ENCEPHALITIS CONFERENCE

2025

Poster Booklet

3RD – 4TH DECEMBER
ROYAL COLLEGE OF PHYSICIANS, LONDON AND VIRTUALLY

KEYNOTE SPEAKERS:

- **Dr Nicoline Schiess,** World Health Organization
  "WHO Technical Brief on Encephalitis: Way Forward"

- **Prof Romana Höftberger,** Medical University of Vienna, Austria
  "Contributions of Pathology to the Understanding of Antibody-mediated Neurological Diseases"

GUEST SPEAKERS:

- **Prof Tom Solomon CBE**, The Pandemic Institute, Academy of Mecical Sciences & University of Liverpool, UK
  "EAN-ESCMID Guidelines on the Diagnosis and Management of Encephalitis in Adults Caused by Infection"

- **Dr Andreas Pilz,** Pfizer Corporation, Austria
  "Tick-borne Encephalitis (TBE) – From Epidemiology to Vaccination – Where Do We Stand?"

Encephalitis International
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Dr Alessandro Santagostino Barbone

University of Genoa, Italy & Evelina London Children's Hospital at Guy's and St Thomas' NHS Foundation Trust, UK

Brain 18F-FDG Positron Emission Tomography (PET) findings in NMDA receptor antibody encephalitis: an individual patient data meta-analysis

Dr Alessandro Santagostino Barbone is a paediatric neurology resident at the University of Genoa, currently training at the Gaslini Institute, a tertiary paediatric referral centre in Italy. Alessandro has recently completed a clinical and research fellowship in neuroinflammation at Evelina Hospital, London, under Prof. Ming Lim. During his residency, his interest in neuroimmunology has grown through direct clinical experience, participating in the diagnosis and management of children with complex neuroimmune diseases, including autoimmune encephalitis, which are highly relevant in the pediatric setting.
His academic focus is on neuroimmune disorders in children and adolescents, with particular exposure to complex cases of autoimmune and infectious encephalitis. While still in training, his career goal is to contribute to international research in paediatric neuroimmunology and to pursue doctoral studies at an international institution to deepen his expertise. The Encephalitis Conference 2025 represents a unique opportunity to expand his knowledge of advances in the diagnosis and management of encephalitis, while also strengthening links with colleagues and centres worldwide, fostering collaborations essential for his future clinical and research development.

META-ANALYSIS OF ^{18}F-FDG PET INDIVIDUAL PATIENT REPORTS IN NMDA RECEPTOR ANTIBODY ENCEPHALITIS

Alessandro Santagostino Barbone[1,2], Margherita Nosadini[3], Ming Lim[2,4], Michael Eyre[2,5]

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BACKGROUND

^{18}F -fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) is frequently abnormal in anti–N-methyl-D-aspartate receptor encephalitis (NMDARE), but reported abnormalities are variable[1], and mainly derived from case reports. We carried out an individual patient data meta-analysis of 59 reports with the aim of defining regional metabolic patterns and examining associations with clinical variables and outcome

METHODOLOGY

- Eligibility: A systematic search in PubMed was conducted. Publications describing acute-phase ^{18}F-FDG PET abnormalities in anti-NMDAR encephalitis were included.
- PET analysis: Regional hyper- and hypometabolism were scored across nine cortical and subcortical regions.

Cluster analysis:
- Multiple correspondence analysis (MCA) with k-means clustering were used to identify metabolic subgroups.
- Optimal MCA dimensions were selected by scree plot elbow; optimal number of clusters by maximising silhouette score.

Outcome definition: Poor outcome was defined as mRS 2-6 after at least 12 months follow-up

Statistical modelling:
- Two multivariable logistic regression models were fitted with poor outcome as the dependent variable:
- Model 1: evaluated k-means cluster assignments as independent predictors of poor outcome.
- Model 2: evaluated number of hypometabolic and hypermetabolic regions as independent predictors of poor outcome.
- Both were adjusted for NEOS[2] covariates: ICU admission, No clinical improvement after 4 weeks, No treatment within 4 weeks, CSF WBC count >20/µL, Abnormal brain MRI

RESULTS

122 patients (29 children, 60% female) were included from 59 publications. PET abnormalities were reported in 121/122 (99%) patients. Hypermetabolic regions were identified in 80/122 (66%) (Figure 1A) and hypometabolic regions in 98/122 (80%) (Figure 1B); 56/122 (46%) had both hyper- and hypometabolic abnormalities.

Characteristic	Value
Median age (IQR)	24 years (18–33)
Children (<18 yrs)	29/122 (24%)
Female sex	70/116 (60%)
Tumour detected	22/100 (22%)
Abnormal EEG	54/64 (84%)
Abnormal MRI	45/113 (40%)
Hypermetabolism	80/122 (66%)
Hypermetabolism	98/122 (80%)

Age-stratified analysis:
- Temporal hypermetabolism observed in 6/29 (21%) children vs 48/93 (52%) adults (p=0.003).
- Temporal hypometabolism observed in 15/29 (52%) children vs 24/93 (26%) adults (p=0.009).

