered mentation	4 (60)
Generalized seizures	3 (40)
Headache	2 (30)
Meningismus	2 (30)
Time to onset of cerebellar symptoms(days)	3
Pancerebellar dysfunction	7 (100)
Opsoclonus Myoclonus ataxia	2 (30)
Imaging characteristics	
Normal imaging	5 (70)
Cerebellar edema	1 (15)
Raised Intracranial pressure	1 (15)
Cerebrospinal fluid analysis	
Cell counts, median (IQR), Cu mm Lymphocyte, median (IQR), Cu mm	38 (8-225) 38 (7-215)
Protein, median (IQR), mg/dl	98 (91-133)
Glucose, median (IQR), mg/dl	80(34-140)
Management	
Duration of hospitalisation, Median (IQR), days	7(4-8)
Doxycycline	7 (100)
Azithromycin	1 (10)
Alive at discharge	7 (100)
Proportion with good functional outcome (mRS< = 2) at discharge	**5 (75)**
Proportion with good functional outcome (mRS< = 2) at 6 months follow-up	**7 (100)**

Discussion

- **Acute Cerebellitis**, first described by Westphal and Batten in 1872, is an inflammatory syndrome resulting in acute cerebellar dysfunction.
- It can occur as a primary infectious, post-infectious, immune-mediated or post-vaccinal disorder.
- Although meningitis and meningoencephalitis is commonly reported in scrub typhus, pure/isolated cerebellitis in adults has rarely been documented in the past two decades.
- The diagnosis of AC can be made with history and a detailed neurological examination.
- CSF analysis is not required for diagnosis.
- MRI brain may illustrate various patterns of cerebellar involvement in addition to bilateral diffuse hemispheric abnormalities and cortical swelling (or)the MRI may be absolutely normal.
- Management is definitive therapy with doxycycline and supportive management.
- Complete recovery is the norm, with no residual neurological sequelae.

Learning points

- Acute cerebellitis is a rare manifestation of Scrub Typhus, commonly identified by clinical history and examination.
- Imaging is normal in majority of patients and all have an excellent response to doxycycline.
- Scrub Typhus should be considered as a differential diagnosis of acute cerebellitis in the tropics, and early targeted antimicrobial therapy offers good outcomes.

References

1. Bonell A, Lubell Y, Newton PN, et al.. Estimating the burden of scrub typhus: a systematic review. PLoS Negl Trop Dis 2017;11:e0005838. 10.1371/journal.pntd.0005838
2. Misra UK, Kalita J, Mani VE. Neurological manifestations of scrub typhus. J Neurol Neurosurg Psychiatry 2015;86:761–6. 10.1136/jnnp-2014-308722
3. Karanth SS, Gupta A, Prabhu M. Pure cerebellitis due to scrub typhus: a unique case report. Trop Doct 2013;43:41–2. 10.1177/0049475513480775
4. Silpapojakul K, Ukkachoke C, Krisanapan S, et al.. Rickettsial meningitis and encephalitis. Arch Intern Med 1991;151:1753–7. 10.1001/archinte.1991.00400090051010
5. Bhoil R, Kumar S, Sood RG, et al.. Cerebellitis as an atypical manifestation of scrub typhus. Neurology 2016;86:2113–4. 10.1212/WNL.0000000000002717
6. Mahajan SK, Sharma S, Kaushik M, et al.. Scrub typhus presenting as acute cerebellitis. J Assoc Physicians India 2016;64:69–70.

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Expression levels of Interferon Stimulated Genes (ISGs) in the blood of patients with Acute Encephalitis Syndrome: comparison between Japanese Encephalitis virus positive and negative cases.

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Acute Encephalitis Syndrome (AES) is a major cause of acute central nervous system infection, affecting over 50,000 people, especially children, across south-eastern Asia annually. Japanese Encephalitis (JE) is the most common identified cause of AES. Despite JE causing mortality in up to 10% and significant disability in up to 50% of those infected There is no treatment and limited information on pathogenesis of JE. Examining the host response to JE infection may improve understanding about JE pathogenesis and identify potential candidate pathways or mediators for future therapeutic study.

Microarray analysis undertaken in the group prior to this project showed that transcript levels of Interferon stimulated genes (ISGs) were higher in children with JE compared to children clinically identified to have Acute Encephalitis Syndrome , but no pathogen was recovered. In this study, RT-PCR was carried out looking at four key Interferon stimulated genes; OAS1, Mx1, HERC5 and SIGLEC1 in samples from the same hospital as the microarray analysis collected one year on and samples from a second hospital from a different region in Nepal. In the first population OAS1, Mx1 and SIGLEC1 had significantly higher transcript levels in JE positive cases. The second population showed the same trend but this time wasn't statistically significant. When pooled SIGLEC1 was shown to be significantly more abundant , OAS1 and Mx1 showing non significant increases in expression. This work confirms ISGs are involved in JE infection and highlights SIGLEC1 as a potential candidate for future study.

while diagnosis is delayed up to ten days, until the development anti-JE antibodies[2]. Elucidating the host response to JEV infection can identify potential diagnostic markers and therapeutic targets and studying gene expression offers an opportunity to identify these crucial mediators. Increasingly microarray has been used to do this across a large number of genes in infections as well in cancer and autoimmune disorders. A microarray analysis carried out prior to this study identified that genes classified as interferon stimulated had higher transcript abundances in patients with acute encephalitis syndrome (AES) who were JE positive compared to JE negative. **Type I interferon** is well known to be important in the **innate antiviral response** by creating an antiviral state through the expression of certain interferon stimulated genes (Fig.2). A nature review proposed four potent antiviral effector pathways, this involved the OAS RNase L pathway, the ISG15 pathway, Mx1 GTPases pathway and PKR[3]. Other genes and pathways are likely to be equally important.

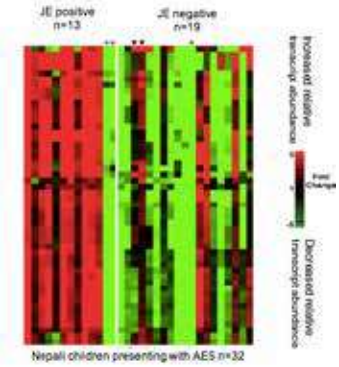

Figure 1 (above): Microarray data showing the relative up-regulation of ISGs shown by the preponderance of red (increased transcript abundance) in the JE positive group compared to the JE negative group. 2021 genes were included. +: Sample found to be JE negative on further testing. *Positive for Dengue Virus by PRNT.

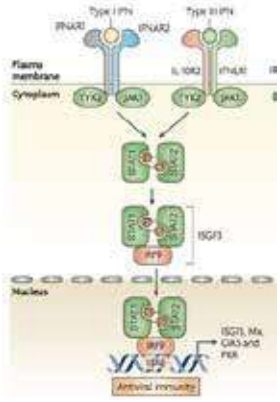

Figure 2 (left): Diagram showing interferon signalling resulting in the expression of Interferon stimulated genes. Type I interferon binds with its cell surface receptor, which causes phosphorylation of tyrosine kinases JAK1 and TYK2 and recruitment of STATs. These associate with IRF9 to form ISGF3, a complex that translocates to the nucleus to induce ISGs. From: Sadler and Williams 2008[3].

The aim of the study was to use RT-PCR on selected ISGs identified in the microarray to examine their relative transcript levels in JE positive and negative patients with AES. This was done on samples from the same hospital one year on and a different hospital, to examine consistency of the response. Three genes involved in the antiviral pathways highlighted in the Nature review were studied, OAS1, Mx1 and HERC5 (a key cofactor in the ISG15 pathway). The fourth was SIGLEC1 (sialoadhesin, CD169), one of the most strongly up-regulated genes according to the microarray.

Methods

Whole blood samples were collected in PAXgene tubes from children presenting to 2 Nepalese hospitals with Acute Encephalitis Syndrome (fever with acute impairment of consciousness and/or seizures). Samples were stored at -80°C and transported to the UK. JE status, determined by IgM capture ELISA was recorded for the participants.

Figure 3: The hospitals were the B. P. Koirala Institute (BPK), Dharan, eastern Nepal and Kanti Children's hospital (KCH), Kathmandu.

RNA isolation and purification was carried out using the PAXgene blood RNA kit (QIAGEN) according to the manufacturers instructions, including a DNA digestion step. RNA quantity and purity was assessed with the NanoDrop 1000 Spectrophotometer (Thermo Fisher Scientific).

A two step real time RT-PCR procedure was used. First, cDNA was synthesised using the RETROscript kit (Applied Biosystems) in a 20µl reaction containing 2µg total RNA. Quantitative PCR was carried out using an Opticon thermocycling machine. 20µl reactions were set up, in duplicate, containing 100ng cDNA, TaqMan gene expression master mix (Applied Biosystems) and primer. Genes studied were OAS1, Mx1, HERC5 and SIGLEC1. DAD1 was used as an internal control. Each primer was the recommended TaqMan gene expression assay purchased from Applied Biosystems. A consistent threshold level of fluorescence was set and the cycles to reach this, C(t), recorded.

Statistical differences between JE positive and negative patients were assessed with the Mann-Whitney U-test. Fold change in gene expression was calculated using the equation $2^{-\Delta\Delta C(t)}$ where $\Delta\Delta C(t)$=(gene of interest- control in JE positive samples)-(gene of interest-control in JE negative)[4].

Results

After sample collection RNA extraction and reverse transcription real time PCR was successfully carried out on 12 JE positive and 11 JE negative samples from BPK, eastern Nepal. Figure 4 shows that there was significantly greater transcript abundance of the genes OAS1, Mx1 and SIGLEC1 in JE positive samples compared to JE negative. There was visibly greater levels of HERC5 but this did not reach statistical significance.

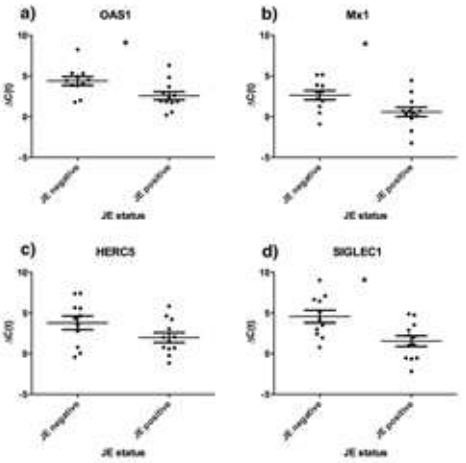

Figure 4: Scatter plot showing the ΔC(t) (difference in C(t) between gene of interest and housekeeping gene) for JE positive and negative samples from BPK . C(t) is the cycle number taken to reach threshold level of fluorescence. As housekeeping gene was more abundant a lower ΔC(t) represents higher transcript level and gene expression. Each point represents one sample (mean of two duplicate C(t) readings). Bars represent mean and standard error of the mean.
* p<0.05. OAS1=2'-5'-Oligoadenylate synthetase 1; SIGLEC= Sialic acid binding Ig-like lectin 1; Mx1=Interferon-induced GTP-binding protein Mx1; HERC5= Probable E3 ubiquitin-protein ligase HERC5.

To see if these results were consistent in samples collected from a different hospital the procedure was repeated on samples collected from KCH, Kathmandu. Figure 5 shows that there was no difference in transcript levels for OAS1 and Mx1. There was a visible difference for SIGLEC1 but this did not reach statistical significance. HERC5 could not be tested in this group for practical reasons.

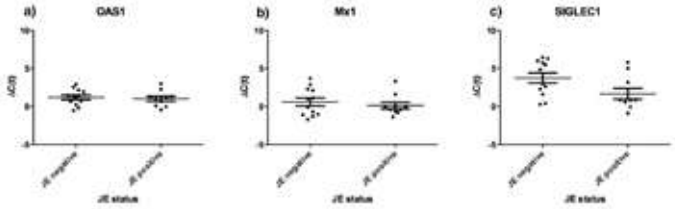

Figure 5: Scatter plots showing the ΔC(t) for JE positive and negative samples from KCH. Set up in same manner as figure 4. none of the genes showed significant difference. Both plots generated on GraphPad Prism v5.

To give a numerical approximation of differences between the groups the fold change of gene expression was calculated using the $2^{-\Delta\Delta Ct}$ equation with results shown in Table 1. This table also shows the fold change and P values when the results from both populations were pooled. A nearly 6 fold change overall was seen for SIGLEC1, whilst for OAS1 and Mx1 the change was more modest and did not reach statistical significance.

Population	Gene	Fold change	P value
BPK	OAS1	3.51	0.021
	Mx1	4.16	0.023
	SIGLEC1	8.13	0.015
	HERC5	3.48	0.13
KCH	OAS1	1.14	0.62
	Mx1	1.37	0.87
	SIGLEC1	4.24	0.070
Collated	OAS1	1.82	0.16
	Mx1	2.29	0.077
	SIGLEC1	5.82	0.0013

Table 1: Table presenting fold change for each gene and p values for difference between JE positive and JE negative samples.

Conclusions

• This work supports the involvement of Interferon pathways and their mediators (ISGs) during Japanese Encephalitis, especially for the gene SIGLEC1 which was strongly up-regulated across two populations.

• Given ISG's are likely to be involved in many viral infections, the results also suggest that among AES JE negative patients (where no pathogen is identified) the low abundance of ISG's may reflect the fact these patients may not have viral cause for their Acute Encephalitis Syndrome.

•The results for OAS1 and Mx1 were not statistically confirmed in both populations. The difference could have arisen from differences in the reliability of JE testing results and differences in the reverse transcription efficiencies in these two groups.

•This work provides descriptive data. Future work could attempt to discern the function of SIGLEC1 in JEV infection through blocking it or stimulating expression and seeing results on infectivity which showed recent interesting results in in HIV[5]. OAS1 and Mx1 could be investigated for their effectiveness against JEV in vitro.

References

1.Solomon T, Dung NM, Kneen R, Gainsborough M, Vaughn DW, Khanh VT. Japanese encephalitis. J Neurol Neurosug Psychiatry. 2000;68:405-415.
2.Rayamajhi A, Ansari I, Ledger E, Bista KP, Impoinvil D E, Nightingale S et al. Clinical and prognostic features among children with acute encephalitis syndrome in Nepal; a retrospective study. BMC Infectious Diseases. 2011;11:294-305.
3.Sadler AJ, Williams BRG. Interferon-inducible antiviral effectors. Nat Rev Immunol. 2008;8:559-568.
4.Livak K J, Schmittittgen T D. Analysis of Relative Gene Expression Data Using Real-Time Quantitative PCR and the $2^{-\Delta\Delta C(t)}$ Method. Methods. 2001;25:402-8.
5.Rempel H, Calosing C, Sun B, Pulliam L.. Sialoadhesin Expressed on IFN-Induced Monocytes Binds HIV-1 and Enhances Infectivity. PloS ONE. 2008;3:e1967.

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Dr Kevin Cham, Dr Derek Cocker, Dr Gosia Wnek.

Dr Marion Le Marechal

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Perspectives on diagnosis and management of encephalitis: a national survey of adult infectious diseases physicians

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BACKGROUND

Encephalitis is widely recognized as a challenging condition to recognize, diagnose and treat. Physicians facing encephalitis need to be able to recognize a wide array of clinical entities. At the onset of illness in most patients, and for the duration of illness in some, it is unclear which category of disease is present.

As is evident, the care of patients with encephalitis is difficult and involves multiple disciplines, including neurologists and infectious disease (ID) physicians. Within neurology, training often occurs as part of a neuro-ID fellowship, although such a pathway does not have formal accreditation status in the U.S. As a result, no formal curriculum exists for training in neuro-ID though a consensus neuro-ID curriculum was developed via a survey evaluated through a modified Delphi method.

OBJECTIVE

To describe the perspectives of ID physicians toward encephalitis, using a cross-sectional questionnaire survey

METHODS

Emerging Infection Network (EIN): The Infectious Diseases Society of America's EIN is a provider-based network developed by the CDC to assist public health authorities with surveillance of emerging infectious diseases and related phenomena. It is a flexible sentinel network composed of approximately 2400 infectious disease specialists primarily from North America, including pediatric infectious disease physicians, and members of the public health community.

Eligible participants: Physician members of the EIN with adult ID practices in the United States.

Survey: The survey was developed by a multidisciplinary team (composed of neurologists and ID physicians), based on the literature. The 11-item questionnaire pilot tested by two additonal ID physicians (A.T. and K.M.), to assess for length and clarity. It was divided into three sections: 1) frequency of encephalitis diagnosis and management; 2) use of new tools for the diagnosis of encephalitis; 3) resources used for encephalitis management.

RESULTS

Practice	Adult infectious diseases		480 (100%)
Region	New England		33 (7%)
	Mid Atlantic		70 (15%)
	Central		169 (35%)
	South Atlantic		98 (20%)
	Mountain		24 (5%)
	Pacific		80 (17%)
	Canada		6 (1%)
Years' experience since ID fellowship		<5 years	67 (14%)
		5-14	155 (32%)
		15-24	90 (19%)
		≥25	168 (35%)
Primary hospital type	Community		134 (28%)
	Non-university teaching		114 (24%)
	University		174 (36%)
	VA hospital or DOD		32 (7%)
	City/county		22 (5%)

Table 1. Characteristics of respondents

	University/non-university teaching hospitals		Other setting (community, VA hospital or DOD, city/county)		p-value
	N = 221	%	N = 153	%	
Frequency in which respondents are involved in the care of autoimmune encephalitis					0.012
Frequently	16	7.2	4	2.6	
Occasionally	65	29.4	36	23.5	
Rarely	123	55.7	90	58.8	
Never	14	6.3	22	14.4	
Who is primarly responsible for a diagnostic evaluation of possible auto-immune encephalitis at your institution					0.487
Only ID physician	4	1.8	1	0.7	
Only neurologist	125	56.6	79	51.6	
Combination of ID and neurologist	55	24.9	47	30.7	
Respondents are uncomfortable in					
Recognizing an AE	81	36.7	67	43.8	0.213
Diagnosing an AE	122	55.2	90	58.8	0.540
Treating an AE	195	88.2	131	85.6	0.791
The experience with advanced NGS tools on the CSF					0.385
Not aware of this test	18	8.1	18	11.8	
Never used this test	107	48.4	75	49.0	
Sent these tests and found them useful	81	36.7	46	30.1	
Sent these tests, but have never found them useful	15	6.8	14	9.2	

Table 2. Answers depending on the institutional setting

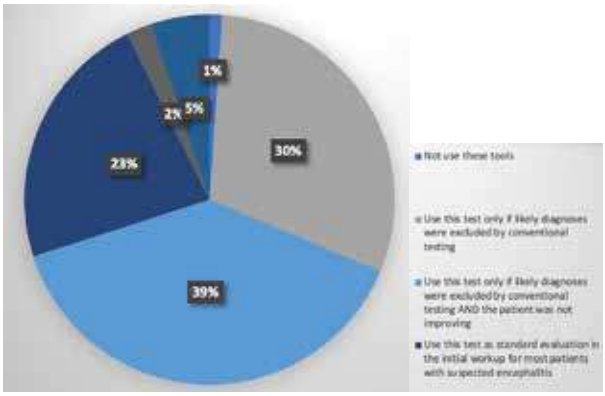

Figure 1. Use of next-generation sequencing that respondents would have if this tool was available at their institution

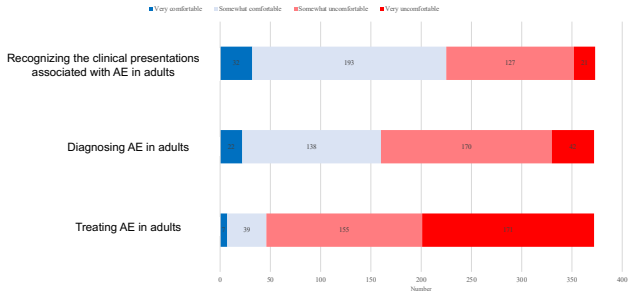

Figure 2. Confidence of respondents in recognizing, diagnosing and treating autoimmune encephalitis

DISCUSSION

1. **ID physicians play an important role in the diagnosis and management of all-cause encephalitis**
2. **Despite exposure to AE, few ID physicians are comfortable in recognizing, diagnosing and treating AE**
3. **There is a marked heterogeneity in the use of advanced NGS in encephalitis**
4. **Training in AE for ID should include a collaborative training with neurologists and rheumatologists on mechanisms and clinical presentations of AE**

There is a need for a formal update of 2008 guidelines on the management of encephalitis

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Development and validation of a clinical prediction score for the risk of autoimmune encephalitis

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BACKGROUND

Encephalitis represents a challenging medical condition to diagnose and treat. Its global incidence is estimated between 3.5-10 per 100, 000 inhabitants per year. The cost of hospitalization in the United States in 2010 for encephalitis was estimated at 2 billion dollars.
However, despite new tools to help in recognizing auto-immune encephalitis, up to 50% of encephalitis cases remain without an identified etiology.