Cluster analysis identified three metabolic phenotypes (Figure 2):
1. Cluster 1 (predominantly hypermetabolic, n=20)
2. Cluster 2 (mixed, n=92)
3. Cluster 3 (predominantly hypometabolic, n=10)

- **Cluster 3** patients were **younger** (median 18.5 years [IQR 9–27.75])
- None of the Cluster 1 patients showed limbic MRI abnormalities, compared to 30% of the Cluster 3 patients (p=0.011).

Multivariable logistic regression
- **Cluster 3** showed increased odds of **poor outcome** (adjusted OR 43.3, 95% CI 1.7–1072, p=0.021).
- A higher number of **hypometabolic** regions independently **predicted poor outcome** (OR 1.65, 95% CI 1.04–2.59, p=0.032).

Figure 1A : PET hypermetabolism according to brain region

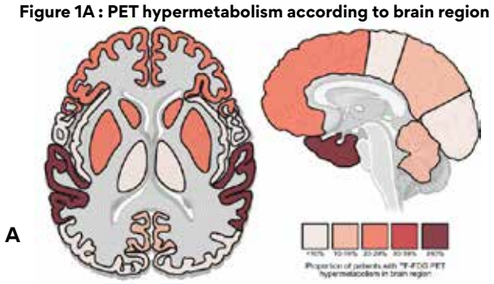

FIG 1A. Hyper: temporal, basal ganglia and prefrontal were the most frequently abnormal regions

Figure 1B : PET hypometabolism according to brain region

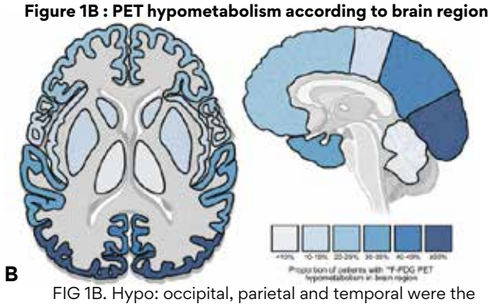

FIG 1B. Hypo: occipital, parietal and temporal were the most frequently abnormal regions

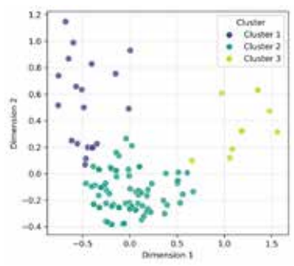

Figure 2A: PET cluster analysis; MCA with clusters

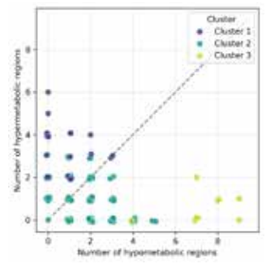

Figure 2B: PET cluster analysis; metabolic pattern distribution

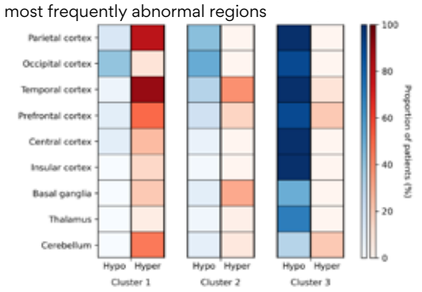

Figure 2C: PET cluster analysis; regional patterns by cluster

CONCLUSIONS

- ^{18}F-FDG PET abnormalities are frequent in anti-NMDAR encephalitis, distinct from MRI abnormalities, and show age-related patterns
- Predominant hypometabolism is independently associated with worse outcomes.
- PET provides clinically relevant information beyond MRI and NEOS, supporting its potential as a prognostic biomarker in NMDARE.

1. Yuan L, Mao G, Zhang Y, et al. Typical metabolic pattern of (18)F-FDG PET in Anti-NMDAR encephalitis in the acute and subacute phases and its correlation with T2 FLAIR-MRI features. BMC Neurosci. England; 2023;24:51.
2. Balu R, Mccracken L, Lancaster E, Graus F, Dalmau J, Titulaer MJ. A score that predicts 1-year functional status in patients with anti-NMDA receptor encephalitis. Neurology. 2019;92:E244–E252.

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Dr Alexandra Shade-Silver

Kings County Hospital, USA

The diagnostic dilemma of neuropsychiatric manifestations in an adolescent

Dr Alexandra Shade-Silver is a currently child neurology resident at SUNY Downstate Medical Center and Kings County Hospital. She is currently completing her second year of residency. She graduated medical school from Trinity College Dublin School of Medicine in Dublin, Ireland and has a Masters of Science Degree from Columbia University in New York City, New York, USA.