Prompt treatment of encephalitis can dramatically impact morbidity and mortality. Accumulating evidence and recent guidelines point to the beneficial effects of early treatment. Indeed, the benefit of immune treatments in autoimmune encephalitis may be blunted in cases with delays in diagnosis and therapy,[19] highlighting the importance of the need for a timely diagnosis.

OBJECTIVE

To develop and validate a risk scoring system that uses clinical and laboratory data present on admission to estimate the risk of autoimmune encephalitis.

METHODS

Study population: A retrospective cohort study of patients with a diagnosis of encephalitis from February 2005 to December 2019 at two tertiary hospital systems in Houston, Texas. Cases that met the criteria for probable or confirmed encephalitis according to IEC were retained in the study.

Statistical analysis method: The outcome of the prediction model was the probability of definite autoimmune encephalitis as defined earlier.
The entire development dataset was used for the construction of the risk model. Clinically relevant and statistically significant (P value <0.05) features were explored further in a bivariate (unadjusted) logistic regression model. The results from the logistic regression were used to determine which variables to include in the final risk score. Independently associated variables with the outcome were used to create a risk score that classified patients as low, intermediate, or high risk of having autoimmune encephalitis. To evaluate the model performance, we assessed model discrimination with an area under the receiver operating characteristics curve (AUC ROC).

External validation : A prospective encephalitis cohort from Johns Hopkins Hospital

RESULTS

Clinical characteristics	Adjusted OR (95% CI)	P value
Age less than 60 years.	4.34 (0.56-33.2)	0.157
Charlson Comorbidity Index <2	6.62 (1.05-41.4)	0.043
Subacute (6-30 days) to chronic (>30 days) onset	22.36 (2.05-243.7)	0.011
Absence of fever	0.23 (0.03-1.44)	0.119
Seizures	7.49 (0.99-56.5)	0.051
Psychiatric and/or memory complaints	203.0 (7.57-5445)	0.002
Movement disorders	7.22 (0.85-61.1)	0.069
Absence of robust inflammation in CSF (WBC <50/ul and Protein <50 mg/dl)	0.05 (0.005-0.50)	0.011

Table 1. Prognostic Factors of Autoimmune Encephalitis by Logistic Regression

Score result	Viral encephalitis		Autoimmune encephalitis	
Development cohort				
	N =88	%	N =36	%
0	18	20.5	0	0.0
1	33	37.5	0	0.0
2	23	26.1	9	25.0
3	14	15.9	26	72.2
4	0	0.0	1	2.8
Validation cohort				
	N =64	%	N =51	%
0	17	26.6	0	0.0
1	31	48.4	1	2.0
2	11	17.2	16	31.2
3	4	6.3	20	39.2
4	1	1.6	14	27.5

Table 2. Distribution of Patients with Autoimmune and Viral Encephalitis According to the Number of Prognostic Factors Associated with Autoimmune Encephalitis Present

Figure 1: ROC Curve of the Risk Score for Autoimmune Encephalitis of the Development Cohort

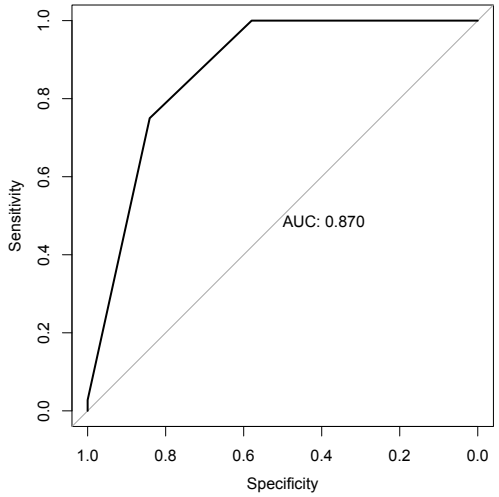
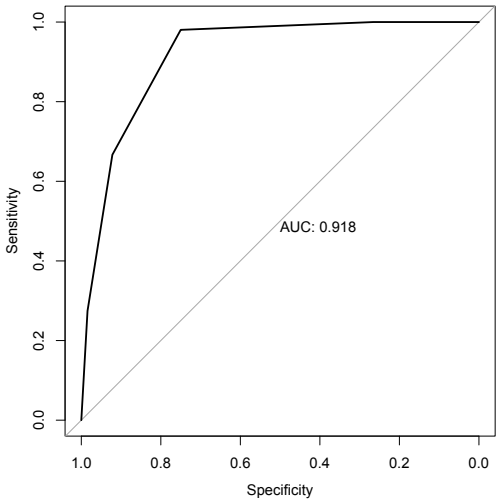
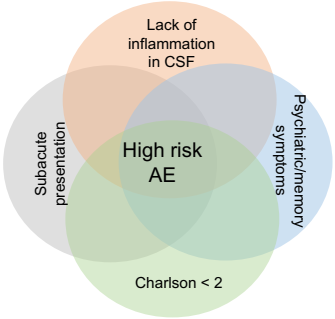


Figure 2: ROC Curve of the Risk Score for Autoimmune Encephalitis of the Validation Cohort



DISCUSSION



1. **The panel testing for neural autoantibodies should also be performed in first-line if the prediction score is high (2 or higher)**
2. **A patient with a high prediction score should be considered earlier for immunotherapy**
3. **The prediction score should be used to decrease burden of autoimmune encephalitis**

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Description of a cohort of seronegative encephalitis patients in a US teaching hospital

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BACKGROUND

Acute encephalitis is a neurological condition characterized by the rapid onset of brain inflammation. Autoimmune encephalitis (AE) syndromes have been increasingly described. Although autoimmune and infectious encephalitis share some aspects of the initial clinical presentation such as neurological and psychiatric clinical symptoms, patients presenting with AE will less frequently have fever or CSF pleocytosis.

The diagnosis of AE has been facilitated by the development of assays to identify and quantify neuronal autoantibodies in the serum and CSF. Comprehensive consensus clinical criteria, as well as a diagnostic and acute treatment approach for AE, have been proposed for such. Importantly, a large subset of these patients may not have detectable antineuronal autoantibodies in the serum or CSF. In these patients, the diagnosis relies on clinical assessment along with CSF, EEG, and imaging characterization. However, this subset of AE might have its own clinical and paraclinical pattern.

OBJECTIVE

To describe the initial presentation of patients with a diagnosis of seronegative auto-immune encephalitis, considering clinical, biological, imaging, and EEG data, in order to assist clinicians in early recognition of this syndrome.

METHODS

Study population: A retrospective longitudinal cohort study in a single tertiary center in the United States (Johns Hopkins Hospital, Baltimore, Maryland), consisting of patients with a definite, possible or probable auto-immune encephalitis according to Graus *et al.*'s criteria.

	Clinical						Biological findings			Imaging
	Rapid onset	Memory symptoms	Psychiatric symptoms	AMS	New CNS findings	Seizures	Pleiocytosis	OCB	Index IgG	MRI signs
Probable encephalitis	X	X	X				X	X	X	X
Possible encephalitis	X	X	X	X	X	X	X			X

Table 1. Classification of possible and probable encephalitis according to Graus et al.

Data collection: We collected data concerning: 1) patient's characteristics; 2) clinical data; 3) biological data; 4) imaging data
CSF was also sent to Mayo Clinic to screen for neuronal autoantibodies as part of routine care. All EEG performed within our center were reviewed independently by K.H. and M.C.
MRI data were blindly reviewed by LS and LL and examined for signs of encephalitis

RESULTS

	N =	%
Female	32	57,1
Age (mean +/- sd)	49.3 (+/- 20.2)	
Charlson comorbidity index	0 [0-2]	
Type of encephalitis		
Probable	49	87,5
Possible	7	12,5
Temporal evolution to nadir		
< 24h	3	5,4
24h-1 week	12	21,4
1-3 weeks	26	46,4
> 3 weeks	15	26,8
Clinical symptoms		
Memory loss	32	57,1
Altered mental status	30	53,6
New onset of seizures	26	46,4
Psychiatric symptoms	26	46,4

Table 2. Characteristics of the patients and main clinical symptoms

	N =	% (/33)
Background frequency range		
Alpha	21	63,6
Theta	9	27,3
Delta	5	15,2
PBR	27	81,8
Focal slowing	7	21,2
Right fronto-temporal	4	
Left fronto-temporal	1	
Right temporal	1	
Asynchronous at times	1	
Periodic and rhythmic pattern	10	30,3
LDP	2	
LRDA	2	
GPD+TW	1	
GRDA	2	
Combination	3	
Epileptiform activity		
Sporadic epileptiform discharge	6	18,2
Electrographic seizure	1	3,0
Electroclinical seizure	1	3,0
BIRDS	1	3,0
EEG reactivity	1	3,0

Table 4. Details of EEG abnormalities

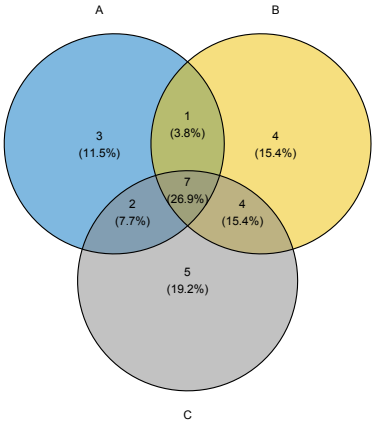

Figure 2. Number and overlaps of abnormal exams (A = MRI, B = CSF, C = EEG)

	Right hemisphere	Left hemisphere
Localization		
Temporal lobe, mesial, including hippocampus and amygdala	9	10
Temporal lobe, lateral	3	4
Insula	3	2
Frontal lobe	6	7
Parietal lobe	3	3
Occipital lobe	0	3
Hippocampus	4	5
Putamen	4	4
Globus pallidus	4	3
Caudate	3	4
Thalamus	4	4
Abnormalities visible on		
FLAIR	20	
T2	18	
T1	7	
Diffusion restriction	10	
Contrast enhancement	9	
Hemorrhage	0	
Mass effect	5	
Normal or non specific white matter changes	27	

Table 3. Details of MRI abnormalities

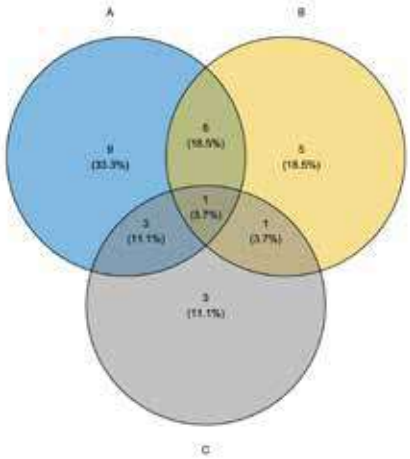

Figure 1. Numbers and overlap of psychiatric symptoms (A = Behavior, B = Mood disorder, C = Hallucinations)

DISCUSSION

1. **Few patients have abnormal EEG, MRI and CSF. A complete and multidisciplinary evaluation is necessary**
2. **Half of patients present with psychiatric symptoms.**
3. **A specific reviewing of imaging and EEG increases sensitivity for encephalitis diagnosis**

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Dr Matteo Gastaldi is a neurologist specialised in the treatment of antibody mediated disorders of the nervous system including Myasthenia Gravis, MOGAD and NMOSD and Autoimmune Encephalitis. He trained in Neurology and obtained a PhD from the University of Pavia. During his PhD he attended as research fellow the Neuroimmunology Laboratory at NDCN in Oxford for a year supervised by Angela Vincent. Later, he spent three months as a research fellow in the neuroimmunology laboratory in IDIBAPS in Barcelona under the supervision of Francesc Graus and Josep Dalmau. During these experiences Matteo acquired skills in the implementation of immunological assays for the detection of neuroglial antibodies. Since 2021 he is the Head of the Neuroimmunology Research Unit in Pavia and the Co-head of the Neuroimmunology Diagnostic Laboratory. He is also involved in patient care and performs once a week a neuroimmunology clinic dedicated to patients with antibody mediated disorders of the nervous system.

Laboratory diagnostic strategies for the identification of antibodies against neuronal synaptic antigens in autoimmune encephalitis

Masciocchi S, Scaranzin S, Morandi C, Zardini E, Businaro P, Marchioni E, Bergamaschi R, Simone A, Ferraro D, Volonghi I, Pilotto A, Padovani A, Farina A, Banfi P, Avolio C, Gagliano A, Foiadelli T, Di Sabatino E, Di Filippo M, Giacomini T, Mancardi M, Massa F, Franciotta D, **Gastaldi M*.**

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Background and aims

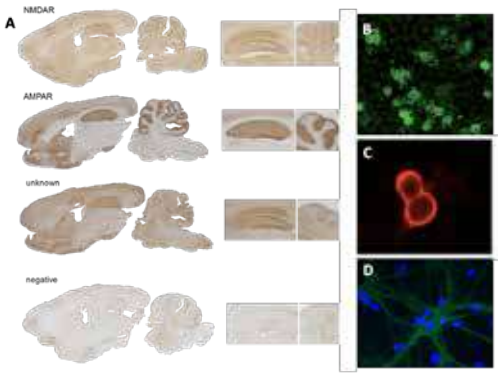
The detection of antibodies against neuronal synaptic proteins (NSAbs) is a crucial step in autoimmune encephalitis (AE) diagnosis.[1] Most laboratories rely on commercial cell based assays (C-CBAs) including the most common NSAbs targets, but It has been suggested that in-house (ih) assays might have a better performance.[2,3] The tissue based assay on lightly fixed rat brain (TBA) offer the advantage to identify many NAbs with one test, even those directed against antigens that are still uncharacterized (unc-NAbs). However, the relevance of unc-NAbs in routine clinical practice is still uncertain.

We aimed to compare the performance of commercial and in-house laboratory assays for NSAbs detection and to define the clinical relevance of unc-Nabs

Methods

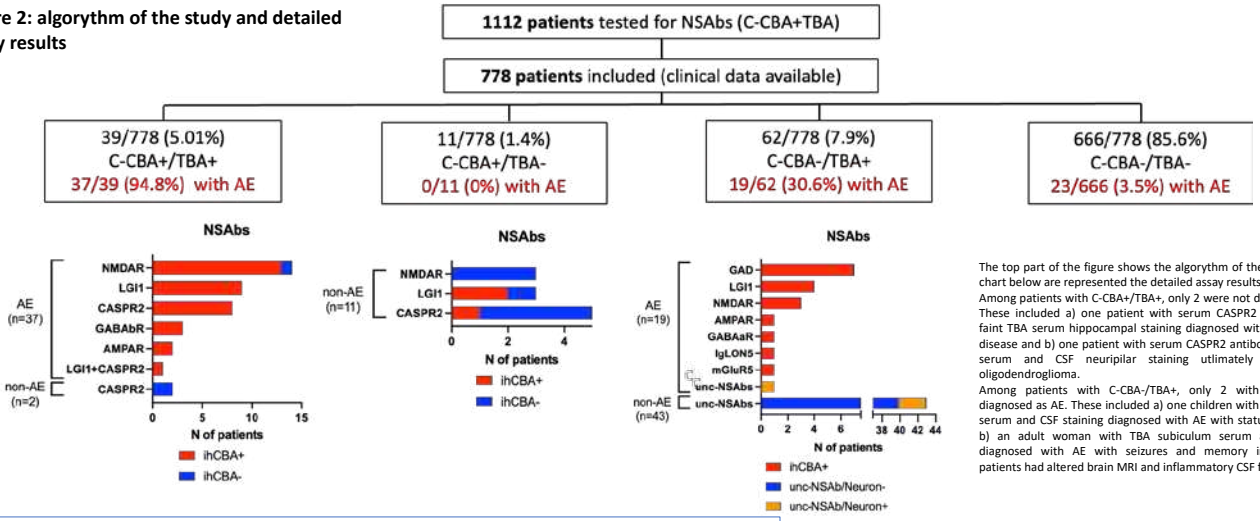
As part of our routine laboratory diagnostic we screened 1112 samples sent for suspect AE for NSAbs using C-CBA [Mosaic 1 panel, Euroimmun AG, NMDAR, LGI1, CASPR2, AMPAR 1/2, GABABR] and TBA.[3] Samples were considered positive on TBA when providing a neuropilar staining suggestive of NSAbs[Fig.1]. Unc-NSAbs were additionally tested using in-house CBAs (according to the staining pattern on TBA) and live rat neuronal cultures. We only included patients with sufficient clinical information. AE diagnosis was assessed according to Graus criteria[1]

Figure 1: assays used in the study



The figure shows examples of a TBA (A) with different staining patterns for defined NSAbs and unc-NSAbs. The other assays used in the study include C-CBA (B), ih-CBA (C) and live neuronal cultures (D)

Figure 2: algorythm of the study and detailed assay results



The top part of the figure shows the algorythm of the study. In the bar chart below are represented the detailed assay results for each group.

Among patients with C-CBA+/TBA+, only 2 were not diagnosed with AE. These included a) one patient with serum CASPR2 antibodies and a faint TBA serum hippocampal staining diagnosed with cerebrovascular disease and b) one patient with serum CASPR2 antibodies and a strong serum and CSF neuripilar staining utlimately diagnosed with oligodendroglioma.

Among patients with C-CBA-/TBA+, only 2 with unc-NAbs were diagnosed as AE. These included a) one children with TBA basal ganglia serum and CSF staining diagnosed with AE with status epilepticus and b) an adult woman with TBA subiculum serum and CSF staining diagnosed with AE with seizures and memory impairment. Both patients had altered brain MRI and inflammatory CSF findings.

Patients and assay results

We included 778/1112 patients with sufficient clinical information to assess the final diagnosis (Fig.2). A total number of 79/778 (10.2%) had AE (17 NMDAR AE, 55 definite limbic AE, 3 NSAb+ definite AE and 4 probable NSAb- AE). Positive NSAbs by any assay were detected in 105/778 patients (13.5%)(fig.2). C-CBA+/TBA+ patients were almost always diagnosed with AE, and all positive results in AE patients were confirmed with ih-CBA except for one. Only 2 patients without AE had serum CASPR2 antibodies. Conversely, patients with C-CBA+/TBA- were never diagnosed with AE, and only 3/11 positives were confirmed with ih-CBA. Patients with C-CBA-/TBA+ were diagnosed with AE only when positive for specific NSAbs detected with ih-CBA or in one patient with positive neurons. The remaining 43 patients had alternative diagnosis, and 3 resulted positive on neurons.