The Diagnostic Dilemma of Neuropsychiatric Manifestations in an Adolescent

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INTRODUCTION

Rationale:
Neuropsychiatric symptoms in adolescents can present a diagnostic challenge due to the overlap of many neurological and psychiatric conditions. This case highlights the complexities of reaching an appropriate diagnosis in an adolescent presenting with unusual neuropsychiatric manifestations and generalized weakness.

Objective:
To explore the diagnostic journey and management of a challenging neuropsychiatric case, emphasizing the role of multidisciplinary care and rapid immunotherapy initiation.

CASE PRESENTATION

A 17-year-old young lady presented with diverse and unusual symptoms: autonomic instability (tachypnea, tachycardia and hypertension to 180's systolics, excess salivation), visual and auditory hallucinations, night terrors, anxiety, nystagmus, ptosis, and upper motor neuron signs (stimulus-induced myoclonus, lower extremity rigidity, hyperreflexia and clonus). Physical exam revealed bilateral conjunctival injection, unilateral ptosis of the left eye, mild posterior pharyngeal erythema, tender left cervical lymphadenopathy, maculopapular rash on right medial thigh, left sided tremor, and impaired coordination.

DIAGNOSTIC APPROACH

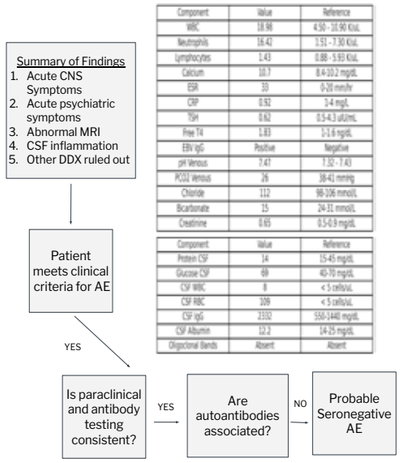
CSF Testing: No albumin-cytological dissociation. Negative meningoencephalitis panel, normal protein and glucose

MRI Brain: Symmetric multifocal areas of cortical signal enhancement in both cerebral hemispheres(possible encephalitis or atypical PRES).

Autoimmune Analysis: Seronegative including: anti-NMDA, anti-MOG, anti-GQ1b, anti-CASPR2 antibodies, oligoclonal antibodies, ANA, systemic immune antibodies

Positive Findings: Elevated urine normetanephrine and plasma metanephrines (initial concern for pheochromocytoma, later ruled out). Mild WBC elevation in CSF

Diagnostic Dilemma: Despite the absence of conclusive serological markers for autoimmune encephalitis, the patient's symptoms strongly pointed to an autoimmune pathology.



Component	Value	Reference
WBC	18.98	4.50 - 10.90 K/uL
Neutrophils	16.42	1.91 - 7.30 K/uL
Lymphocytes	1.43	0.88 - 5.93 K/uL
Calcium	10.7	8.4-10.2 mg/dL
ESR	10	0-20 mm/hr
CRP	0.92	1-4 mg/L
TSH	0.62	0.5-4.3 uIU/mL
Free T4	1.83	1-1.6 ng/dL
EBV IgG	Positive	Negative
pH Venous	7.47	7.32 - 7.43
PCO2 Venous	26	38-42 mmHg
Chloride	112	98-106 mmol/L
Bicarbonate	15	24-31 mmol/L
Creatinine	0.65	0.5-0.9 mg/dL

Component	Value	Reference
Protein CSF	14	15-45 mg/dL
Glucose CSF	69	40-70 mg/dL
CSF WBC	8	< 5 cells/uL
CSF RBC	109	< 5 cells/uL
CSF IgG	2332	550-1440 mg/dL
CSF Albumin	12.2	14-25 mg/dL
Oligoclonal Bands	Absent	Absent

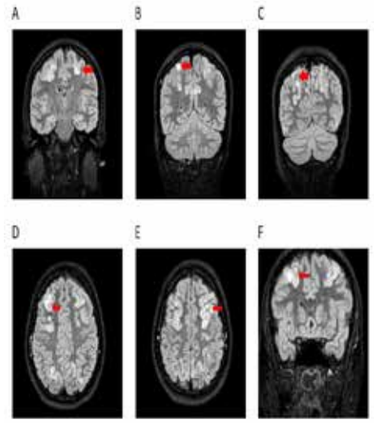


Figure 1. MRI Brain Images of a 17-year-old Female with Bilateral Proptosis and Hypertensive Emergency (6/23/2023).
A-F. Coronal and axial FLAIR-weighted MRI images demonstrate multifocal areas of T2 and FLAIR hyperintensities involving the parasagittal anterior, frontal, parietal, and occipital lobes bilaterally. The insula is more prominently involved on the left side (as seen in images C and D). The hyperintensities do not show restricted diffusion, consistent with a diagnosis of posterior reversible encephalopathy syndrome (PRES).

Component	Result
NMDA Receptor Antibody	Negative
Anti-MOG Antibody	Negative
Anti-GQ1b Antibody	Negative
Anti-CASPR2 Antibody	Negative
Anti-LGI1 Antibody	Negative
NMO (Neuromyelitis Optica)	Negative
Myelin Oligodendrocyte Glycoprotein (MOG)	Negative

MANAGEMENT AND RESPONSE

Initial Treatment:
Immunotherapy: Intravenous Immunoglobulin (IVIG) and corticosteroids were initiated on Day 3 to address suspected autoimmune encephalitis.
Respiratory Support: Intubation for respiratory failure due to autonomic dysfunction and potential central nervous system involvement.

Clinical Course:
Day 4: Extubated, showed improvement in ptosis, but developed spasticity, hyperreflexia, and clonus.
Repeat MRI on Day 5: Resolution of multifocal hyperintensities.
Further improvement following IVIG treatment, confirming diagnosis of autoimmune encephalitis.

DISCUSSION

The diagnostic criteria for seronegative autoimmune encephalitis (AE), proposed by *Graus et al.*, includes subacute onset of memory deficits, altered mental status and/or psychiatric symptoms, along with supportive evidence from CSF analysis, MRI, or the patient's response to immunotherapy following reasonable exclusion of other causes [1]. In this case, the patient's CSF showed elevated white blood cells, indicating inflammation, but was negative for common autoimmune or infectious biomarkers. Symmetric multifocal cortical signal abnormalities on MRI suggested possible encephalitis or atypical PRES [2]. Lack of structural findings on imaging distinguished AE from neoplasm, vasculitis and other structural entities such as CLIPPERS [1]. The diverse presentation of clinical symptoms in the absence of serologic confirmation makes the diagnosis of AE very challenging, but negative antibody panels do not rule out disease. Approximately 50% of cases can be seronegative.

The response to treatment with careful documentation of signs and symptoms was the key to diagnosis. The management of AE involves prompt initiation of immunotherapy to mitigate the immune response attacking the brain [1]. In cases where patients do not respond to the first-line treatments, second-line therapies such as rituximab or cyclophosphamide may be considered. These agents target specific components of the immune system and may be effective in refractory cases [1].Our patient did well with first-line agents, but soon developed a second attack several weeks later. This resolved with desired treatment of IVIG and corticosteroids. Monthly scheduled doses for recurrent symptoms yielded excellent results. Shared decision-making, taking into account the disease severity, possible side effects, and overall health status of the patient should guide treatment.

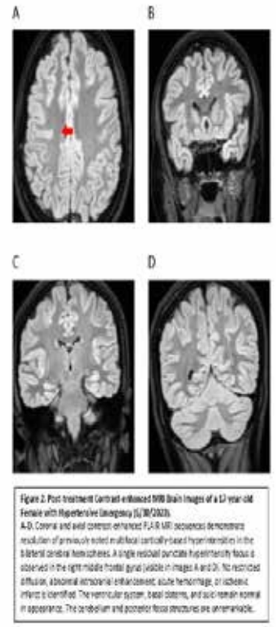


Figure 2. Post-treatment Contrast-enhanced MRI Brain Images of a 17-year-old Female with Hypertensive Emergency (6/30/2023).
A-D. Coronal and axial contrast-enhanced FLAIR MRI sequences demonstrate resolution of previously noted multifocal cortically-based hyperintensities in the bilateral cerebral hemispheres. A single residual punctate hyperintensity focus is observed in the right middle frontal gyrus (visible in images A and D). No restricted diffusion, abnormal intracranial enhancement, acute hemorrhage, or ischemic infarct is identified. The ventricular system, basal cisterns, and sulci remain normal in appearance. The cerebellum and posterior fossa structures are unremarkable.

CONCLUSION

This case underscores the importance of recognizing the diverse presentations of AE and the need for a high index of suspicion, especially in seronegative cases. Clinicians should rely on clinical judgment, supported by imaging and CSF findings, and initiate prompt immunotherapy for best patient outcomes in suspected cases.

Clinical Relevance: This case emphasizes the importance of considering autoimmune causes in neuropsychiatric cases and the role of a multidisciplinary approach in managing such cases.