Table 1: analytic performances

Assay	Sensitivity %(CI)	Specificity %(CI)	Accuracy %(CI)	Positive Likelihood Ratio (CI)	Negative Likelihood Ratio (CI)
C-CBA	46.3 (35.0-57.8)	98.1 (96.8-99.0)	92.8 (90.8-94.5)	24.8 (13.8-44.7)	0.5 (0.5-0.7)
TBA	71.8 (60.1-80.8)	93.7 (91.6-95.4)	91.4 (89.2-93.3)	11.3 (8.2-15.5)	0.3 (0.2-0.4)
ih-CBA	94.8 (85.6-98.9)	94.6 (84.9-98.9)	94.7 (88.8-98.0)	17.4 (5.8-52.3)	0.1 (0.0-0.2)
C-CBA+TBA	61.7 (48.2-73.9)	99.7 (98.9-99.9)	96.5 (94.8-97.7)	198.9 (49.1-804.9)	0.4 (0.3-0.5)
ih-CBA+TBA	100 (93.4-100)	100 (63.1-100)	100 (94.2-100)	-	-

Serum and CSF testing

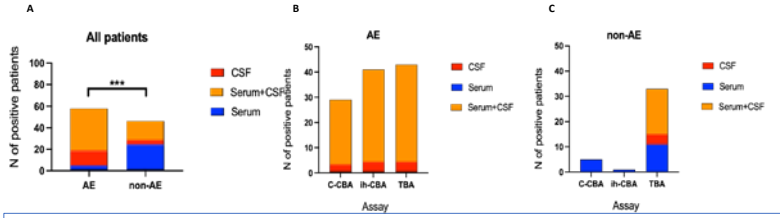
Paired serum and CSF were available for 442/778 patients (56.8%), while 312 had serum (40.1%) and 24 CSF only (3.1%). Considering all patients, a positive result in serum only was more frequent in patients without AE vs those with AE (36.4% vs 7.4%p<0.001)(fig.3). Considering patients with paired samples, positive results in serum only were found exclusively in non-AE patients, more frequently using TBA.

Assays analytic performances

The TBA showed a higher Negative Likelyhood Ratio, suggesting a role as the ideal screening test (Table 1). Importantly, the combination of ih-CBA+TBA provided a higher accuracy compared to other assays.

Ih-CBA identified NSAbs in 18 C-CBA negative patients, 10 for antigens not included in the C-CBA, and 8 for antigens included in the panel.

Figure 3: NSAbs testing in serum and CSF



The figure shows NAbs results in serum and CSF for all patients (A) and only for those with paired serum+CSF samples (B,C).

TBA quantitative and qualitative evaluation

Among 101 TBA+ patients only 56 had CBA-confirmed NSAbs, and 57 had AE. We analysed quantitative (positive samples were scored 1-4 according to intensitiy) and qualitative evalutation (anatomical distribution) of the staining patterns. we found that CSF staining, staining score >2 and staining in HC or HC+cerebellum, but not cerellum alone were associated with the detection of CBA-confirmed NSAbs and with AE diagnosis (p<0.001)

Discussion and conclusions

Commercial panels for AE show limitations in NSAbs detection, and are exposed to both false positives and false negatives. The latter can be partly explained by the identification with the TBA of antigens not included in the C-CBA, some of which (such as GAD) can be identified by other commercial kits. However, a lack of sensitivity was detected also for NSAbs included in the C-CBA. The best laboratory strategy for NSAbs detection should include TBA as screening followed by C-CBA, and eventually ih-CBAs, testing preferably paired serum and CSF. Quantitative/qualitative TBA staining evaluation can help to predict the relevance of a positive result. The detection of unc-NSAbs is rarely associated with a diagnosis of AE. In this setting, additional data are needed to define the role of neuronal cultures.

Bibliography:

[1] Graus F et al. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol. 2016 Apr;15(4):391-404.

[2] Ruiz-García R et al. Limitations of a Commercial Assay as Diagnostic Test of Autoimmune Encephalitis. Front Immunol. 2021 Jun 29;12:691536.

[3] Gastaldi M et al. Subgroup comparison according to clinical phenotype and serostatus in autoimmune encephalitis: a multicenter retrospective study. Eur J Neurol. 2020 Apr;27(4):633-643.

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AUTOIMMUNE ENCEPHALOPATHY FOLLOWING COVID 19 INFECTION; CASE REPORT

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Abstract

A variety of neurological involvement can be seen both during and following Covid-19 infection. In this study we are presenting a severe case of possible autoimmune encephalopathy occurring early after infection followed by a prolonged long-covid syndrome. The aim here is to raise awareness on the toll of Covid-19 on the nervous system with both acute and chronic involvements.

Introduction

Post-Covid Syndrome, and colloquially as Long-Covid, has been defined by WHO in April 2022 by WHO with Delphi consensus report as; history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of Covid-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, and cognitive dysfunction.[1]
The underlying mechanisms are still largely unknown, but hypotheses include inflammatory or autoimmune processes, organ damage and scarring, hypercoagulability, endothelial damage, or even persistent viral protein in the body. Evidence suggests that seeding and persistence of SARS-CoV-2 in different organs, reactivation, and response to unrelated viruses such as EBV.[2] Females were twice as likely as males to experience long covid with one in eight (12.7%) patients with Covid-19 likely to experience long term symptoms according to a recent study.[3]
WHO regional director urges all countries in the WHO European region to recognise long covid as a serious health issue that requirses a drastic response to prevent further worsening in the condition of those already affected.[4] Neurological manifestations comprise one of the many facets of 'Long Covid' syndrome. We are reporting here a Post-Covid possible autoimmune encephalopathy experienced by one of our authors (MO).

Case Report

➢A 39-year-old female presented in March 2021 with a brain fog complaint 21 days after her second Covid-19 infection. She initially experienced loss of smell and taste as well as headache. The patient's complaints started during her 8-year-old son's hospitalization in the ICU with a preliminary diagnosis of MIS-A secondary to Covid infection. Her medical history was unremarkable apart a first covid infection in February 2020 from which she recovered with respiratory infection symptoms. She had received two doses of inactivated CoronaVac vaccine and was tested positive for SARS-CoV PCR a month later.
➢The patient was examined on the 21st day following Covid-19, when her PCR tested negative. SARS-IgG was 2120 AU/ml.
➢Neurological exam: Confusion, slowed speech, decreased perception and concentration with no motor or sensory signs.
➢Brain MRI: Normal; EEG: 4-5 Hz slow wave activity in the left fronto-temporal areas.
➢Lumbar puncture: Slight elevation of albumin levels, no pleocytosis (See Table).
➢While waiting for the cultures and serological tests she was started with antiviral therapy (acyclovir 30 mg/kg/day), high dose intravenous steroids (1000 mg/day methyl prednisolone).
➢Neurological complaints progressed after the third day of hospitalization. Headache and periods of drowsiness were increasing in severity. The patient started to experience left hearing loss with tinnitus as well as generalized feeling of severe weakness and neuropathic pain in the extremities despite normal motor examination. Losses in recent and immediate memory were noted as well a near vision impairment. Myoclonic seizures up to 6-8 times a day were noted.
➢Repeated MRI: Normal; EEG: Rhythmic left fronto-parietal slow wave activity accompanied by a disruption of the basal activity (EEG Images).
➢Hearing tests and EMG were normal, laboratory examinations were negative for inflammatory markers. Fundoscopic examination was normal but pupillary accommodation was incomplete with 70% pupil dilatation.
➢On the 8th day of hospitalization, the patient's neurological status began to improve. There was an improvement in alertness, awareness, balance and recent memory.
➢On the 14th day of hospitalization, the patient was discharged on: Levetiracetam 4000 mg/day, duloxetine 60 mg/day, acetylsalicylic acid 100 mg/day, enoksaparin 0,4 ml/day. EEG showed a basal 9-10 Hz alpha activity and left fronto-temporal focal spike and slow activity.
➢Myoclonic seizure frequency increased in the second month after discharge. The patient was started on a valproic acid 1000 mg/day; than following two generalized seizures at night a third antiepileptic (lacosamide 400 mg/day) was added.
➢The patient is now at the 19th month after discharge. EEG is normal under antiepileptics treatment and the patient is without seizures for nearly 6 months.
➢ Eye site improved 90%. Hearing is normal. There is slowly reduction in neuropathic pain with duloxetine 60 mg/day.
➢Her functional capacity is low compared to the pre-disease state, she still has discomfort in the legs and shortness of breath with one flight of stairs. She is experiencing a feeling of slowing down and stagnation in her whole body and mind when under physical and mental strain.

Laboratory Test Results

CSF Tests

Cell Count	Clear/Negative	-
Glucose	51,5 mg/dL	40-70
Protein	27,7 mg/dL	15- 45
Albumin	**40,9 mg/dL**	10- 30
Chlor	122,4 mg/dL	118- 132
LDH	6 U/L	10- 40

Meningitis Viral Panel PCR	Negative
Oligoclonal Band	Negative
IgG,CSF	34,4 mg/L
IgG, Plasma	12,34 g/L
IgG BOS/ Plasma	2,78
Albumin CSF	409
Albumin Plasma	41,4 mg/L
Albumin CSF/Plasma	9,8 g/L

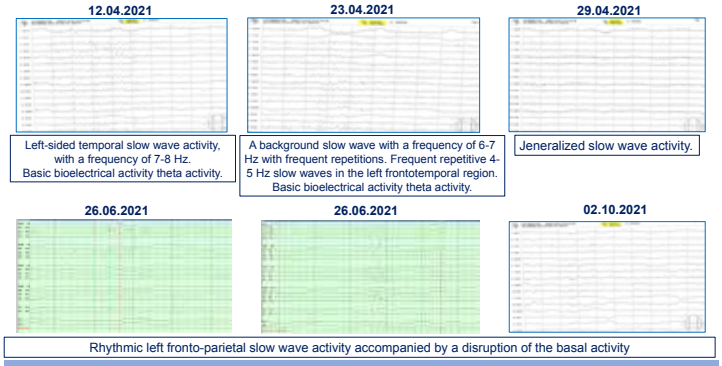
Autoimmune Tests	Result
ANA-IFA	**Hep 20-10/Liver Monkey**
FANA Form	**Nükleolar (AC-8)**
FANA Quantitative	**1:1000**
FANA Qualitative	**Positive**
Anti ENA Profile	Negative
Anti CENP B	**Weak positive**

D-Dimer	Result (N:0-500)
12.04.2021	138 ng/mL
19.04.2021	89 ng/mL
12.08.2021	348 ng/mL
12.09.2021	**599 ng/mL**
25.09.2021	376 ng/mL

Discussion

✓This report presents a patient with a myriad of neurological manifestations starting in the early phases of the disease and lasting well over a year.
✓Considering the patient's son was treated with a MIS-C, it is possible that there is a genetic predisposition in this case. However, there were no known personal or familial history of neurologic and/or epilepsy before Covid infection.
✓The patient was diagnosed as Post-Covid reactive autoimmune encephalopathy and as her clinical findings improved with steroid treatment, intravenous immunoglobulin therapy or plasmapheresis were not considered.
✓To this day, more than a year and a half from infection the patient has not fully recovered and reports myoclonia, increased headaches and peripheral neuropathic pain episodes in association physical and mental fatigue.
✓Although she returned to her original job, she is still requiring intermittent rest periods in order to function efficiently in her daily activities thus emphasizing the impact of Post - Covid on the lifes of young adults.

EEG Images



MRI Images

Conclusion

The patient described as «a case» in this poster is the first author: Dr. Melek Ongun.
I am grateful to my dear neurologists Prof. Afsar and Dr. Bolluk whom both followed me up. I am not a neurologist so I did not submit this to a journal. But I lived though this ordeal, I survived. I wanted to tell my own experience with the eyes of a doctor and a patient. I think that physicians like me who experience Post-Covid episodes have a great responsibility to explain Post-Covid and raise awareness. This is a new life with a new self and body. Even though I was a doctor for a long time, I could not find the words to describe how I felt to my relatives, I felt that some of my colleagues did not believe me. We all are struggling, and health policies should start doing something for post-covid survivors. There is still a long way to go in the treatment of this syndrome, and all countries, pharmaceutical companies and associations should come together on this issue.

1.Soriano JB, Murthy S, Marshall JC, Relan P, Diaz JV.. Lancet Infect Dis. 2022;22:e102–e107.
2. Alberto M., Long Covid: where we stand and challenges ahead, Cell Death & Differentiation; https://doi.org/10.1038/s41418-022-01052-6
3. Covid-19: WHO urges action as 17 million long covid cases are estimated in Europe.BMJ 2022;378:o2232
4. Jacqui W. Covid-19: WHO urges action as 17 million long covid cases are estimated in Europe, BMJ 2022;378:o2232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A rare cause of encephalitis with hypothermia and hyponatremia

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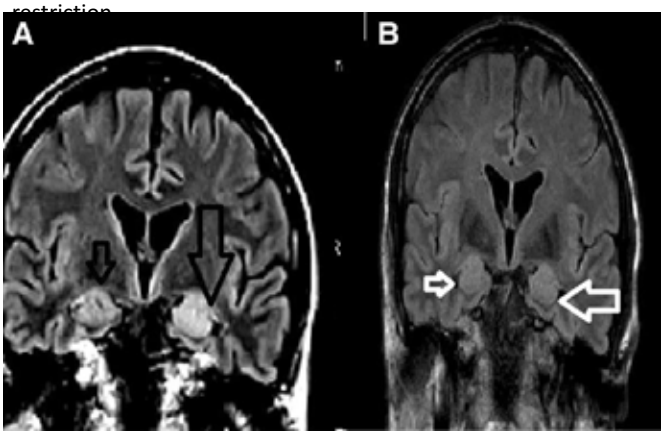
Department of Neurology, University Hospital Plymouth NHS Trust

An elderly Caucasian man was admitted with new-onset facio-brachial-dystonic seizures (FBDS) and behavioral disturbances for 5 months. The clinical examination showed no focal abnormalities. The magnetic resonance imaging (MRI) of the brain revealed high T2 signals of the mesial temporal structures bilaterally (left more than right Fig. 1a). Routine EEG showed no obvious epileptiform activity. The lumbar puncture showed normal cell count, glucose, protein, and cytology. He was started on prednisolone 60 mg once daily and levetiracetam 250 mg twice daily. However, the behavioral disturbances persisted. Five days after the admission, he developed hypothermia without shivering and piloerection. The average core body temperature was less than 35 degrees Celsius (lowest temperature of 33 degrees). The serum sodium (Na) dropped from 134 mmol/l (during admission) to 117 mmol/l in 5 days. The paired urine and serum osmolality testing revealed the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The core body temperature normalized after 4 days of intravenous immunoglobulin infusion. The serum Na slowly came up to 134 mmol/l after the immunoglobulin therapy and fluid restriction.



Hypothermia (body temperature less than 35 C) is an established feature of the autonomic dysfunction [1]. hypothalamus is the central thermoregulatory center. The mechanisms for cold defense include cutaneous vasoconstriction, piloerection, and heat production by shivering. However, our patient had no shivering or piloerection; so the hypothermia was likely central in origin, secondary to an alteration of the thermoregulatory mechanisms in the hypothalamus.Around 50–60% of patients with the LGI-1 antibodies and FBDS are hyponatremic. The hyponatremia may be secondary to excess ADH release because of the hypothalamic dysfunction. However, LGI-1 is also expressed in the renal tubules raising the possibility of a direct antibody efect on the tubules.

The computed tomogram of the thorax, abdomen, and pelvis showed no obvious source of malignancy. The whole-body positron emission tomogram (PET) was also normal (supplementary fgure). The paraneoplastic antibodies screening was negative. However, serum voltage-gated potassium channel (VGKC) complex antibody was detected with a high leucinerich glioma-inactivated 1 (LGI1) antibody titer. The second course of intravenous immunoglobulin (total dose of 2 g/kg over 5 days) was given 6 weeks after the first course as the behavioral disturbances (suspected to be due to the auto-immune encephalitis) persisted in our patient. The prednisolone 60 mg daily was continued in between those two IVIg doses. A repeat MRI head 3 months after the second course of immunoglobulin showed an improvement of the temporal lobe signal abnormality. Another MRI scan after six months of the second IVIg infusion showed a complete resolution of the temporal lobe signal changes (Fig. 1b). He reported no seizures during the subsequent review after twelve months. Prednisolone was slowly reduced to 20 mg daily in the last 12 months.

The serum VGKC complex antibodies are mostly targeted against the LGI-1 and the CASPR2 neuronal proteins. The limbic encephalitis associated with the voltagegated potassium channel complex antibody (VGKC-Ab) is a syndrome characterized by behavioral and memory disturbances, encephalopathy, neuromyotonia, and facio-brachial dystonic seizures (FBDS) [1]. Autonomic dysfunction like hypothermia was rarely described with the VGKC complex antibodies-associated encephalitis [1].

References
1)Jacob S, Irani SR, Rajabally YA, Grubneac A, Walters RJ, Yazaki M, Clover L, Vincent A (2008) Hypothermia in VGKC antibodyassociated limbic encephalitis. J Neurol Neurosurg Psychiatry 79:202–204

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Anti-Ma2 brainstem encephalitis in an elderly woman: a case for cancer therapy in advanced paraneoplastic syndromes.

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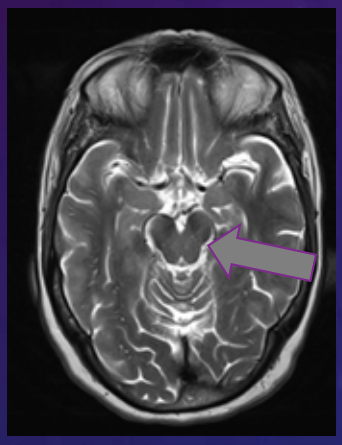
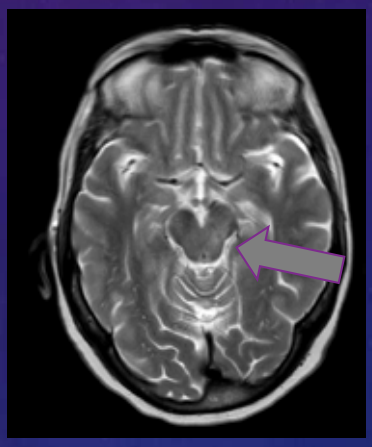
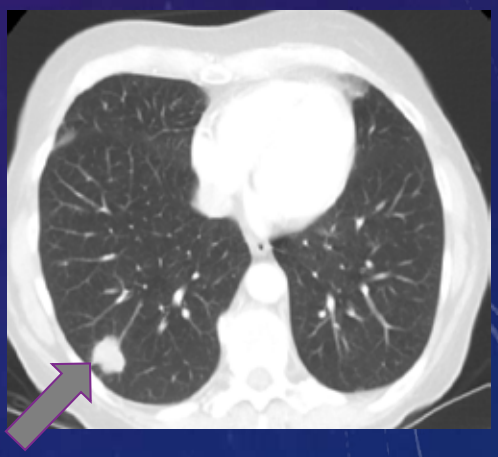
We present a case of an elderly woman with anti-Ma2 brainstem encephalitis secondary to a subsequently diagnosed lung adenocarcinoma.The patient presented with rapidly progressive visual acuity deterioration, ophthalmoplegia and ataxia, that led to total gaze paresis, counting-fingers only eyesight and severe gait impairment. Serial MRIs were initially normal, but subsequently showed changes in the midbrain and thalamus. Her cancer work-up revealed a new lung lesion that was biopsied and revealed a right lung T1c N3 M0 adenocarcinoma. Ophthalmological assessment and electroretinography also revealed concomitant possible cancer-associated retinopathy. She had a background of previously treated pancreatic cancer, managed with Whipple's procedure and adjuvant chemotherapy, but there was no evidence of recurrence. She was treated with steroids and plasma exchange and had mild improvement. Due to frailty reasons, chemotherapy was initially felt to not be appropriate, but a course of radiotherapy improved her neurological symptoms further, including mobility, and chemotherapy was reconsidered and arranged. The patient, nevertheless, rapidly declined after a community acquired pneumonia and died, prior to chemotherapy or further immunosuppression.

Initial MRI on admission



MRI 40 days later





Discussion

The case demonstrates how onconeuronal antibody paraneoplastic encephalitides can often present with a rapidly progressive syndrome and normal neuroimaging, making differential diagnosis harder. In this case, initial CSF showed only 5 lymphocytes, before oligoclonal bands, neurofilaments and the anti-Ma2 antibodies returned abnormal later. Immunotherapy had some benefit, as usually seen in anti-Ma2 encephalitis cases, but more importantly, despite general frailty and symptom progression, there was improvement of the patient's paraneoplastic syndrome with cancer therapy. It is important in similar situations to explore and balance preceding comorbidities with burden of paraneoplastic syndrome disability when determining appropriate cancer therapy, as even in severe syndromes, it can lead to improvement of quality of life and reduce disability associated morbidity and/or mortality.

Anti Ma-2 is an intracellular protein targeting antibody. It is most commonly associated with testicular and Lung cancer. This syndrome can cause a Limbic, Brainstem or Diencephalic syndrome. When investigating it is important to repeat the MRI scan as 30% of initial MRI's are normal.2/3rds of CSF studies are abnormal (cells, inflammation, OCB).In Diencephalic syndrome CSF may show low hypocretin. CSF and serum antibodies would show anti-Ma1 and anti-Ma2. To investigate the primary cancer CT TAP,PET scan,Testicular USS/ Mammogram would be warranted. The best treatment option is the removal of the cancer. Immunosuppressive agents may be tried but have variable success rates.

References
Binks S, Uy C, Honnorat J, Irani SR. Paraneoplastic neurological syndromes: a practical approach to diagnosis and management. Practical Neurology 2022;22:19-31.
Ortega Suero G, Sola-Valls N, Escudero D, Saiz A, Graus F. Anti-Ma and anti-Ma2-associated paraneoplastic neurological syndromes. Síndromes neurológicos paraneoplásicos asociados a anticuerpos anti-Ma y anti-Ma2. Neurologia (Engl Ed). 2018;33(1):18-27.

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Dr Namrata Kumari has completed her PhD in Molecular Virology from the Department of Bioengineering and Technology from Gauhati University, Assam in 2018. She has worked as a Guest Faculty under Bioengineering and Technology Dept for one year, where she used to teach Microbiology. In 2019 December she got selected as a “Women Scientist” under Department of Health Research, ICMR. Presently she is working with molecular and pathological aspects of Japanese Encephalitis Virus in the population of Assam. She has participated in various national and international workshops and seminars. In 2016 she participated as a member from Gauhati University for “INDIA CHINA Alliance for cooperation”. She published 12 papers to date.

Detection of Japanese encephalitis virus RNA in the population of Assam, India

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Introduction: Japanese encephalitis, a mosquito-borne disease affecting Asia, is caused by the Japanese encephalitis virus (JEV), a member of the genus Flavivirus. Due to the characteristically short and low viremia, detection of JEV RNA remains difficult to achieve. Despite the availability of the vaccine, JE infections and deaths have become common in Assam, a rural region of India, suggesting that the vaccine is only covering a portion of the population or that a new strain of JEV has emerged. Subsequently, research was conducted to describe and compare the gene for the complete envelope (E) protein.

Methodology: We performed a thorough analysis of qualitative PCR techniques. To find viral RNA, we focused on region E. The primary medical centre for Northeast India, Gauhati Medical Hospital in Assam, received JEV IgM-positive individuals. CSF and serum samples were collected from the patient, which was further processed using JEV RNA detection kits. RNA was also transformed into cDNA before use for detection. The JEV E gene could subsequently be identified using cDNA and Sanger sequencing was used to confirm the existence of the virus.

Fig1: PCR detection of JEV E gene (390bp size)

Fig3:Chromatogram representation of JEV GENOTYPE III

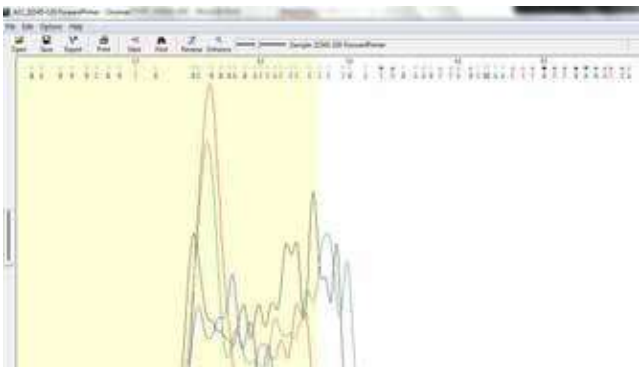
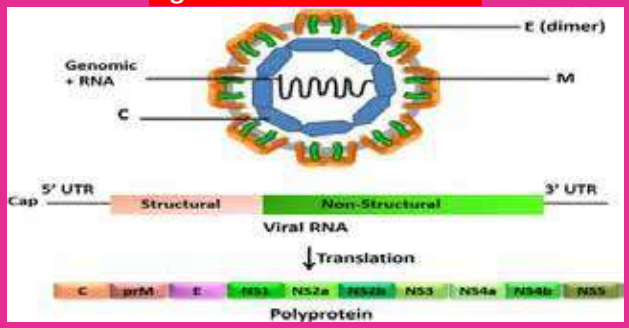
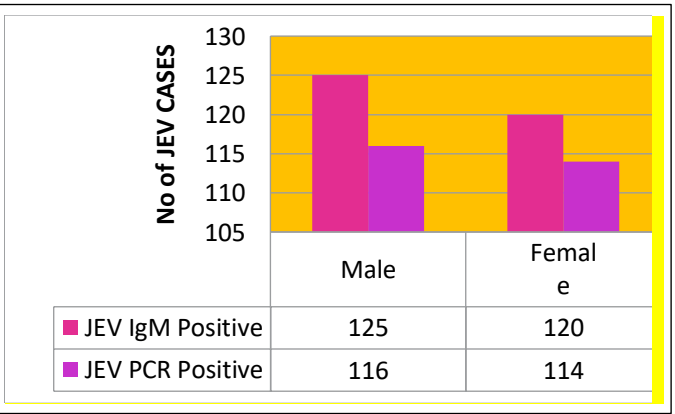


Fig2:JEV Genome structure





Conclusion: This study demonstrates the critical role surveillance plays in maintaining public health and provides compelling evidence that JEV is spreading among the Assamese people in Northeast India. A One Health strategy must be put in place that includes surveillance, a collaboration between public health and wildlife managers, and mosquito population control.

Acknowledgement: We would like to thank to DHR, Delhi,INDIA for providing funds to carry out this research.

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Dr Omer Adam is currently a paediatric trainee, working in the Neurology department at Sheffield Children's Hospital. He has always enjoyed being a caretaker and being able to make a difference to the community, especially for someone who was originally born and lived in a very poor developing country (Sudan). After lengthy consideration, Omer eventually decided to focus his goals on becoming a neurologist in order to pursue his interest in neuroscience and medical research while also being able to help people. He thinks that working as a neurologist would give him the ability to stretch himself while being under constant challenge.

Atypical 'incomplete 'Bickerstaff brainstem encephalitis in paediatrics- A case report

*Omer Adam Paediatric trainee ; Santosh R Mordekar Consultant Paediatric Neurologist

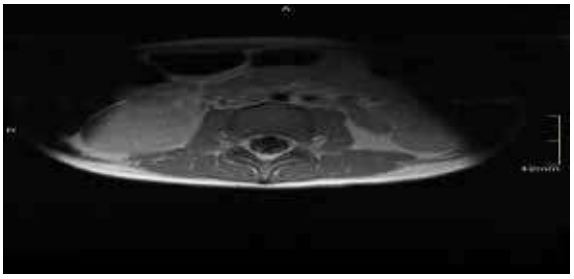
Abstract

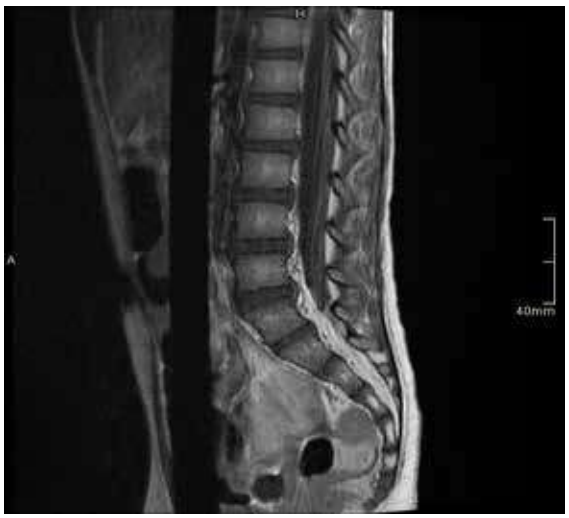
Bickerstaff Brainstem Encephalitis (BBE) is a rare autoimmune encephalitis, characterized by acute ophthalmoplegia, ataxia and altered state of consciousness. Understanding the clinical spectrum of BBE continues to evolve and relies on systematic review of published reports.
In his original case series1 Bickerstaff described marked ocular paresis in six of his eight patients.
Although our patient had no ophthalmoplegia, a negative GQ1b profile, the presence of drowsiness, altered consciousness, dysarthria, facial weakness, subtle ataxia, prominent hyperreflexia, and ascending weakness favours, MRI Spine features of GBS favour the diagnosis of possible/ incomplete form of BBE.

Introduction

The estimated annual incidence of BBE is 0.078/100000.[2] Majority of patients see a preceding infectious illness, upper respiratory tract infection being most common (94%).Usually associated antecedent pathogens include herpes simplex virus, cytomegalovirus, Epstein–Barr virus, varicella-zoster virus, measles virus, salmonella typhi, mycoplasma pneumonia, and campylobacter jejuni enteritis.[2] There is substantiating evidence that antiganglioside antibodies work via molecular mimicry with infectious agents.[3]
Central nervous system manifestations included drowsiness (45%), stupor, semi-coma or coma (29%), hyperreflexia (34%), Babinski's sign (40%) and deep sensory impairment (16%). Other common neurological features included ptosis, mydriasis, facial weakness, bulbar palsy, and nystagmus [4]
Along with Guillain–Barre syndrome (GBS) and Miller–Fisher syndrome, BBE forms a part of spectrum of post-infectious demyelinating diseases. The binding of GQ1b antibodies to cranial nerves and muscle spindles induces Fisher syndrome, whereas their binding to GQ1b antigen in the brainstem induces BBE, manifesting as an additional evidence of central involvement in form of altered level of consciousness (confusion, hyper-somnolence, or unconsciousness) and/or hyperreflexia differentiating BBE from these other two entities[4]

Imaging





MRI Spine whole with contrast : enhancement of the cauda equina on the post contrast imaging raises the possibility of a GB syndrome- Brain MRI(D5) :

Case Description

A previously healthy 4-year-old boy ,who had a recent chicken pox, treated initially(D2) as a case of LRTI by his local GP because of 48hrs sore throat, moderate grade fever, vomiting, lethargy, weakness, next day(D3)he has been admitted to a local DGH, with ongoing lethargy, weakness, reduced speech, drowsiness, and increased work of breathing, had A chest Xray with features of Pneumonia, started on low flow oxygen, escalated to high flow O2 The following day(D4) he needed intubation and ventilation because of progressive respiratory depression despite being on high flow on 100% FIO2.Transferred to a tertiary unit for ongoing medical care .
Treated with triple antibiotics and antiviral for possible encephalitis. While intubated in ICU, Noted on(D5) to have unequal pupils(3+/4+) both were responsive to light , Pupils size were 3+/3+ on D6 and afterwards, Brain CT scan performed(D5), reported as normal.
O/E :

- No internal or external ophthalmoplegia
- Facial muscle weakness, with low volume, and slurred speech. Other cranial nerves were normal
- Generalised hypotonia, hyperreflexia(exaggerated deep tendon reflexes in 4 limbs), no clonus noted, with bilateral upward plantar reflex, Babinski equivocal to down-going by D9
- Gait : ataxia was only evident on tandem gait with subtle swaying on heel shin testing.
- The sensory system difficult to assess. Grossly felt to be normal
- No seizures activities noted- EEG done b/c of encephalopathy
- Required NG feeds for about 4 weeks- unsafe swallowing.
- Had some pain during movement, especially on trunk and hip flexion, appeared more neuropathic as neural tissue stretched.
- Overflow incontinence/ constipation- had laxative
- Urinary Catheterization- catheter removed on D10
- Progressive asymmetrical weakness in limbs
- Intubated on D5 of presentation – extubated on D6 but reintubated again on D6- then extubated on D8. He was SVIA D10
- CVS : Noted to have Hypertension(on day 7 of illness) - treated with IV labetalol, shifted to and discharged on PO amlodipine. ECHO: showed Structurally normal heart. Mildly impaired left ventricular ejection fraction. repeated echo showed Mild concentric LVH. No coarctation seen. Normal IVC size and filling. Good LV and RV systolic function.
- Immunization : up to date
- Developmental : appropriate for his age

Timeline

D7MRI brain
D8 EEG : Abnormal eeg , however likely secondary to sedation, but encephalopathy/ encephalitis can not be excluded. No evidence of subclinical seizure or status.
D9 MRI spine-Patient received IVIG at 400mg/kg/day for 5 days.
D9 LP
D10 Start to lift both arms + wiggle his toes, introduction of soft diet. D11 able to lift legs briefly.
D12 able to sit and stand with support
D15 walking unsteadily + laxative stopped
D16 nerve conduction study : NAD
D19 run unsteadily #
D28 Pain medications paracetamol ibuprofen and gabapentin weaned D30 NG Feeds stopped , discharged home to be followed locally.

Laboratory Results

complete blood count, biochemical parameters(including U.Es, LFT, TFT, Renin and Aldosterone, Urine HVA and VMA, Urine Catecholamines, and coagulation profile were normal. Cerebrospinal fluid examination showed albumino-cytological dissociation with raised proteins (proteins 0.5g/L, glucose 4.4mmol/l -CSF / Plasma glucose ratio 0.86, white cells 4/cumm, rbc 12/cumm). CSF Gram stain revealed no cells or microorganisms, and the cerebrospinal fluid culture was sterile.
Ganglioside GQ1b Antibodies , IgM Anti-Gm1 Ganglioside Ab , IgG Anti-Gm1 Ganglioside Ab were negative.
No evidence of oligoclonal IgG in serum or CSF
Blood culture and urine culture sterile
CSF culture sterile. CSF was negative for Enterovirus, HS, VZ, AFB
CSF lactate normal 1.1
Stool culture was negative . Faecal pcr negative for : Rotavirus, Norovirus, Astrovirus and Group F Adenovirus (type 40,41), Toxigenic C. difficile , Salmonella, Verotoxin producing E.coli, Campylobacter, Shigella and Enteroinvasive E.coli(EIEC), Cryptosporidia, Giardia, Entamoeba histolytica
Covid negative

Discussion

The classic triad of acute bilateral ophthalmoplegia, ataxia, and encephalitis are highly suggestive of BBE. However, the absence of any one of these symptoms or presence of additional symptoms does not rule out the diagnosis[5]. The diagnosis of BBE is largely clinical, though other lab tests and imaging can be useful. Most significantly, positive serum analysis for anti-GQ1b antibodies with consistent clinical presentation is very supportive for the presence of BBE or other syndromes in the disease spectrum. However, a negative test does not rule it out. A study of over 500 cases showed anti-GQ1b antibody seropositivity in only 68% of patients[6].
Barring disease complications such as pneumonia or seizures, disease prognosis is good. Most patients make a complete recovery within 6 months, even without medical intervention[7].
In our patient , structural, ischaemic and infective causes were excluded. There was no history of drug intoxication although this was not tested for.
Although our patient's MRI brain was normal. MRI abnormalities in the form of T2 hyperintense lesions in the brainstem (especially midbrain), cerebellum, and thalamus have been seen in 30% of BBE patients [4].

Conclusions

In view of acute onset progressive bilateral ascending weakness with altered level of consciousness, brisk deep tendon reflexes in all four limbs with positive Babinski sign bilaterally, and ataxia on tandem walking, along with albuminocytological dissociation in CSF, the patient was diagnosed as "Possible BBE" and treated with Intravenous Immunoglobulin (Ivlg) 0.4 mg/kg for 5 days, showing great recovery at 1 month. Our patient discharged with plan to be followed locally with hope for a full recovery.

References

1. Bickerstaff ER. Brain-stem encephalitis: further observations on a grave syndrome with benign prognosis. Br Med J 1957;1:1384–7
2. Koga M, Kusunoki S, Kaida K, Uehara R, Nakamura Y, Kohriyama T, Kanda T. Nationwide survey of patients in Japan with Bickerstaff brainstem encephalitis: epidemiological and clinical characteristics. J Neurol Neurosurg Psychiatry. 2012 Dec;83(12):1210-5. doi: 10.1136/jnnp-2012-303060. Epub 2012 Jul 31. PMID: 22851608
3. Mori M, Kuwabara S, Fukutake T, Yuki N, Hattori T. Clinical features and prognosis of Miller Fisher syndrome. *Neurology.* 2001;56:1104–6
4. Shahrizaila N, Yuki N. Bickerstaff brainstem encephalitis and Fisher syndrome: Anti-GQ1b antibody syndrome. J Neurol Neurosurg Psychiatry. 2013;84:576–83..
5. Yuki N. Fisher syndrome and Bickerstaff brainstem encephalitis (Fisher-Bickerstaff syndrome). J Neuroimmunol. 2009 Oct 30;215(1-2):1-9. doi: 10.1016/j.jneuroim.2009.05.020. Epub 2009 Jul 29. PMID: 19643503
6. Ito M. Bickerstaff's brainstem encephalitis and Fisher syndrome form a continuous spectrum: clinical analysis of 581 cases. Journal of Neurology 2008. 255:674–82.
7. Shameem, Raji, et al. "Expert Opinion: Bickerstaff's Brainstem Encephalitis: A Rare Variant Of The Anti-Gq1b Antibody Syndrome." Practical Neurology, Bryn Mawr Communications, 2013, practicalneurology.com/articles/2013-sept-oct/bickerstaffs-brainstem-encephalitis-a-rare-variant-of-the-anti-gq1b-antibody-syndrome

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Clinical relevance and utility of GAD65 antibodies in neurological disease: an eight-year cohort study

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BACKGROUND

Glutamic acid decarboxylase (GAD) is the rate-limiting enzyme in the conversion of glutamate to gamma-aminobutyric acid (GABA). Antibodies to GAD (GAD-Abs) are associated with autoimmune diabetes, and an heterogenous group of neurological disorders including stiff person syndrome (SPS), epilepsy, ataxia, encephalitis, and mixed syndromes.

Due to its intracellular location, antibodies to GAD are not thought to be pathogenic. Titres can range from the tens to the millions causing difficulty with interpretation, especially with regards to treatment decisions for which there are few guidelines.

We conducted a retrospective review of patients with positive GAD-Abs, treated within our centre 2012-2020.

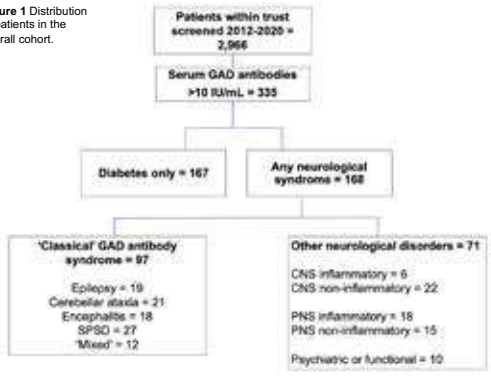
METHODS

All GAD antibodies were measured by indirect ELISA (Euroimmun assay) in our accredited Neuroimmunology and CSF Laboratory. Values >10 IU/mL were deemed positive as specified. For initial results >2000 IU/mL (i.e. the top of the standard curve), sera were diluted to identify accurate titres. For each patient the first available accurate titre was used in analysis. Titres recorded as >1,000,000 IU/mL were plotted as this number at graphing. Electronic records were reviewed for demographics, clinical and laboratory data, treatment history and outcomes.

Final diagnoses were those allocated by the treating neurologist and agreed by RB and MPL. We considered positive response to treatment as an objective improvement in a clinical score such as mRS, or a definite improvement in the opinion of the treating neurologist.

OVERALL COHORT

Figure 1 Distribution of patients in the overall cohort.