REFERENCES

1. Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis. *The Lancet Neurology*. 2016;15(4):391-404. doi:10.1016/S1474-4422(15)00401-9
2. Cellucci T, Van Mater H, Graus F, et al. Clinical approach to the diagnosis of autoimmune encephalitis in the pediatric patient. Neurol Neuroimmunol Neuroinflamm. 2020;7(2):e663. doi:10.1212/NXI.0000000000000663

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Dr Alexis García-Sarreón

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Antibody testing in autoimmune encephalitis and paraneoplastic neurological syndromes: aligning clinical suspicion with diagnostic yield

Dr Alexis García is a Clinical Research Fellow in Neuroimmunology at Hospital Santa Caterina and Hospital Josep Trueta in Girona, Spain. His research focuses on the characterization and treatment of neuroinflammatory disorders, including autoimmune encephalitis, multiple sclerosis (MS), neuromyelitis optica spectrum disorder (NMOSD), and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD). He has specialized expertise in biomarker analysis, including ELISA, SIMOA, ELLA, and kappa free light chain (KFLC) quantification, as well as the statistical evaluation of large-scale clinical datasets to identify prognostic and therapeutic predictors in MS. His work supports the development of predictive models for severe neuroimmunological disease courses and the refinement of intravenous immunoglobulin (IVIG) treatment strategies. Before his current position, Dr García trained as a Multiple Sclerosis and Neuroimmunology Fellow at CEMCAT (Vall d'Hebron, Barcelona), where he studied cerebrospinal fluid and serum biomarkers associated with MS progression and participated in the clinical management of complex neuroinflammatory cases. Dr García is committed to enhancing patient care in neuroimmunology through methodical clinical research and collaborative multidisciplinary approaches.

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Antibody Testing in Autoimmune Encephalitis and Paraneoplastic Neurological Syndromes: Aligning Clinical Suspicion with Diagnostic Yield

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Background

- Neuronal and glial antibody panels are pivotal in diagnosing autoimmune encephalitis (AE) and paraneoplastic neurological syndromes (PNS).
- Their growing use, however, raises questions about cost-effectiveness and specificity when clinical suspicion is low.
- We therefore examined how frequently real-world requests align with clinical suspicion and which bedside variables

Methods

- We retrospectively reviewed 226 consecutive requests for neuronal/glial antibodies (March 2022 – March 2024).
- Each case was classified as high, intermediate or low pre-test probability of AE/PNS using established criteria, complemented by a "flexible clinical reasoning" category reflecting real-world uncertainty (table 1).
- Multivariable logistic regression identified independent predictors of (i) a final AE/PNS diagnosis and (ii) seropositivity. Additional models explored factors guiding the decision to submit paired serum + CSF.

Table 1. Clinical classification of antibody test requests.

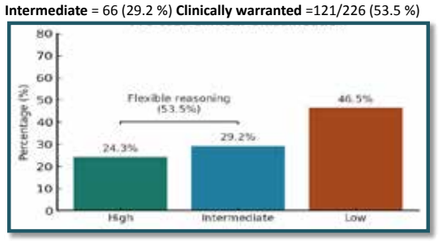
	Risk Tier	Definition
Flexible clinical reasoning	**High/ Strict criteria**	Meets possible AE [1] or high-risk PNS phenotype [2]
	Intermediate	Does not meet strict criteria but judged warranted due to atypical evolution, mixed features, or inconclusive ancillary tests (e.g., intermediate PNS phenotypes[2] or some AE clinical/paraclinical clues not fulfilling full diagnostic criteria[1]).
	Low	The remaining cases, considered low likelihood based on clinical judgment.

Results:

Figure 1. Pre-test assessment

Variable	Value
Median age, years (IQR)	63 [47–73]
Male sex	136 (60%)
Symptom onset to first contact, mo (IQR)	3.8 [0.4–19.1]
First visit to antibody test, mo (IQR)	0.4 [0.1–2.8]
Neurological comorbidity present	51 (22.8%)
Cancer comorbidity present	42 (18.8%)
Autoimmune comorbidity present	8 (3.6%)
Polysymptomatic presentation (≥2 sx)	43 (19.0%)
Paraneoplastic antibody suspected	21 (9.8%)
Neuronal surface antibody solicited	117 (52.9%)
Serum sample sent	211 (93.4%)
CSF sample sent	105 (46.5%)
Paired serum + CSF sent	96 (42.5%)

Figure 1. Pre-test assessment High = 55/226 (24.3 %)
Intermediate = 66 (29.2 %) **Clinically warranted** =121/226 (53.5 %)



Diagnostic yield. Ten patients (4.4 %) were seropositive; 16 (7.1 %) received a final AE/PNS diagnosis.

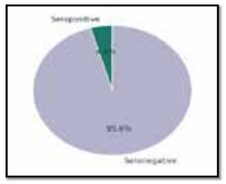


Figure 2. Percentage of seropositives

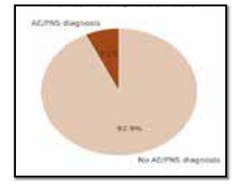


Figure 3. Percentage of AE/PNS diagnosis at last follow-up.

Table 3. Independent predictors of AE/PNS diagnosis, Ab seropositivity, and paired sample requests in multivariable logistic regression models. All models adjusted for age, sex, time from symptom onset, clinical presentation, and test strategy.