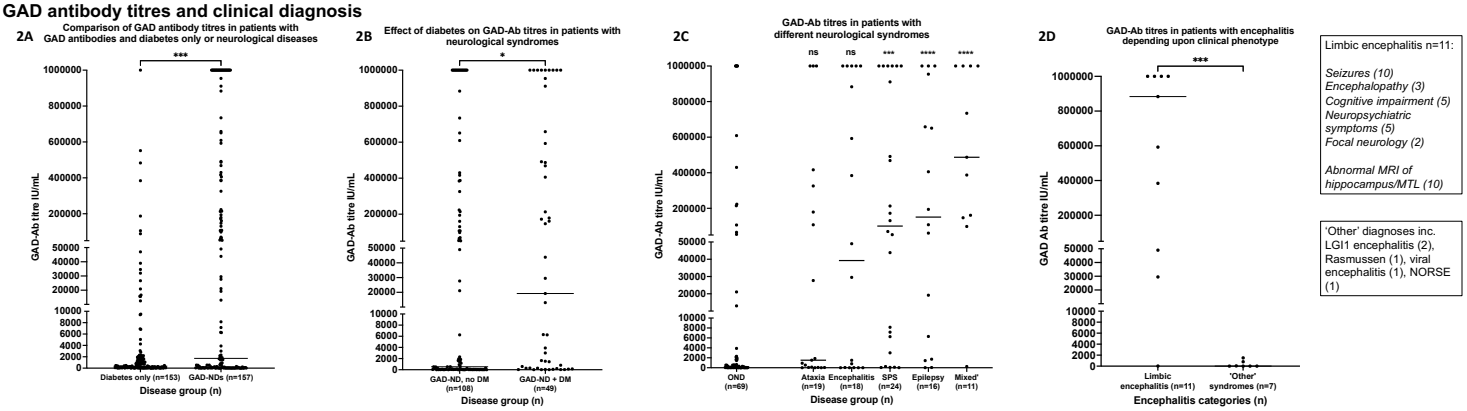


	Epilepsy (n=19)	Ataxia (n=21)	Encephalitis (n=18)	SPSD (n=27)	Mixed (n=12)	Other neurological disorders (n=71)
Median age at onset (years)	25 (7-65)	60 (12-76)	31 (13-82)	48 (23-78)	38 (16-61)	49 (16-78)
Female, n (%)	15 (79)	13 (62)	10 (56)	17 (63)	10 (83)	42 (59)
Time to GAD ab test <1 year, n (%)	2 (11)	9 (43)	15 (83)	13 (48)	3 (25)	22 (31)
Other AI diseases, n (%)	**14 (74)**	**13 (62)**	**7 (39)**	**18 (67)**	**8 (67)**	**29 (41)**
T1DM or LADA (IDDM), n (%)	9 (47)	3 (14)	5 (28)	12 (44)	6 (50)	18 (25)
AI thyroid disease, n (%)	8 (42)	7 (33)	3 (17)	12 (44)	6 (50)	5 (7)
>1 AI disease diagnosed, n (%)	9 (47)	3 (14)	1 (6)	11 (41)	5 (42)	9 (13)
Other neuronal antibodies, n (%)	**2 (11)**	**1 (5)**	**6 (33)**	**9 (33)**	**4 (33)**	**15 (21)**
Other neuronal or thyroid antibodies (n)	VGKC 1, VGCC 1 (CSF), thyroid 3	AChR 1, thyroid 1	GlyR 1, LGI1 2, VGKC 1, GABA-B 1, thyroid 3	GlyR 4, amphiphysin 1, Sox1 2, Zic4 1, VGKC 1, thyroid 5	GlyR 3, Sox1 1,Zic4 1, thyroid 3	PND 5, AChR 3, MuSK 2, Gangliosides 2, MAG 1, Neurofascin 155 1, GlyR 1, MOG 2, thyroid 4
Malignancy, n (%)	**0 (0)**	**2 (10)**	**4 (22)**	**5 (19)**	**1 (8)**	**12 (17)**

Table 1 Summary of clinical features of patients with GAD-Abs and neurological syndromes

RESULTS

GAD antibody titres and clinical diagnosis



Limbic encephalitis n=11:

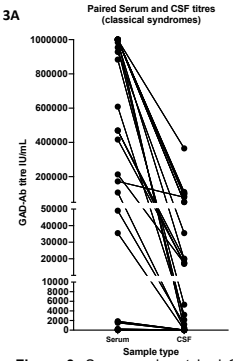
Seizures (10)
Encephalopathy (3)
Cognitive impairment (5)
Neuropsychiatric symptoms (5)
Focal neurology (2)

Abnormal MRI of hippocampus/MTL (10)

'Other' diagnoses inc. LGI1 encephalitis (2), Rasmussen (1), viral encephalitis (1), NORSE (1)

Figure 2A-D: GAD-Ab titres were higher in patients with GAD-Abs and neurological diseases (GAD-NDs) compared to diabetes only (**2A**). In patients with GAD-NDs, GAD-Ab titres were higher than those with concomitant diabetes (**2B**). Patients with SPS, epilepsy or mixed syndromes had significantly higher GAD-Ab titres than patients with non-classical syndromes (OND); those with ataxia were not significantly different to OND **(2C).** The encephalitis group included patients with otherwise seronegative LE and high GAD-Ab titres, and patients with other encephalitis syndromes e.g. LGI1 and Rasmussen's, and low GAD-Ab titres **(2D).** Overall, a range of titres was seen in all groups. A suggested 'cut-off' of 10,000 IU/mL would exclude 34/88 (39%) patients with 'classical' syndromes, and include 17/153 (11%) patients with diabetes only and 14/69 (20%) with ONDs.

CSF GAD antibody titres



3B

Syndrome	Serum:CSF GAD-Ab ratio	Ratio cut-off for intrathecal synthesis (ITS) set at 150
Ataxia	27.75	ITS
Ataxia	280.42	No ITS
Ataxia	23.60	ITS
Ataxia	26.14	ITS
Ataxia	56.06	ITS
Encephalitis	13.35	ITS
Encephalitis	41.14	ITS
Encephalitis	166.70	Borderline
SPS	32.94	ITS
SPS	2.17	ITS
SPS	12.28	ITS
SPS	23.31	ITS
Epilepsy	287.33	No ITS
Epilepsy	190.69	No ITS
Epilepsy	443.94	No ITS
Epilepsy	788.89	No ITS
Mixed	49.95	ITS
Mixed	3.79	ITS

Figure 3: Serum and matched CSF GAD-Ab titres were highly variable (**3A**). Evidence of ITS (defined as reduced serum:CSF ratios) was found in ataxia, encephalitis, SPSD and mixed syndromes but not in epilepsy **(3B)**.

GAD antibody titres, disease group and treatment response

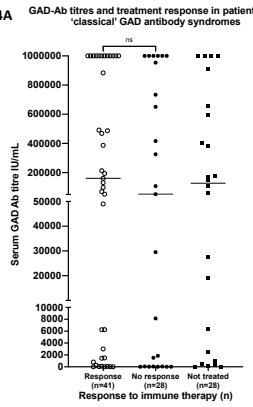


Figure 4A: GAD-Ab titres in different disease groups: GAD-Ab titres were not associated with response to immune therapy

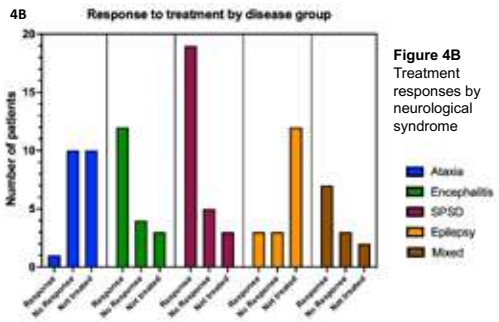


Figure 4B Treatment responses by neurological syndrome

Within our cohort, treatment decision making and outcomes were syndrome related. Patients with SPSD, LE and mixed syndromes were most likely to be treated and have positive responses. Caveats to these data include highly heterogeneous treatment regimes. Degree of response also varied from small, non-sustained improvement, to significant sustained improvement.

CONCLUSIONS

Interpretation of GAD antibodies requires caution. In our cohort, in which sera/CSF were tested by a commonly used ELISA-based assay, a range of titres were seen in each disease group making it difficult to establish a 'cut off' titre for neurological disease. Serum titres did not correlate with treatment response. Consideration of clinical phenotype remains most important in making treatment decisions. The evidence for treatment responses was limited but SPSDs and encephalitis appeared to have the best responses. There is a need for new biomarkers to better understand the underlying immune pathophysiology of these disorders, and identify those patients most likely to benefit from immune therapies.

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Case report: NORSE after the first dose of the BNT162b2 vaccine

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INTRODUCTION AND METHODS

Vaccination against coronavirus disease (COVID-19) is considered one of the most effective strategies to control the pandemic. Although mild and self-limited neurological symptoms following vaccination are common, major neurological complications have been scarcely reported despite the unproven causality. We report a rare case of NORSE (New-onset refractory status epilepticus) on a healthy teenager 25 days after the first dose of the BNT162b2 vaccine.

Case report based on medical report review.

RESULTS

A previously healthy 16-year-old female of African Brazilian ethnicity was admitted to an emergency department of another hospital due to seizures characterized by a fear sensation, evolving into behavioral arrest and a bilateral tonic-clonic seizure, lasting for 5-10 minutes. She had complained of a headache a week before. There was no history of fever, infection, previous seizure episodes, or family history of epilepsy. She received the first dose of the BNT162b2 vaccine 25 days before seizures onset. On the same day, she developed frequent seizures without consciousness recovery between the episodes.

Treatment with initial anti-seizure medications (diazepam, phenytoin, phenobarbital) failures to abort seizures. The patient needed orotracheal intubation, continuous IV midazolam, propofol, and ketamine, as well as oral topiramate, lamotrigine, and oxcarbazepine. Electroencephalography (EEG) disclosed seizures with acute waves in the right frontotemporal area. Initial general exams were normal, as well as brain MRI and CSF analysis, including infectious investigation. Antibody against N-methyl-D-aspartate (NMDA) receptor also resulted negative. The patient was treated with IV methylprednisolone and immunoglobulin. She also received IV antibiotics and antivirals.

She was then transferred to our intensive care unit. After tapering anti-seizure drugs, she presented with complex visual hallucinations with electrographic correlation, persisting with unmotivated laughter, disconnected answers, memory loss, and sleep disorders. A new CSF analysis yielded normal results, and a new brain MRI disclosed leptomeningeal enhancement. Oral anti-seizures drugs were adjusted with the resolution of symptoms.

The patient was discharged five weeks after the onset with oral levetiracetam, topiramate, clobazam, phenobarbital, and quetiapine. At her last outpatient visit, more drugs were tapered, and the patient had a normal neurologic examination. She was already at school without learning difficulty.

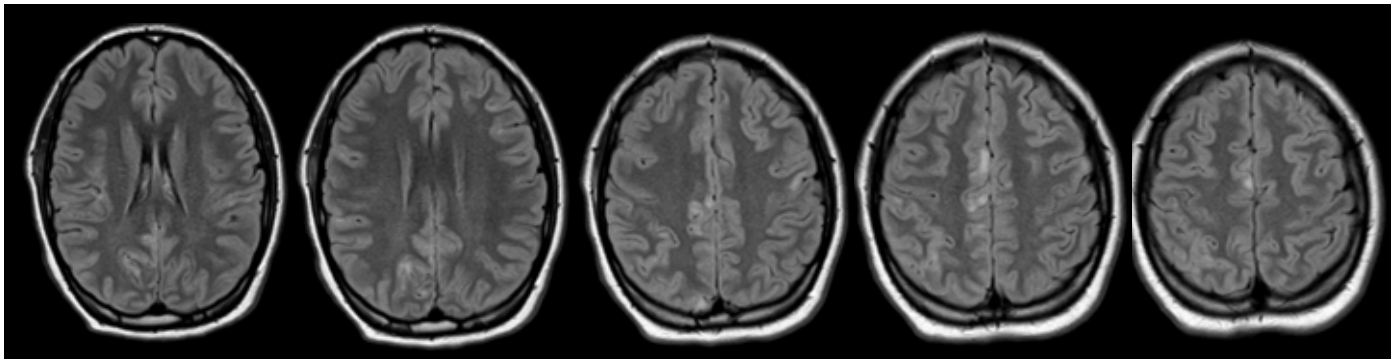

Figure. Second Brain MRI disclosing leptomeningeal enhancement.

DISCUSSION

To our knowledge, this is the first reported case of NORSE after the BNT162b2 vaccine. One adult patient presented with NORSE Moderna vaccine. Vaccination was considered the aetiology of NORSE in this case due to the temporal association and the lack of risk factors for epilepsy in the patient. Healthcare providers should be aware of the possibility of post-vaccination epilepsy.

REFERENCES

Hirsh LJ, Gaspard N, van Baalen A, Nabbout R, Demeret S, Loddenkemper T, Navarro V, Specchio N, Lagae L, Rossetti AO, Hocker S, Gofton TE, Abend NS, Gilmore EJ, Hahn C, Khosravani H, Rosenow F, Trinka E. Proposed consensus definitions for new-onset refractory status epilepticus (NORSE), febrile infection-related epilepsy syndrome (FIRES), and related conditions. Epilepsia. 2018 Apr;59(4):739-44. doi:10.1111/epi.14016.

New-onset refractory status epilepticus following the ChAdOx1 nCoV-19 vaccine. Aladdin Y, Shirah B. Journal of Neuroimmunology. 2021,37: 577629

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Evidence for accelerated long-term forgetting in Autoimmune Limbic Encephalitis using 'The Crimes Test': a neuropsychological single case series

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Background of ALE participants

Inclusion criteria:
Patients (18-65 years of age) who had a previous diagnosis of autoimmune limbic encephalitis (ALE) and have recovered from the acute phase of their illness were invited to take part in this research.

Patients had no significant head injury (other than ALE), had no significant visual/hearing impairments and do not suffer from frequent seizures (more than 1 per week).

All participants were recruited through the Encephalitis Society.

Participant		
1	Antibody Type	NMDA
	Age	26
	Gender	Female
	Date of diagnosis	Sep-15
	Date of treatment completion	2018
	Treatment	Steroids, IVIg
3	Antibody Type	VGKC
	Age	64
	Gender	Male
	Date of diagnosis	Jun-16
	Date of treatment completion	still taking medication
	Treatment	Steroids
4	Antibody Type	NMDA
	Age	20
	Gender	Female
	Date of diagnosis	Apr-20
	Date of treatment completion	still taking medication
	Treatment	Steroids
5	Antibody Type	NMDA
	Age	44
	Gender	Female
	Date of diagnosis	Jan-13
	Date of treatment completion	Feb-13
	Treatment	Steroids, plasma exchange, immunoglobulin
6	Antibody Type	NMDA
	Age	32
	Gender	Female
	Date of diagnosis	Sep-17
	Date of treatment completion	Apr-19
	Treatment	Steroids, IVIg
7	Antibody Type	LGI-1
	Age	63
	Gender	Male
	Date of diagnosis	May-19
	Date of treatment completion	Sep-19
	Treatment	Steroids, plasma exchange
10	Antibody Type	NMDA
	Age	28
	Gender	Female
	Date of diagnosis	Dec-19
	Date of treatment completion	Nov-20
	Treatment	Steroids, IVIg
11	Antibody Type	Anti-DPPX
	Age	58
	Gender	Male
	Date of diagnosis	Apr-21
	Date of treatment completion	still taking medication
	Treatment	Steroids, IVIg, plasma exchange
13	Antibody Type	LGI-1
	Age	54
	Gender	Male
	Date of diagnosis	Oct-17
	Date of treatment completion	Apr-18
	Treatment	Steroids, IVIg
14	Antibody Type	LGI-1
	Age	57
	Gender	Male
	Date of diagnosis	Sep-17
	Date of treatment completion	still taking medication
	Treatment	Steroids, IVIg

* IVIg = intravenous immune globulin

Background

Autoimmune limbic encephalitis (ALE) is a neurological disease which causes inflammation to temporal lobe structures. A key neuropsychological consequence of this condition following medical recovery is impairments in long-term memory. Although these impairments often lead to subjective complaints about memory and impact the day-to-day functioning of patients, the impairments can be mild or even go undetected in standard neuropsychological tests (Helmstaedter et al., 2019).

ALE is characterised by cognitive dysfunction and psychiatric symptoms, including hallucinations, depression, anxiety and seizures at the time of diagnosis (Mori et al., 2002; Butler et al., 2014). ALE is associated with different antibodies, and it is the presence of these antibodies that characterise the disease (Nascimento Alves et al., 2017). In recent years there has been an increase in the number of ALE cases (Graus et al., 2016) with medical advances in the ability to identify specific neuronal antibodies (Agarwal et al., 2019).

ALE patients often suffer from persistent cognitive impairments after treatment has been completed, particularly in memory. There is evidence that inflammation in the hippocampus can cause hippocampal atrophy (Loane et al., 2019). Hippocampal atrophy has been most commonly found in VGKC (Timaus et al., 2021), and LGI-1 encephalitis (Griffith et al., 2020), with some evidence of this in NMDAR encephalitis too (Finke et al., 2016).

One of the core long-term consequences of ALE is thought to be associated **with accelerated long-term forgetting (ALF)** with some recent work reporting this in ALE (Witt et al., 2015). The phenomenon of accelerated long-term forgetting (ALF) refers to unimpaired memory retrieval after short delays of up to 30 minutes with significant subsequent forgetting with multiple longer-term follow-up intervals (i.e. hours to weeks) relative to healthy controls (Elliott et al., 2014).

The current study uses a task that was specifically developed to test ALF. It was hypothesised that ALE patients will show **significant long-term forgetting** over a 1-month period compared to healthy controls. It was of particular interest to find out whether long-term forgetting is present in patients with any antibody types or just a subset of them. This may help us better understand why some patients report subjective memory complaints despite them not being picked up by standard clinical tools.

Method – The Crimes Test (Baddeley et al., 2014)

Participants:

8 Encephalitis Patients and 8 Healthy controls

Antibody Type	Total
NMDA	3 (M; Aged 26, 32, 44)
LGI-1	3 (M; Aged 54, 57, 63)
VGKC	1 (M; Aged 64)
Anti-DPPX	1 (M; Aged 58)

Procedure:

Testing verbal forgetting over a 1-month period.

Participants listened to a description of four crimes which were assessed in the follow four test phases:

- Session 1: Study and immediate test
- Session 2: one day delay
- Session 3: one-week delay
- Session 4: one-month delay

Session 1 – Study and Immediate Test

- Listened to 4 short crimes around 15 seconds long
- 1 minute distractor task
- Answer 20 questions related to these four Crimes
- Learning criterion of 75% (15/20)
- Up to 5 trials to reach criterion

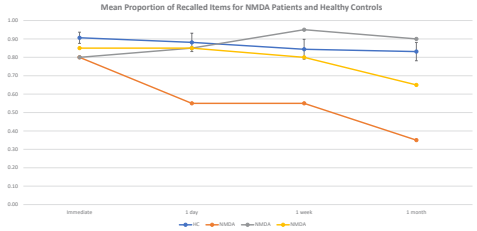
Session 2 – 1 Day delay
Session 3 – 1 Week delay
Session 4 – 1 month delay

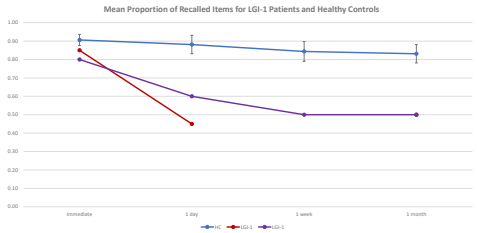
- Recall task: Answer 20 questions related to the four crimes they listened to in Session 1

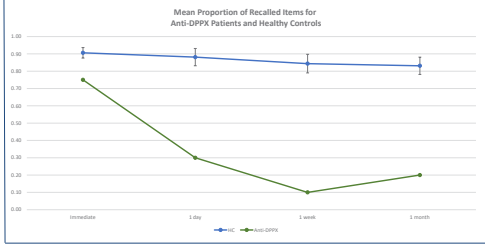
- An old Russian lady was walking back to her hotel across the river.
- As she approached the bridge a speeding car veered onto the pavement and hit her.
- The driver, a teenage girl, leapt out and ran away.

1 What was the age/sex of the victim of the stabbing crime? *Young man*
2 Who committed the crime against the Indian person? *Tramp*
3 What was the age/sex of the victim from Russia? *Old lady*
4 What was the crime committed against the young woman? *Handbag snatch*

Results







Antibody	Session 1 - Immediate		Session 2 – 1 day		Session 3 – 1 Week		Session 4 – 1 Month	
	(t)	(p value)	(t)	(p value)	(t)	(p value)	(t)	(p value)
NMDA	1.7	0.118	0.94	0.372	0.93	0.341	0.82	0.401
NMDA	-0.69	0.257	0.94	0.372	-0.72	0.248	-1.48	0.091
NMDA	1.7	0.118	3.37	0.015	2.63	0.017	3.57	0.004
LGI-1	1.7	0.118	2.94	0.042	3.01	0.009	3.53	0.019
LGI-1	0.69	0.257	2.99	0.209			3.53	0.019
Anti-DPPX	1.7	0.049	4.87	0.002	4.96	0.00078	4.93	0.001

The t and p values above compare patient test scores against the control sample (using the modified t-test developed for single case research (Crawford & Garthwaite, 2011)).

The values in **red** are significantly below the control mean. The Anti-DPPX patient has a t-score of -6 which shows a severe impairment.

Both LGI-1 and Anti-DPPX type Encephalitis patients demonstrated significant forgetting in each follow up point from 1 day delay to 1 month delay.

Only 6/8 participants reached criterion - 1 VGKC and 1 LGI-1 patient did not reach criterion. The VGKC patient reached 45% after 5 trials and the LGI-1 patient scored 5% after 3 trials, then was withdrawn due to task difficultly. This highlights the severe impairment in this specific antibody group. These two participants who did not reach criterion were not included in the analyses.

1 of the NMDA patients also demonstrated significant forgetting from 1 day delay to 1 month delay. However, the other 2 NMDA patients did not show any significant impairment across any of the time delays.

Discussion

Results support our hypothesis that ALE patients show significant impairment in memory retention over a 1-month period.

LGI-1/Anti-DPPX participants showed significant forgetting after the immediate test phase - VGKC (and subgroups) has been suggested to be more **hippocampal dependent** (Loane et al., 2019) which could explain the impairment here.

1/3 NMDA showed significant impairment after the immediate test phase – some limited evidence for **reduced hippocampal volumes** in literature (Finke et al., 2016) which could explain why only 1 NMDA patient showed impairments.

Our results support previous research that accelerated long-term forgetting occurs in ALE (Witt et al., 2015) more predominantly in VGKC Encephalitis (Hansen., 2019).

Helps us to understand why patients might report subjective complaints despite not being confirmed by standardised memory tests (Helmstaedter et al., 2019) as their forgetting occurs after longer intervals than usually tested in standardised assessment. In our study, significant forgetting is evident after 1 day.

Agarwal, K. A., Albertolle, M., & Tiru, M. (2019). *Case Report Autoimmune Limbic Encephalitis in a Patient with Acute Encephalopathy and Hyponatremia*. https://doi.org/10.1155/2019/9051738
Baddeley, A., Rawlings, B., & Hayes, A. (2014). Constrained prose recall and the assessment of long-term forgetting: The case of ageing and the Crimes Test. *Memory*, *22*(8), 1052–1059. https://doi.org/10.1080/09658211.2013.865753
Butler, C. R., Miller, T. D., Kaur, M. S., Baker, I. W., Boothroyd, G. D., Ilman, N. A., Rosenthal, C. R., Vincent, A., & Buckley, C. J. (2014). Persistent anterograde amnesia following limbic encephalitis associated with antibodies to the voltage-gated potassium channel complex. *Journal of Neurology, Neurosurgery and Psychiatry*, *85*(4), 387–391. https://doi.org/10.1136/jnnp-2013-306724
Crawford, J. R., & Garthwaite, P. H. (2011). Single-case research in neuropsychology : A comparison of five forms of t -test for comparing a case to controls. *CORTEX*, *48*(8), 1009–1016. https://doi.org/10.1016/j.cortex.2011.06.021
Elliott, G., Isaac, C. L., & Muhlert, N. (2014). Measuring forgetting: A critical review of accelerated long-term forgetting studies. *Cortex*, *54*(1), 16–32. https://doi.org/10.1016/j.cortex.2014.02.001
Finke, C., Kopp, U. A., Pajkert, A., Behrens, J. R., Leypoldt, F., Wuerfel, J. T., Ploner, C. J., Prüss, H., & Paul, F. (2016). Structural Hippocampal Damage Following Anti-N-Methyl-D-Aspartate Receptor Encephalitis. *Biological Psychiatry*, *79*(9), 727–734. https://doi.org/10.1016/j.biopsych.2015.02.024
Graus, F., Titulaer, M. J., Balu, R., Benseler, S., Bien, C. G., Cellucci, T., Cortese, I., Dale, R. C., Gelfand, J. M., Geschwind, M., Glaser, C. A., Honnorat, J., Höftberger, R., Iizuka, T., Irani, S. R., Lancaster, E., Leypoldt, F., Prüss, H., Rae-Grant, A., Dalmau, J. (2016). A clinical approach to diagnosis of autoimmune encephalitis. In *The Lancet Neurology* (Vol. 15, Issue 4, pp. 391–404). Lancet Publishing Group. https://doi.org/10.1016/S1474-4422(15)00401-9
Griffith, S. P., Malpas, C. B., Alpitsis, R., O'Brien, T. J., & Monif, M. (2020). The neuropsychological spectrum of anti-LGI1 antibody mediated autoimmune encephalitis. *Journal of Neuroimmunology*, *345*(April). https://doi.org/10.1016/j.jneuroim.2020.577271
Hansen, N. (2019). Long-Term Memory Dysfunction in Limbic Encephalitis. *Frontiers in Neurology*, *10*(April), 1–5. https://doi.org/10.3389/fneur.2019.00330
Helmstaedter, C., Winter, B., Melzer, N., Lohmann, H., & Witt, J. A. (2019). Accelerated long-term forgetting in focal epilepsies with special consideration given to patients with diagnosed and suspected limbic encephalitis. *Cortex*, *110*, 58–68. https://doi.org/10.1016/j.cortex.2018.01.003
Loane, C., Argyropoulos, G. P. D., Roca-Fernández, A., Lage, C., Sheerin, F., Ahmed, S., Zamboni, G., MacKay, C., Irani, S. R., & Butler, C. R. (2019). Hippocampal network abnormalities explain amnesia after VGKCC-Ab related autoimmune limbic encephalitis. *Journal of Neurology, Neurosurgery and Psychiatry*, *90*(9), 965–974. https://doi.org/10.1136/jnnp-2018-320168
Mori, M., Kuwabara, S., Yoshiyama, M., Kanesaka, T., Ogata, T., & Hattori, T. (2002). Successful immune treatment for non-paraneoplastic limbic encephalitis. *Journal of the Neurological Sciences*, *201*(1–2), 85–88. https://doi.org/10.1016/S0022-510X(02)00188-0
Nascimento Alves, P., Maruta, C., Albuquerque, L., & Martins, I. P. (2017). Dissociation findings between short-term and long-term memory in autoimmune limbic encephalitis. In *Journal of the Neurological Sciences* (Vol. 381, pp. 126–127). Elsevier B.V. https://doi.org/10.1016/j.jns.2017.08.016
Timäus, C., Gottberg, P. Von, Hirschel, S., Lange, C., Wiltfang, J., & Hansen, N. (2021). *brain sciences KCNA2 Autoimmunity in Progressive Cognitive Impairment : Case Series and Literature Review*.
Witt, J. A., Vogt, V. L., Widman, G., Langen, K. J., Elger, C. E., & Helmstaedter, C. (2015). Loss of autonoetic consciousness of recent autobiographical episodes and accelerated long-term forgetting in a patient with previously unrecognized glutamic acid decarboxylase antibody related limbic encephalitis. *Frontiers in Neurology*, *6*(MAY). https://doi.org/10.3389/fneur.2015.00130

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Prof Irani is a consultant neurologist and clinician scientist, who leads the Oxford Autoimmune Neurology Group. Prof Irani has doctoral and postdoctoral experience in cellular, biochemical, and molecular aspects of neuroimmunology. He specialises in antibody-mediated encephalopathies and epilepsies and has discovered novel antigenic targets and phenotypes amongst these patients. Prof Irani runs the UK's major clinic dedicated to the care of these patients. His clinical and laboratory-based research team is currently studying the mechanisms of the underlying cellular immunology and modelling methods to treat these conditions. This interaction is being undertaken by Prof Irani as an individual outside of his employment at the University of Oxford.

CIELO: A Randomised, Double-blind, Placebo-controlled, Phase 3 Basket Study of Satralizumab in Patients with NMDAR- or LGI1-antibody Encephalitis

Sarosh R. Irani[1], Hesham Abboud[2], Soon-Tae Lee[3], Hideto Nakajima[4], Amanda Piquet[5], Sean J. Pittock[6], E. Ann Yeh[7], James Overell[8], Sharmila Rajan[9], Muna El-Khairi[10], Jeffrey M. Gelfand[11]

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Introduction and objectives

- Autoimmune encephalitis (AIE) is a group of rare, severe, antibody-mediated neurological diseases characterised by prominent neuropsychiatric symptoms[1,2]
- The most common subtypes of AIE are those with antibodies targeting the N-methyl-D-aspartic acid receptor (NMDAR) or leucine-rich glioma-inactivated 1 (LGI1)[2]
- There are currently no approved treatments for AIE, and evidence-based treatments that reduce long-term cognitive and physical disability, as well as persistent seizures and disabling symptomology, are needed[3,4]
  - A recent randomised trial suggested the benefit of intravenous immunoglobulin (IVIG) in reducing seizure frequency in certain AIE subtypes[5]
- People with AIE have elevated levels of the multifunctional cytokine interleukin-6 (IL-6)[6]
- Processes regulated by IL-6 signalling, such as B- and T-cell differentiation, B-cell proliferation, survival and functioning of autoantibody producing plasma cells, and blood−brain barrier regulation, are thought to have a role in AIE pathogenesis[6–10]
- Anecdotal reports of IL-6 receptor (IL-6R) inhibition in AIE have described clinical benefits; hence, IL-6R is a therapeutic target of interest[11]
- Satralizumab is a humanised, monoclonal recycling antibody that targets the soluble and membrane-bound forms of the IL-6R, blocking IL-6 signalling[12]
- CIELO (NCT05503264) is the first study of satralizumab in patients with AIE

Methods

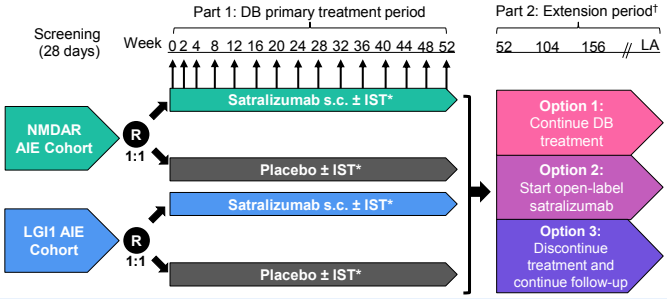
- CIELO will enrol ~102 patients aged ≥12 years with a diagnosis of probable or definite NMDAR AIE and ~50 patients aged ≥18 years with LGI1 AIE who have:
  - Onset of AIE symptoms ≤9 months prior to randomisation
  - Modified Rankin Scale (mRS) score ≥2 at randomisation
- Patients will be stratified as "new onset" or "incomplete responder" (**Table 1**)
- CIELO (**Figure 1**) includes a 52-week double-blind primary treatment period (Part 1), followed by an optional extension period (Part 2)
- In Part 2, participants can either continue double-blind treatment, receive open-label satralizumab, or discontinue treatment and continue follow-up assessments

Table 1. Definitions of "New onset" and "Incomplete responder" for inclusion criteria

	New onset	Incomplete responder
Acute first-line therapy	≤6 weeks before randomisation	>6 weeks before randomisation
Prior treatment	No immunotherapy additional to acute first-line therapy	Treatment with other immunotherapy in addition to acute first-line therapy*

*RTX initiated ≥2 months before screening (last dose ≥4 weeks before randomisation), IST treatment ≥2 months before screening, OCS, or repeated pulse therapy; patients should have no improvement in mRS score within 4 weeks before randomisation with prior immunotherapy, and patients who have received repeated courses of acute first-line therapy must have completed treatment ≥2 weeks before randomisation. IST, immunosuppressive therapy; mRS, modified Rankin Scale; OCS, oral corticosteroids; RTX, rituximab.

Figure 1. CIELO study design summary



†Treatment administered. *Incomplete responders may continue to receive the following background IST treatments: AZA, MMF, and intravenous cyclophosphamide. Patients may receive baseline OCS, which must be tapered from Week 4. All patients are permitted to receive symptomatic AIE medications. †The extension period lasts ~2 years from when the last patient enters the extension period. AIE, autoimmune encephalitis; AZA, azathioprine; DB, double-blind; IST, immunosuppressive therapy; LA, last administration; LGI1, leucine-rich glioma-inactivated 1; MMF, mycophenolate mofetil; NMDAR, N-methyl-D-aspartic acid receptor; OCS, oral corticosteroids; R, randomised; s.c., subcutaneous.

Study endpoints

Primary endpoint

- Proportion of patients with a mRS score improvement ≥1 from baseline without the use of rescue therapy at Week 24

Secondary endpoints

Not in hierarchical order, and will be tailored to the individual cohort

- Time to mRS score improvement ≥1 from baseline without the use of rescue therapy
- Time to rescue therapy
- Time to seizure freedom or cessation of status epilepticus without the use of rescue therapy
- Change in Clinical Assessment Scale of Encephalitis (CASE) score from baseline at Week 24
- Montreal Cognitive Assessment (MOCA) total score at Week 24
- Rey Auditory Verbal Learning Test (RAVLT) score for LGI1 AIE cohort at Week 24
- mRS score for NMDAR AIE cohort at Week 24, as measured on a 7-point scale

Safety

- Incidence, seriousness, and severity of adverse events
- Change from baseline in targeted vital signs, electrocardiogram parameters, and clinical laboratory test results

Pharmacokinetics and Pharmacodynamics

- Serum IL-6 and soluble IL-6R
- Serum and/or cerebrospinal fluid concentrations of satralizumab

Exploratory endpoints

- Degree of disability, clinical severity, mood, quality of life, and functional living
- Additional exploratory biomarker assessments including longitudinal assessments

Conclusions

- Randomised evidence to guide treatment decisions is urgently required in AIE
- CIELO will assess the efficacy, safety, pharmacokinetics, and pharmacodynamics of IL-6 inhibition with satralizumab in patients with NMDAR AIE and LGI1 AIE
- CIELO will recruit participants from approximately 83 sites across 15 countries, with 22 sites across European countries including Austria, Czech Republic, France, Italy, the Netherlands, Poland, and Denmark

To find recruiting sites near you, scan this QR code

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References

1. Graus F, et al. *Lancet Neurol* 2016;15:391–404; **2.** Dalmau J and Graus F. *N Engl J Med* 2018;378:840–851; **3.** Abboud H, et al. *J Neurol Neurosurg Psychiatry* 2021;92:757–768; **4.** Trewin BP, et al. *Curr Opin Neurol* 2022;35:399–414; **5.** Dubey D, et al. *Ann Neurol* 2020;87:313–323; **6.** Ciano-Petersen NL, et al. *Brain Comm* 2022;4:fcac196; **7.** Lehmann-Horn K, et al. *Neurol Neuroimmunol Neuroinflamm* 2020;7:e669; **8.** Kishimoto T, et al. In: Nakao K, et al (eds). Innovative Medicine: Basic Research and Development. Tokyo: *Springer* 2015, 131–147. DOI:10.1007/978-4-431-55651-0_11; **9.** Bien CG, et al. *Brain* 2012;135:1622–1638; **10.** Sun B, et al. *Nat Rev Neurol* 2020;16:481–492; **11.** Lee W-J, et al. *Neurotherapeutics* 2016;13:824–832; **12.** Yamamura T, et al. *N Engl J Med* 2019;381:2114–2124.

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Dr Sukhvir Wright is a clinician-scientist undertaking research into autoimmune epileptic encephalopathies. Her research group within the Neuroscience laboratory at the Institute of Health and Neurodevelopment at Aston University, Birmingham, UK, investigates the pathogenicity and epileptogenicity of neuronal autoantibodies in animal models. The aim is to develop a precision medicine approach for treating these autoimmune associated epilepsies and improve patient outcomes. Dr Sukhvir Wright is also a consultant paediatric neurologist at Birmingham Children's Hospital and part of the Neuroimmunology team.

Peripherally-derived monoclonal LGI1 antibodies cause epileptic seizures in a passive transfer animal model

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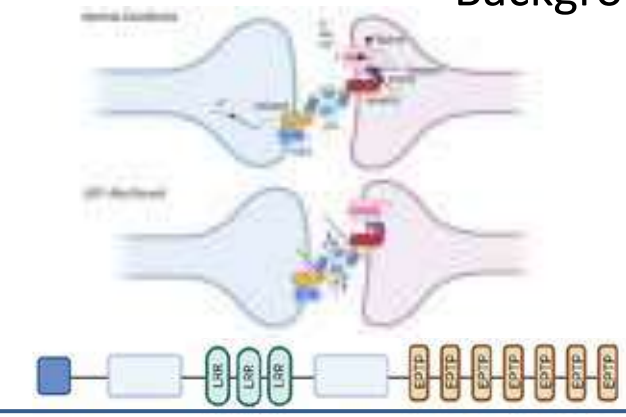
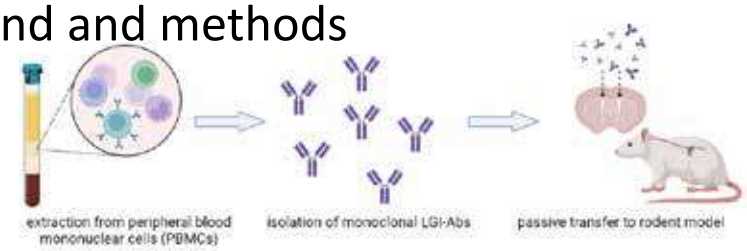
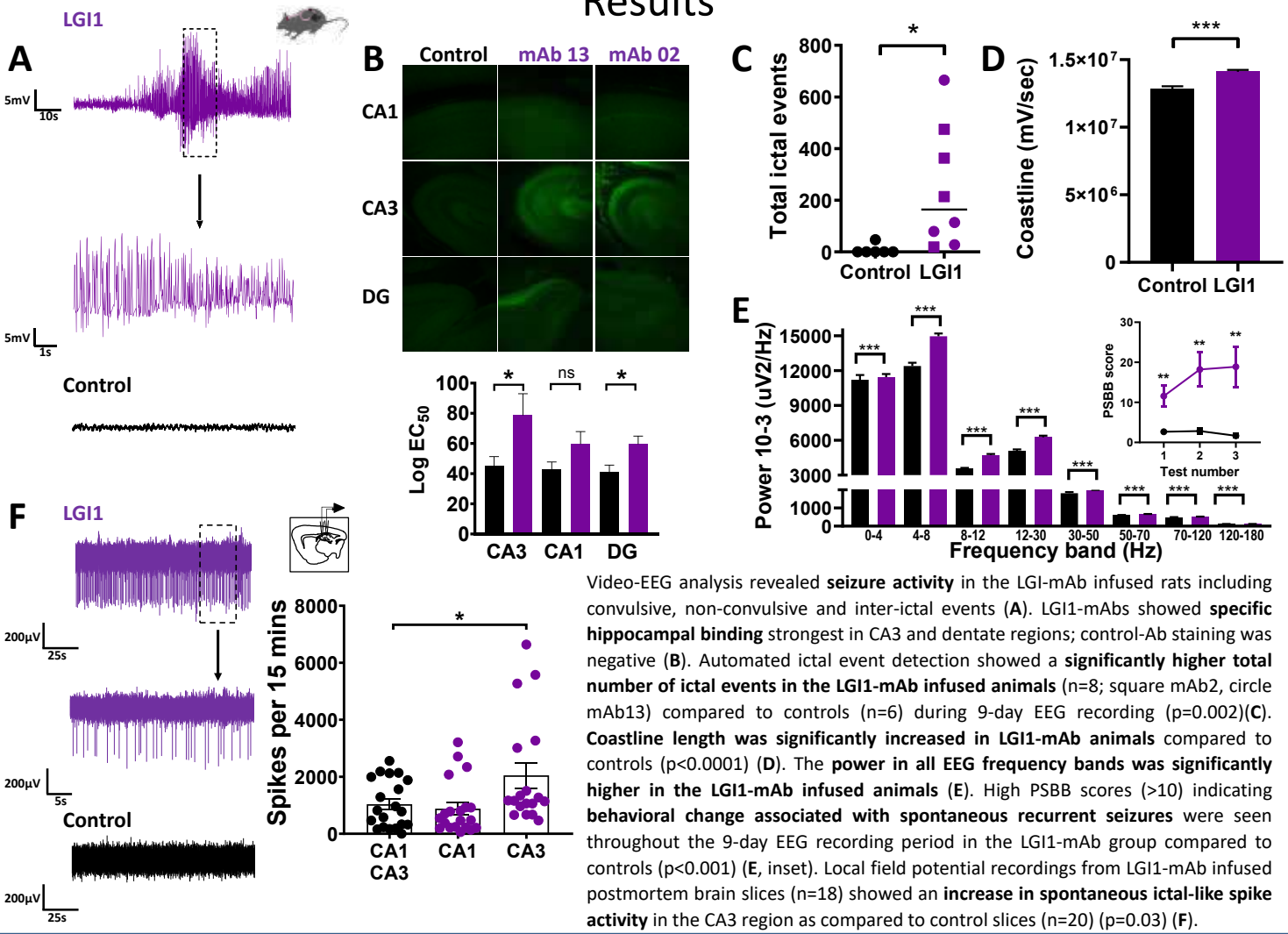
Background and methods





Autoantibodies to the leucine-rich glioma inactivated 1 (LGI1) protein are associated with **facio-brachial dystonic seizures** (FBDS), limbic encephalitis and cognitive impairment. Using **peripherally-derived human monoclonal LGI1 antibodies** (LGI1-mAbs) directed towards the two protein domains - **Leucine-Rich Repeat (LRR; mAb2) and Epitempin-repeat (EPTP; mAb13)** - we specifically explored the *in vivo* and *in vitro* epileptogenic effects using a **passive transfer** rodent model.