Predictor	Outcome	OR (95% CI)	*p-value*
Epileptic seizures at onset	AE/PNS diagnosis	4.44 (1.18–17.26)	*0.027*
Multisymptomatic presentation	AE/PNS diagnosis	3.30 (1.11–10.05)	*0.032*
Epileptic seizures	Seropositivity	7.09 (1.33–41.49)	*0.022*
Epileptic seizures	Paired sample request	2.67 (1.11–6.87)	*0.033*
Isolated peripheral phenotype	Paired sample request ↓	0.14 (0.02–0.51)	*0.010*

Conclusion:

Antibody testing is most informative when clinical suspicion is underpinned by seizures or a multisymptomatic picture, and when both serum and CSF are analysed. In presentations limited to a single or peripheral symptom, the diagnostic return is low. Adopting a structured, evidence-based algorithm could streamline testing, curb costs, and expedite accurate diagnoses.

Acknowledgements: this work could not have been carried out without the collaboration of all the patients involved.

Disclosures:

García-Sarreón A: has nothing to disclose.; Martínez Follana C, Saurina Navarro I, Vera Cáceres C: have nothing to disclose.; Gifreu-Fraixinó A: has received academic support from UCB Pharma, Bial Pharmaceutical, Angelini Pharma, Merck, Bristol-Myers-Squibb, Biogen, Novartis.; Boix A: has nothing to disclose.; Gutiérrez J: has nothing to disclose.; Álvarez-Bravo G: has received academic support from Merck, Sanofi, Biogen, and TEVA.

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Ms Ana Vasconcelos

University of Coimbra, Portugal

Co-designing infographics with and for autoimmune encephalitis patients

Ana Vasconcelos is a scientific illustrator and PhD student at the Center for Neuroscience and Cell Biology of the University of Coimbra (CNC-UC), developing a project in the field of visual science and health communication. Her research focuses on using participatory approaches to design infographics about Autoimmune Encephalitis to support communication with patients and their families. She has a BSc in Biomedical Sciences (University of Aveiro) and an MSc in Cellular and Molecular Biology (University of Coimbra), where she studied the pathogenic mechanisms of CASPR2-antibody encephalitis. Ana has training in scientific illustration and information design applied to life sciences and regularly collaborates on science communication projects in the fields of health and neurosciences.

Co-designing infographics with and for Autoimmune Encephalitis patients

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Our thanks to all those involved in the co-design process, including healthcare professionals, people affected by Autoimmune Encephalitis and their families.

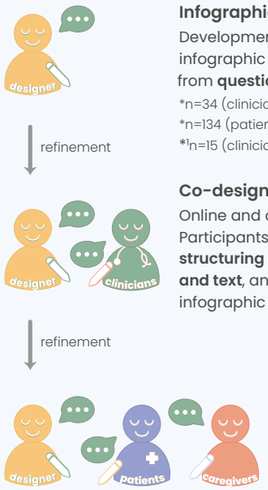
Introduction

This project explores **how to design information to promote effective communication about Autoimmune Encephalitis** (AE). We aim to design **understandable**, **adequate**, **engaging** and **relatable infographic leaflets** to facilitate conversations between healthcare professionals, AE patients, and their families, while also promoting health literacy about AE.

Workflow and results

6th co-design session with medical professionals (n=11)

1. Develop infographic leaflets using a participatory design approach



Infographics production

Development of an initial version of two infographic leaflets based on data from **questionnaires*** and **focus groups***[1]

*n=34 (clinicians)
*n=134 (patients and families)
*[1]n=15 (clinicians)

Co-design with clinicians

Online and onsite sessions. Participants (n=21) contributed to **structuring content**, **refining illustration and text**, and **addressing gaps** in the infographic leaflets.

Co-design with patients and caregivers

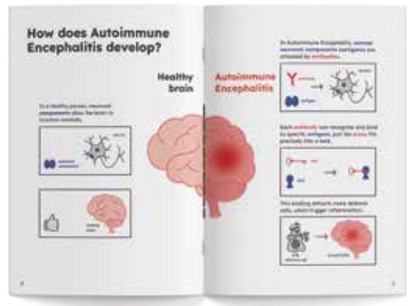
Online sessions. Participants (n=7) **validated the accessibility** of the text and illustrations, **suggested new themes**, and **shared personal stories about AE.**

2. Raise awareness about Autoimmune Encephalitis and disseminate the leaflets

Creation of the Portuguese patient and professional group **GENIE - Grupo de Estudos em Neuroimunologia e Encefalites**

- Launch of a website ***encefalites.pt*** with content for professionals, patients & families;
- **1st GENIE meeting** '25— for professionals;
- **2nd GENIE meeting** '26 — for professionals, patients and families;
- Celebration of **World Encephalitis Day** 2024 & 2025;
- Launch of **GENIE's social media;**
- Collaboration with **Encephalitis International.**

GENIE website



Final co-designed infographic from the leaflet "What is Autoimmune Encephalitis?"