Results



Video-EEG analysis revealed **seizure activity** in the LGI-mAb infused rats including convulsive, non-convulsive and inter-ictal events (**A**). LGI1-mAbs showed **specific hippocampal binding** strongest in CA3 and dentate regions; control-Ab staining was negative (**B**). Automated ictal event detection showed a **significantly higher total number of ictal events in the LGI1-mAb infused animals** (n=8; square mAb2, circle mAb13) compared to controls (n=6) during 9-day EEG recording (p=0.002)(**C**). **Coastline length was significantly increased in LGI1-mAb animals** compared to controls (p<0.0001) (**D**). The **power in all EEG frequency bands was significantly higher in the LGI1-mAb infused animals** (**E**). High PSBB scores (>10) indicating **behavioral change associated with spontaneous recurrent seizures** were seen throughout the 9-day EEG recording period in the LGI1-mAb group compared to controls (p<0.001) (**E**, inset). Local field potential recordings from LGI1-mAb infused postmortem brain slices (n=18) showed an **increase in spontaneous ictal-like spike activity** in the CA3 region as compared to control slices (n=20) (p=0.03) (**F**).

Discussion

LGI1-Abs are associated with facio-brachial dystonic seizures, tonic-clonic and temporal lobe seizures in affected patients. Despite this strong epileptic phenotype, in previous animal models seizures were not seen. Using peripherally derived human monoclonal LGI1 antibodies infused into the CSF of juvenile Wistar rats, we have demonstrated that these antibodies *are* epileptogenic *in vivo*. This model will be used to facilitate research into novel therapies for affected patients.

Dr Tim J. Hartung

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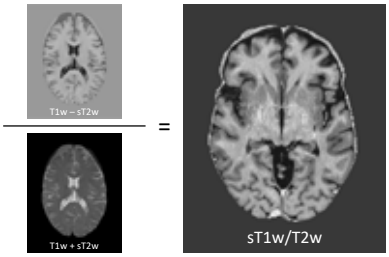
Dr Tim Hartung is investigating imaging markers of neuroimmunological diseases using methods such as resting-state and quantitative MRI. Coming from a background in psycho-oncology and clinical neurology, he has a keen interest in epidemiology and psychometrics. He holds degrees in psychology and philosophy (M.A., University of Cambridge) and medicine (M.D., Leipzig University).

The standardized T1-weighted/T2-weighted ratio as a biomarker of anti-NMDA receptor encephalitis

Tim J. Hartung, Graham Cooper, Valentin Jünger, Darko Komenic, Lara Ryan, Josephine Heine, Claudia Chien, Friedemann Paul, Carsten Finke

Method

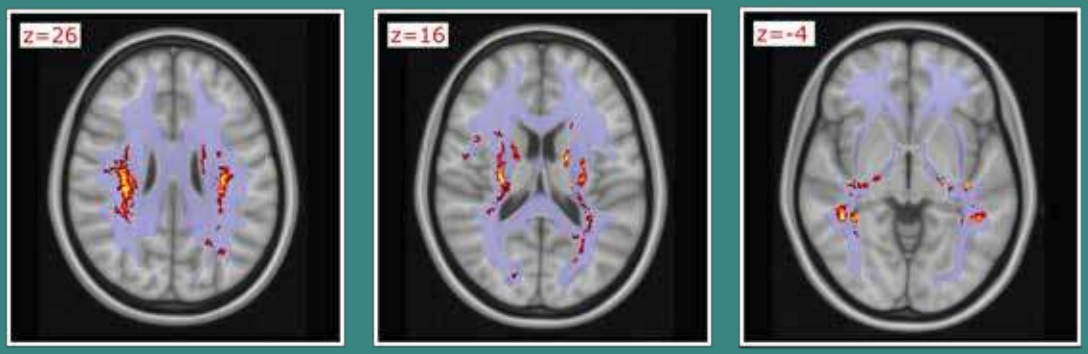
- sT1w/T2w ratio is calculated from standard clinical MRI
- No additional scanning time
- Standardized values across scanners and patients



Participants

- N = 53 patients with NMDARE
- Mean disease duration: 3.3 years
- All patients had cognitive deficits
- N = 53 sex- and age-matched controls

The **T1/T2 ratio** is a **biomarker** of **white matter damage** in **routine clinical MRI**



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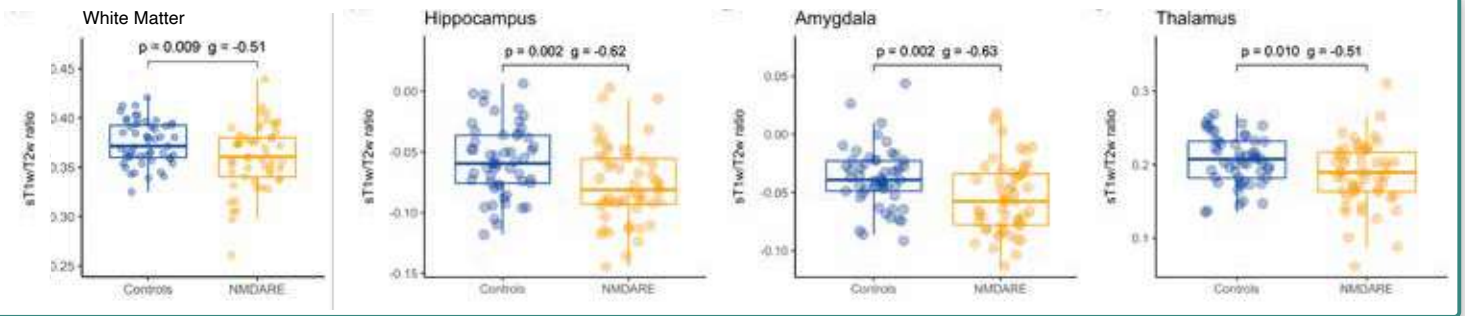
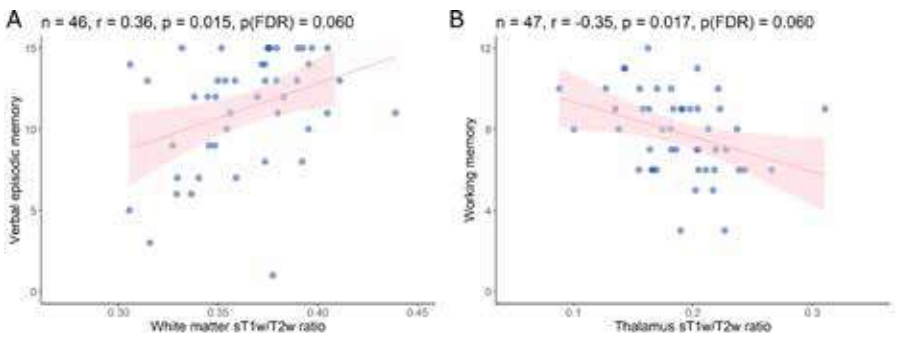


T1/T2 ratio correlates with cognitive impairment



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Dr V H Ganaraja is currently practicing as clinician- neurologist in Bangalore, India. Recently he completed five years of Neurology residency and training and one additional year of senior residency practice in National Institute of Mental Health and neurosciences (NIMHANS) Bangalore India. He got admission in this Institute for neurology training by securing 3rd rank in national level competitive examination. During his training period he developed keen interest in the field of Neuroinfections and chose to work on Tuberculosis meningitis and its cognitive outcome in long term follow-up as my dissertation topic. He has also completed Fellowship in European Board of Neurology recently (2021) and he has contributed to 28 publications in a period of five years, highlighting his commitment towards scientific world in addition to clinical learning.

ATYPICAL MANIFESTATIONS OF SUBACUTE SCLEROSING PANENCEPHALITIS: CASE SERIES

Ganaraja V H, Kavya Mala, Suresha Kodapala
Department of Neurology, Vydehi Institute of Medical Sciences and Research Centre, Bangalore.

INTRODUCTION

❖ Subacute Sclerosing Panencephalitis (SSPE) is a rare, progressive degenerative disease of the brain caused by reactivation of aberrant measles virus.
❖ It can occasionally present with varied atypical manifestations which makes diagnosis difficult.

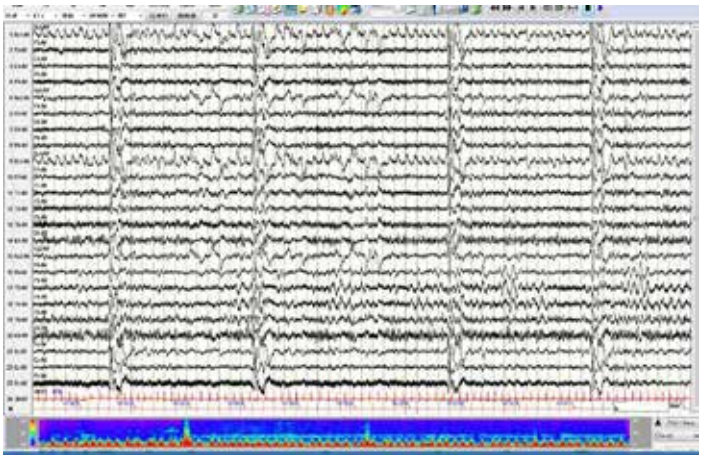
OBJECTIVE

❖ To report two patients with unusual manifestations of SSPE.

INVESTIGATIONS

❖Case 1:

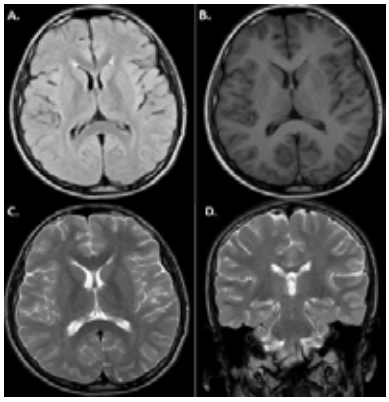
- 21-year-old man from Eastern India
- Presented with behavioral changes and memory disturbances of 1-year duration.
- Initially – reduced interest in interpersonal interactions, searching for his belongings in the wrong place.
- Gradual worsening of symptoms with development of involuntary jerky movements in both right upper and lower limbs.
- On examination – impairment of attention with relative preservation of other cognitive domains.
- Continuous slow myoclonic jerks in the right upper and lower limbs was present, mainly involving the right upper limb proximal joints which did not resolve with attempted distraction.
- Brain MRI showed diffuse cerebral atrophy with normal brain parenchyma.
- EEG revealed long interval frontally dominant generalized high amplitude periodic discharges time-locked with myoclonic jerks.



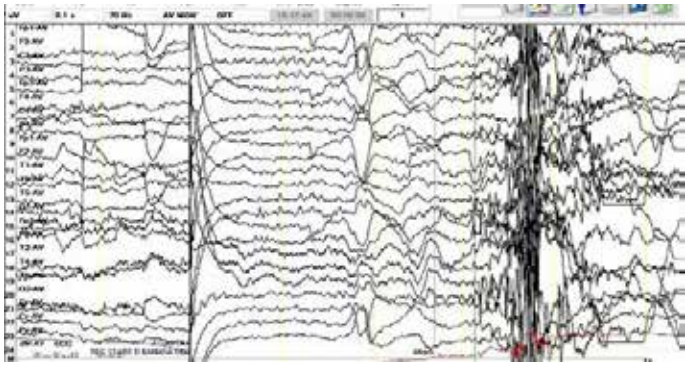
- CSF analysis showed acellurity with elevated protein (101.6 mg/dL) and glucose (69.18 mg/dL) with high titer of IgG antibodies to measles virus (1:625).
- Overall features were suggestive of subacute sclerosing panencephalitis.

❖Case 2:

- 14-year-old boy
- Presented with recurrent falls of 9 months duration
- The falls were abrupt, mainly observed while standing or walking, without any warning signs, and each episode lasted for 2-3 seconds followed by complete recovery with a frequency of 40-50 falls/day.
- This was demonstrated on clinical examination, with trunk extension and knee flexion during the fall. The patient fell mostly backwards and sometimes forwards.



- Brain MRI was normal with non-specific subcortical white matter signal changes.
- EEG showed periodic, long interval generalized bursts of high amplitude slow-wave discharges with corresponding clinical episodes of myoclonic jerks.



- CSF was acellular with mildly elevated protein (48mg/dL) and elevated glucose (64mg/dL) with high titer of IgG measles antibodies (1:625)
- Overall it was suggestive of SSPE.

CONCLUSION

❖ **Though SSPE presents with cognitive decline and myoclonic jerks, atypical presentations have to be kept in mind to make a swift diagnosis of this potentially fatal disease.**
❖ **SSPE is associated with a bad prognosis, however, early diagnosis and institution of appropriate treatment may help improve the quality of life in these patients.**

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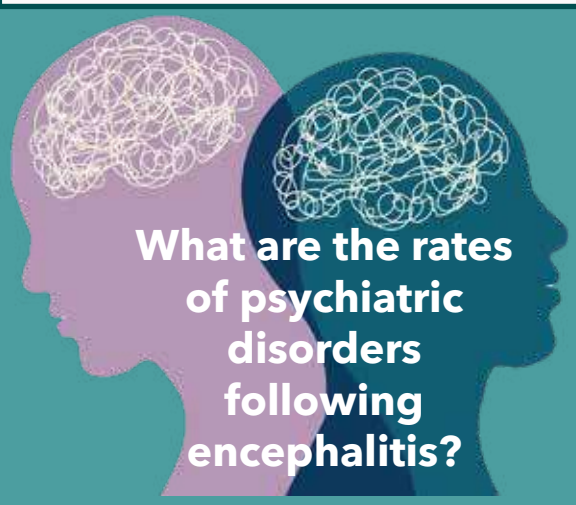
Dr Butler is a registrar in psychiatry and a clinical academic. He graduated with undergraduate medical and postgraduate research degrees from the University of Manchester before moving to work at South London and Maudsley mental health trust. He is a member of the Royal College of Psychiatrists and is currently based at the Institute of Psychiatry, Psychology and Neuroscience at King's College London researching neuropsychiatric disorders and psychopharmacology. He is due to start a Wellcome funded doctoral fellowship in 2023.

Mental health outcomes of encephalitis

An international web-based study



Method

We conducted a large online study of mental health outcomes following encephalitis

Sample

Mean age 50y; 65.8% female

Autoimmune	29.7%	Infectious	65.4%
Anti-NMDAR	9.3%	HSV	41.0%
Anti-LGI1	3.2%	VZV	4.7%
Anti-VGKC	1.5%	Tick-borne	2.0%
Anti-CASPR2	0.2%	EBV	0.7%
ADEM	3.4%	JEV	0.5%
Other	8.4%	Other	7.4%

Aetiology

No difference in symptom rates in autoimmune vs infective causes

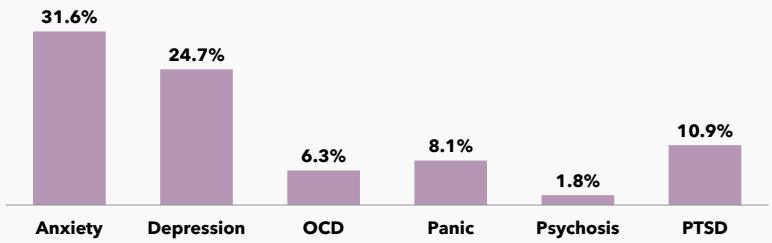
Access to care

53.5% reported poor access to mental healthcare

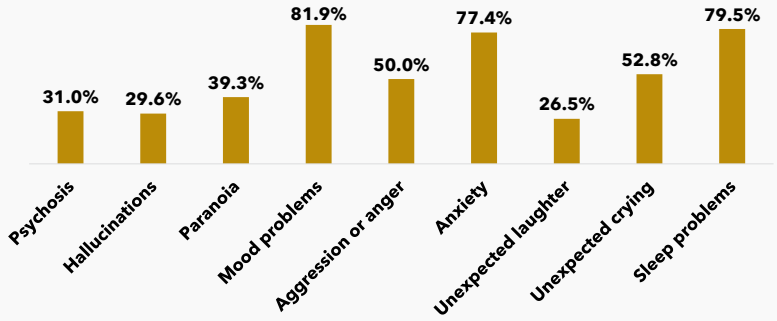
Hypersensitivity

78.5% had at least one (light, sound, etc) after encephalitis

Mental health diagnoses after encephalitis



Symptom prevalence after encephalitis



Suicide

37.5% had thought about, 4.4% had attempted

Misdiagnosis

47.2% felt they had been initially misdiagnosed

Misdiagnosis type:
Psychiatric illness 18.2%
Physical illness 66.0%

Summary

Psychiatric symptoms & hypersensitivities following encephalitis are common
Some disorders may be missed, and care provision may not be optimal

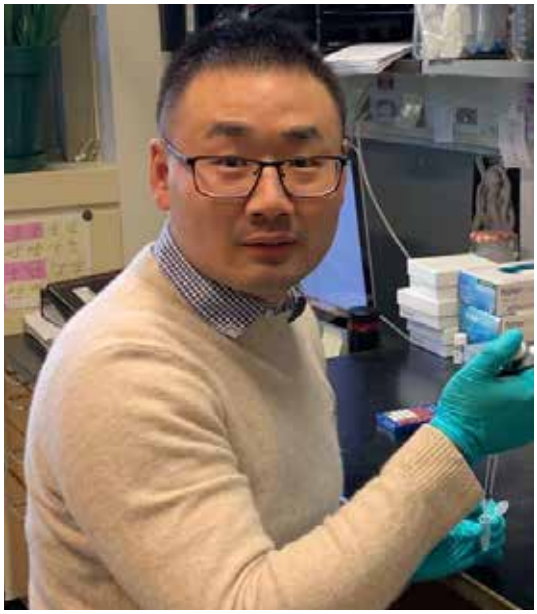
Recommendations

There is a need for increased provision of psychiatric care in this patent group

ENCEPHALITIS SOCIETY
The brain inflammation charity

Yasmin Abdat, Matt Butler, Michael Zandi, Ben Michael, Tim Nicholson, Ava Easton, Tom Pollak

KING'S College LONDON



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Zhiyong Liu majored in Pharmaceutical Engineering during his undergraduate studies from Shandong Normal University in China. And he received his PhD in immunology from Zhejiang University, working on the molecular mechanisms of antiviral innate immunity with mice models. To study antiviral immunity in natura, he joined Casanova Lab as a postdoctoral associate in early 2019. His work mainly focuses on discovering new genetic determinants of childhood herpes simplex virus encephalitis (HSE) and post-HSE autoimmune encephalitis, which are rare and life-threatening neurological diseases, and caused mainly by type I herpes virus (HSV-1) infection. Since the outbreak of coronavirus pandemic, Zhiyong has also been studying previous healthy young patients with life-threatening COVID-19, searching for host genetic variations that may explain their insufficient immunity to SARS-COV-2.

Encephalitis and poor neuronal death-mediated control of herpes simplex virus in human inherited RIPK3 deficiency

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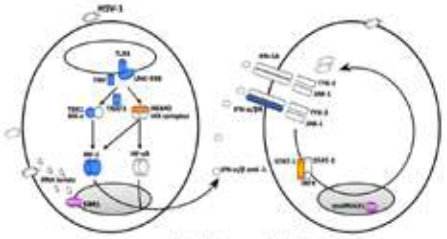
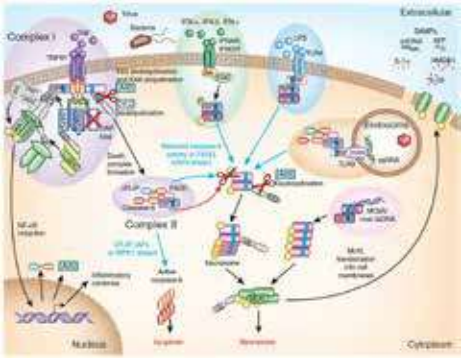
INTRODUCTION

Herpes simplex virus-1 (HSV-1) encephalitis (HSE) is a rare and life-threatening complication of HSV-1 infection. HSE is the most common sporadic viral encephalitis in Western countries occurring at a rate of 2-4 cases per million people every year. The pathogenesis of HSE remained elusive until our previous discoveries of the first 8 human genetic etiologies of isolated HSE. Except for *DBR1 and SNORA31*, mutations in other six genes, all involved in the TLR3-IFNAR1 circuit and have been found in some forebrain HSE patients. Mutations affecting the two connected pathways impair cortical neuron and oligodendrocyte cell-intrinsic type I IFN immunity to HSV-1. TLR3 pathway gene mutations impair tonic and dsRNA-inducible levels of type I IFNs, whereas IFNAR1 pathway gene mutations impair cellular responses to type I IFNs. Overall, HSE appears to result from inborn errors of CNS-resident cell-intrinsic antiviral immunity in at least 5-10% of children with this rare disease.



Hum Genet. 2020 Jun;139(6-7):911-918.

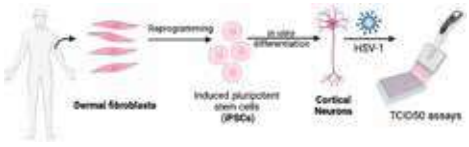
RIPK3 is a ubiquitous cytoplasmic serine/threonine protein regulating cell death outcomes, including apoptosis and necroptosis, which have been shown to be involved in host defense against herpesviruses, including HSV-1, in both cell culture and in mice. We hypothesize that RIPK3 deficiency may be HSE-causing due to impairment of RIPK3-dependent cell-death-mediated control of viral growth in CNS neurons.



Nat Immunol. 2015 Jul;16(7):689-97.

METHODS

- **Whole Exome Sequencing (WES) was used to identify candidate mutations in P1. and Sanger sequencing was used to confirm the *RIPK3* mutations.**
- **Western blotting, luciferase reporter assay, protein immunoprecipation and cell viability assay were used to investigate the biochemical characterization of the mutations.**
- **TOPO-TA cloning, RT-qPCR, Western blotting, cell viability assay and LegendPlex assays were used to investigate the cellular characterization with the patient cells.**
- **hPSCs-derived cortical neurons and TCID50 viral titration method was used to illustrate the causality between the clinical phenotypes and genotypes.**



CONCLUSION

- **P1 is an HSE patient carrying two compound heterozygous variants in *RIPK3* gene: nonsense (R422*) and frameshift (P493fs9*), which defines the first AR deficiency of RIPK3 in human and a novel genetic etiology of HSE.**
- **The two RIPK3 mutations lead to truncated forms of the RIPK3 proteins. RIPK3 R422* variant is loss of function in RIPK3-dependent cell death. The P493fs9* protein are prone to degradation.**
- **RIPK3 proteins were undetectable in P1's cells due to the nonsense mRNA-mediated decay of R422* and the instability of the P493fs9* protein.**
- **RIPK3-deficient dermal fibroblasts and hPSC-derived cortical neurons are highly susceptible to HSV-1 due to defective necroptotic and apoptotic cell death-dependent antiviral defense.**

ACKNOWLEDGEMENTS

We warmly thank the patient and her family; the members of the laboratory from both New York and Paris branches for their constructive advices. Tatiana Kochetkov for technical assistance; Erin Williams, Lazaro Lorenzo, Yelena Nemirovskaya, Dana Liu and Mark Woollett for administrative assistance. Many thanks to the patient and her family!

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RESULTS

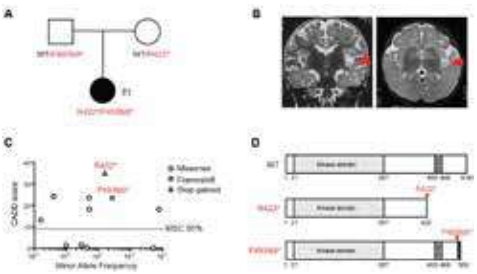

Figure 1. Compound heterozygous *RIPK3* mutations in a patient with HSE. A. Family pedigree with allele segregation of the two *RIPK3* mutations. The proband (patient 1, P1), in black, is compound heterozygous for the p.Arg422* (R422*) and p. Pro493fs9* (P493fs9*) mutations. Each parent is heterozygous for one mutant allele. **B**. Images of the brain of P1, showing lesions affecting the left insula. **C**. Graph showing the CADD scores of all homozygous RIPK3 nonsynonymous or essential-splicing variants reported by the gnomAD database, and their minor allele frequency (MAF). MSC 95%: mutation significance cutoff for a 95% confidence interval. **D**. Schematic representation of the structure of the RIPK3 protein and the impact of the two mutations.

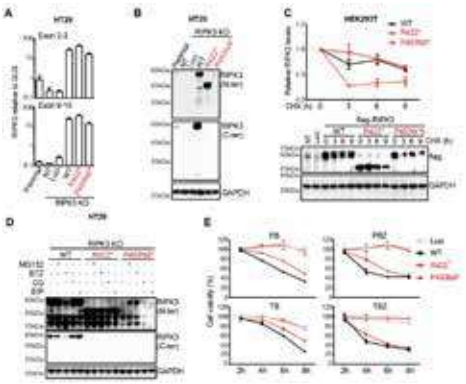

Figure 2. *In vitro* production and function of the RIPK3 variants after stable transduction in HT29 cells. A. *RIPK3* mRNA levels were determined by RT-qPCR in parental HT29 cells, or RIPK3 knockout (KO) HT29 cells left non-transfected (NT) or stably transfected with a mock vector (Luci) or with WT or mutant RIPK3 constructs in a lentiviral system. **B**. Immunoblotting analysis of RIPK3 protein levels in the parental HT29 cells, and in RIPK3 KO HT29 cells, as in (**A**). **C**. Pulse-chase analysis to measure WT and mutant RIPK3 protein degradation. HEK293T cells were transfected with FLAG-tagged WT and mutant RIPK3 plasmids and treated with cycloheximide (CHX) and subjected to WB (lower panel). **D**. Immunoblotting analysis of RIPK3 levels in RIPK3 KO HT29 cells stably expressing WT and mutant RIPK3, treated with protein degradation inhibitors (5 nM bortezomib (BTZ) for 12 h, 10 mM MG132, 50 mM chloroquine diphosphate (CQ), or 10 mg/mL E64d plus 10 mg/mL pepstatin) for 6 h. The red asterisk indicates the bands corresponding to RIPK3. **E**. Viability of RIPK3$^{-/-}$ HT29 cells stably expressing WT and mutant RIPK3 constructs, treated with PB (poly(I:C) + BV6), TB (TNF + BV6), PBZ complex (consisting of poly(I:C), BV6 and Z-VAD), or TBZ complex (containing TNF, BV6 and Z-VAD) for the indicated times.

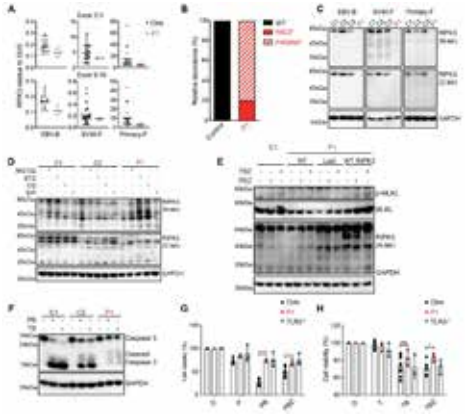

Figure 3. Impaired RIPK3 production and function in P1's cells. A. *RIPK3* mRNA levels were measured by RT-qPCR in EBV-B cells (EBV-B), SV40-fibroblasts (SV40-F) and primary fibroblasts (Primary-F) from healthy controls (Ctrls) and P1. **B**. Relative abundance of the RIPK3 cDNA generated from mRNA from P1 SV40-F assessed by TOPO-TA cloning. **C**. Immunoblot analysis of endogenous RIPK3 levels in EBV-B, SV40-F and Primary-F from healthy controls (C1, C2, C3) and P1. **D**. Immunoblot analysis of endogenous RIPK3 levels in SV40-F from healthy controls (C1, C2) and P1 treated with protein degradation inhibitors. The red asterisks indicates the bands of RIPK3. **E**. Immunoblot analysis of p-MLKL levels in SV40-F from a healthy control (C1) and P1, either left non-transfected (NT) or transiently transfected with Luci or WT RIPK3, and then stimulated with PBZ or TBZ. The red asterisks indicates the bands of RIPK3. **F**. Immunoblot analysis of caspase 3 in SV40-F from healthy controls and P1, treated with PB or TB complex. **G**. Viability of primary fibroblasts from healthy controls (Ctrls), P1 and a TLR3$^{-/-}$ HSE patient, treated with DMSO solvent (D), or with poly(I:C), PB, or PBZ complex. **H**. Viability of primary fibroblasts from healthy controls, P1 and a TLR3$^{-/-}$ patient, treated with DMSO solvent (D), TNF, TB, or TBZ complex.

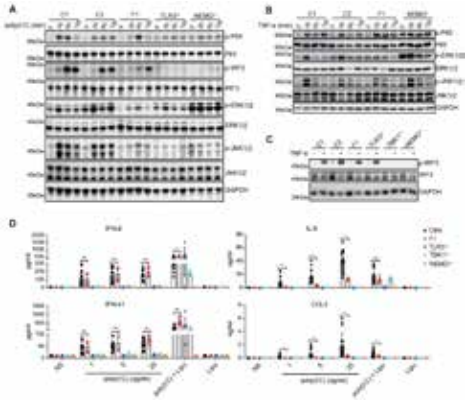

Figure 4. Intact signaling via the TLR3- and TNFR1-dependent NF-κB, IRF3 and MAPK pathways in P1 fibroblasts. A. Immunoblot analysis of total and phosphorylated P65, IRF3, ERK1/2 and JNK1/2 in SV40-F from healthy controls (C1, C2), P1, TLR3$^{-/-}$ and NEMO$^{-/-}$ patients, after stimulation with 25 μg/ml poly(I:C) for the indicated times. The results shown are representative of three independent experiments. **B**. Immunoblot analysis of total and phosphorylated P65, ERK1/2 and JNK1/2 in SV40-F from healthy controls, P1 and a NEMO$^{-/-}$ patient, after stimulation with 20 ng/ml TNF for the indicated times. The results shown are representative of three independent experiments. **C**. Immunoblot analysis of total and phosphorylated IRF3 in SV40-F from healthy controls, P1, TLR3$^{-/-}$, TBK1$^{-/-}$ and NEMO$^{-/-}$ patients, after stimulation with 20 ng/ml TNF for 24 h. The results shown are representative of three independent experiments. **D**. SV40-F from healthy controls (Ctrls, *n*=3), P1 and TLR3$^{-/-}$, TBK1$^{-/-}$ and NEMO$^{-/-}$ HSE patients were left unstimulated (NS) or were stimulated with various doses of poly(I:C) alone, Lipofectamine alone (Lipo), or both (poly(I:C)+Lipo), for 24 h. The amounts of IFN-β, IFN-λ1, IL-6 and CCL3 in culture supernatants were determined with Legendplex cytometric bead arrays.

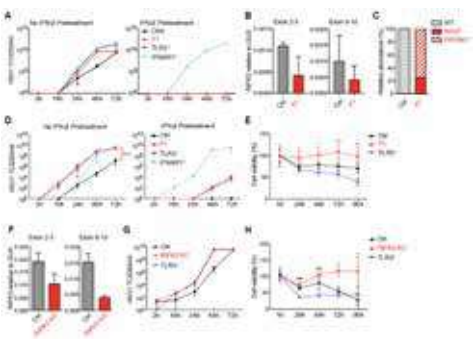

Figure 5. Enhanced susceptibility of *RIPK3*-deficient fibroblasts and hPSC-derived cortical neurons to HSV-1. A. SV40-F from healthy controls (Ctrls), P1 and other HSE patients with AR TLR3 or IFNAR1 deficiencies were left untreated or were pre-treated with IFN-β for 24 h, then infected with HSV-1 (MOI =0.001) and virus replication levels measured by the $TCID_{50}$ virus titration method. **B**. *RIPK3* mRNA levels, as measured by RT-qPCR, in cortical neurons differentiated from the hPSCs of healthy controls and P1. **C**. Relative abundance (in percentages) of the RIPK3 cDNA generated from mRNA extracted from hPSC-derived cortical neurons from a healthy control and P1, assessed by TOPO-TA cloning. **D**. hPSC-derived cortical neurons from healthy controls, P1 and other HSE patients with AR TLR3 or IFNAR1 deficiencies, with or without IFN-β pretreatment and were infected with HSV-1 and virus replication levels measured as in **(A)** . **E**. Viability of hPSCs-derived cortical neurons from a healthy control, P1 and a TLR3$^{-/-}$ HSE patient, left not infected (NI), or infected with HSV-1 (MOI=0.001). **F**. *RIPK3* mRNA levels, as measured by RT-qPCR in cortical neurons from parental and *RIPK3* KO hPSCs. **G**. hPSC-derived cortical neurons from parental healthy control cells, *RIPK3* KO cells and HSE patients with AR TLR3 were infected with HSV-1. HSV-1 replication was quantified as in **(A)** . **H**. Viability of hPSC-derived cortical neurons from parental healthy control cells, *RIPK3* KO cells and a TLR3$^{-/-}$ HSE patient, left not infected, or infected with HSV-1 (MOI=0.001) for the indicated times.

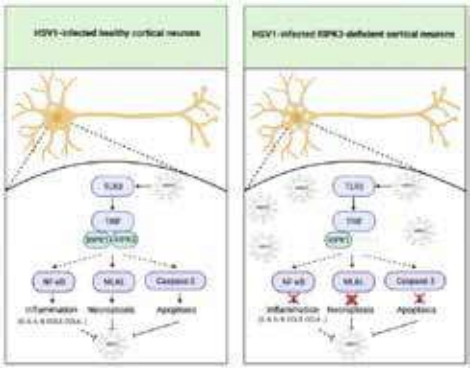

Figure 6. Proposed working model for human inherited RIPK3 deficiency underlying the etiology of HSE. On the left panel, the healthy neurons could defense HSV1 infection efficiently via RIPK3-dependent necroptosis, apoptosis and proinflammatory cytokines induction in the downstream of TLR3. On the right panel. in RIPK3-deficient cortical neurons during HSV-1 infection, necroptosis is completely abolished. Meanwhile, apoptosis and proinflammatory cytokines induction were impaired. These defects result in the out of control for HSV1 replications in the cells and might underlie the clinical phenotype of the patient.

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Dr. Rodelia C. Pascua is a graduating Neurology Resident from Baguio General Hospital and Medical Center. She has been interested in Neuroimmunology, specifically in Multiple Sclerosis and Autoimmune Encephalitis since she was a first-year resident, and she plans to do further studies after her graduation. But first, she is working in Research, Epidemiology and Public Health in Neurology. Her institution has completed a case series report of all established cases of autoimmune encephalitis and prospective studies regarding the impact and duration of therapy and outcomes, direct and indirect costs of the whole treatment are in place. Her plan is to collaborate with other institutions for a multicentre epidemiologic study of autoimmune encephalitis in her country.

CLINICAL SPECTRUM AND MANAGEMENT OF ANTI-NMDA RECEPTOR ENCEPHALITIS AMONG FILIPINO ADULTS

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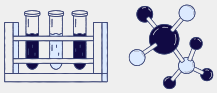
INTRODUCTION

The typical course of Anti-NMDAR encephalitis includes a prodromal phase of nonspecific symptoms in the first week, followed by psychiatric manifestations and seizures. Most of the patients will undergo the third stage of unresponsiveness that necessitates intensive care because of hypoventilation, autonomic dysregulation, abnormal movements or dyskinesias, and even coma. And finally, the recovery phase where deficits are observed to be prolonged until their full recovery.



DISCUSSION

In developing countries like the Philippines where there is a lack of access to a comprehensive initial work-up for autoimmune encephalitis, this condition is based highly on clinical findings of the patient. Although Anti-NMDAR encephalitis tends to have a phasic progression based on the different symptoms and duration, here, we were able to note that the clinical spectrum is still varied and depends on each patient. Only one patient had viral-like prodrome and all of the first psychiatric manifestations were present in the first week which persisted up to 4-6 weeks. Moreover, during this phase, all of our patients were simultaneously exhibiting autonomic instability and central hypoventilation and only five recovered. As such, the psychiatric phase may overlap with the unresponsive phase which may last for more than 6 weeks to months. All of them received the first-line treatment of high-dose steroid and IVIg, four were given Rituximab infusion. Medications given for different symptoms like dyskinesias, autonomic dysfunction, and seizures were individualized based on the other concomitant medical condition of each patient.

OBJECTIVE

To describe the clinical spectrum of Anti-NMDAR encephalitis among Filipino Adults in a tertiary hospital

METHODOLOGY

Unicenter, cross-sectional study using total enumeation of all confirmed adult Filipino cases

RESULTS/FINDINGS

- Seven (7) confirmed adult Filipino cases of Anti-NMDAR encephalitis admitted in our institution in June 2016-June 2022
- The mean age is 24 years old, with 5:2 female to male ratio with a median length of hospitalization of 36 days
- All patients presented with acute psychiatric symptoms, focal and generalized seizures, hypoventilation, dyskinesias, and autonomic instability
- Six patients needed airway support, two had refractory epilepsy, one had persistent chorea and orofacial dyskinesia.
- Imaging studies of the brain included contrast-enhanced CT and MRI showed unremarkable findings.
- CSF analysis revealed positive for the antibodies, while CSF lymphocytic pleocytosis was only seen in two patients while protein elevation in 6/7
- They underwent electroencephalogram (EEG) studies which revealed diffuse delta-theta slowing without epileptiform discharges with one with extreme delta brush who presented with persistent chorea and orofacial dyskinesias
- They all received high-dose steroid; only four patients were able to undergo Rituximab infusion

CONCLUSION

Anti-NMDAR encephalitis involves a wide spectrum of clinical manifestations such that proper recognition and diagnosis and management is tantamount to better outcomes.

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