3. Evaluate the effectiveness of the infographic leaflets as communication products

4. Create a toolkit about designing infographic leaflets using a participatory design approach

Conclusion

By engaging healthcare professionals, patients, and families, this work highlights how health communication can **bridge clinical knowledge and lived experience** to create information resources that **enhance understanding**, **support clinical dialogue**, and **empower patients and families**.

This project is funded by national funds through FCT – Fundação para a Ciência e a Tecnologia, I.P., under grant 2022.09588.BD, by Fundação Santander through the "2023 Seed Projects for Interdisciplinary Research", and by the UC Institute of Interdisciplinary Research through the "Promotion of Scientific Culture 2025" program. This project is carried out at CNC-UC, which is part of CiBB. CiBB is a Research and Development Unit funded by FCT (UID/04539/2025) and an Associated Laboratory (LA/P/0058/2020).

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Ms Anne Caroline Marcos

Oswaldo Cruz Institute-Fiocruz, Brazil

Herpes simplex virus type 1 infection induces mitochondrial dysfunction and alters dynamics in neural cells: implications for neurodegeneration

Anne Caroline da Silva Braga Marcos is a pharmacist, holds a Master's degree in Cellular and Molecular Biology from the Oswaldo Cruz Institute (Fiocruz), and is currently a PhD student in the Postgraduate Program in Tropical Medicine (PGMT/IOC-Fiocruz). Her research focuses on how viral infections such as HHV-1, Zika, and Enteroviruses may contribute to neurodegenerative processes. Throughout her academic journey, she has developed strong experience in neuroscience, virology, molecular biology, and cellular models, with a particular interest in the interface between infection, inflammation, and neurological damage. She has received academic honors such as the FAPERJ Nota 10 Fellowship, an Honorable Mention at the UFF Neuroscience Congress, and the Toxo XVI Travel Award. She also worked as a Research Associate at the University of Miami, where she strengthened her expertise in translational research and international collaboration. Currently, Anne serves as the student representative in her graduate program and is one of the organizers of the international NeuroID course, held in partnership with the University of Liverpool, which focuses on neurological infectious diseases. In addition to her scientific work, she has been a volunteer since 2017 with the NGO Sonhar Acordado, which supports hospitalized children through humanization and educational activities.

Herpes Simplex Virus type 1 infection induces mitochondrial dysfunction and alters dynamics in neural cells: implications for neurodegeneration

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ABSTRACT

Conditions such as Alzheimer's Disease (AD) and Parkinson's Disease (PD) are characterized by progressive neuronal loss and the accumulation of misfolded proteins that aggregate into amyloid fibrils. Growing evidence suggests that proteins like β-amyloid and α-synuclein can acquire pathogenic conformations through prion-like mechanisms. In this context, viral infections have emerged as potential contributors to the etiology of neurodegenerative diseases.

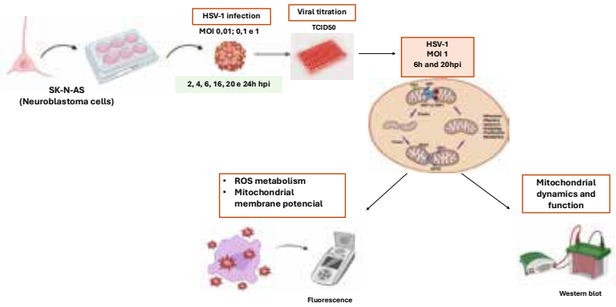
Viruses are capable of invading the central nervous system, triggering neuroinflammation, and promoting neurodegenerative processes. Herpes Simplex Virus type 1 (HSV-1), the leading cause of sporadic infectous encephalitis, has been implicated in AD pathogenesis.

Neurological manifestations associated with viral infections are often linked to mitochondrial dysfunction, which affects cellular metabolism and can lead to apoptosis. Mitochondria are essential for energy production and metabolic pathways, and their impairment is a critical factor in the progression of neurodegenerative diseases. This work aims to investigate how HSV-1 infection may contribute to neurodegeneration.

OBJECTIVE

To investigate how HSV-1 infection in neural cells disrupts mitochondrial dynamics and induces severe dysfunction. This work aims to identify the specific molecular pathways utilized by the virus to compromise neuronal energy metabolism, thus potentiating neurodegenerative pathology.

METHODOLOGY



RESULTS

Viral Replication Kinetics and Cell Viability in SK-N-AS Cells

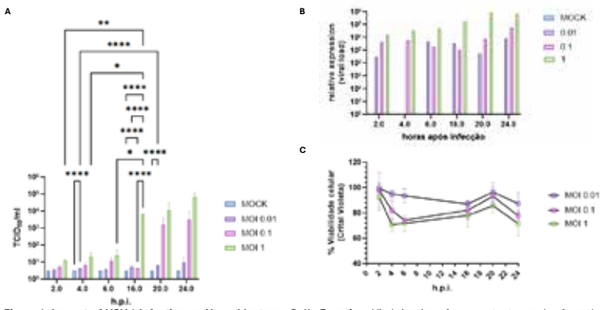


Figure 1: Impact of HSV-1 Infection on Neuroblastoma Cells Function. Viral titration of supernatant samples from the kinetics assay was performed using the TCID50 technique (**A**) and viral load by RT-PCR (**B**). Panel **C** assesses cell viability over 24 hpi, revealing a time-dependent decrease, with the sharpest initial decline observed at MOIs 0.1 and 1 (0-6 hpi). Viability subsequently showed stabilization (16 hpi), partial recovery (20 hpi), and a final drop (24 hpi). Data are plotted as the mean standard deviation of three (03) independent experiments.

FINANCIAL SUPPORT

RESULTS

HSV-1 Infection Compromises Bioenergetic Efficiency and Modulates Mitochondrial Function

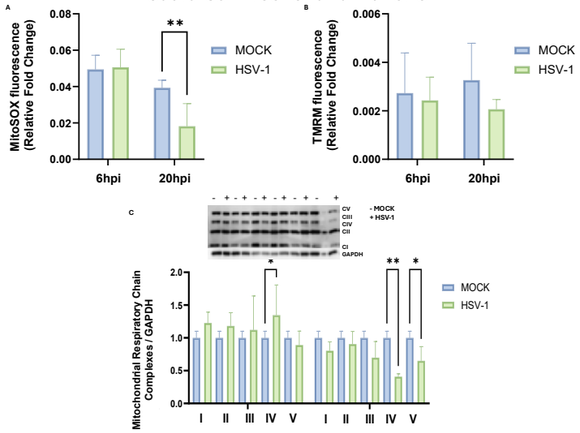


Figure 2: ROS Levels, Membrane Potential, and Respiratory Complex Expression in HSV-1 Infected Cells. Cells were evaluated at different time points post-infection (6 hpi and 20 hpi). **A)** A significant reduction in **ROS levels** was observed at 20 hpi. **B) No detectable alteration** in the mitochondrial membrane potential. **C)** The evaluation of the expression of mitochondrial respiratory chain complex proteins during HSV-1 infection revealed an increase in **Complex IV** at 6 hpi, followed by a reduction in **Complexes IV and V** at 20 hpi. Data are expressed as the mean standard deviation of three (3) independent experiments.

Dysregulation of Mitochondrial Dynamics by HSV-1 Infection

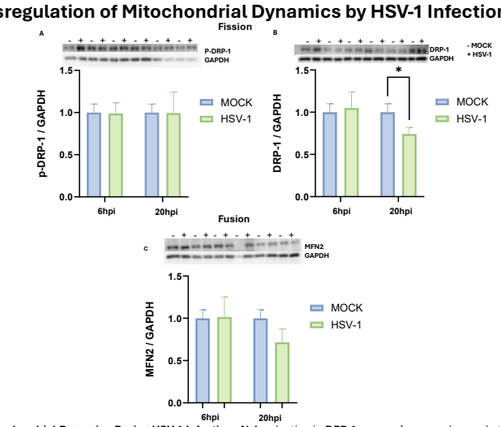


Figure 3: Mitochondrial Dynamics During HSV-1 Infection. A) A reduction in **DRP-1 expression** was observed at 20 hpi, with **no detectable alterations** in the phosphorylated form. **B)** Meanwhile, the expression of **Mitofusin 2 (MFN2)** remained unchanged, indicating maintenance of the balance between mitochondrial fission and fusion.

CONCLUSION

HSV-1 infection in SK-N-AS neural cells is productive and dose-dependent cytotoxic. The virus transiently modulates mitochondrial function, causing an early increase followed by a marked reduction in respiratory complex activity, without affecting membrane potential or fission/fusion dynamics. These results demonstrate that HSV-1 disrupts cellular bioenergetics, reinforcing its potential role in neurodegenerative mechanisms. Future work will explore mitochondrial and protein aggregation changes in iPSC-derived neurons to validate these effects in a more physiologically relevant human model.

REFERENCES

- Manczak M, Anekonda TS, Henson E, Park BS, Quinn J, Reddy PH. 2006. Mitochondria are a direct site of Aβ accumulation in Alzheimer's disease neurons: implications for free radical generation and oxidative damage in disease progression. Human Molecular Genetics 15(9):1437–49.
- Berry, N., Suspène, R., Caval, V., Khalfi, P., Beauclair, G., Rigaud, S., Blanc, H., Vignuzzi, M., Wain-Hobson, S., & Vartanian, J. P. (2021). Herpes Simplex Virus Type 1 Infection Disturbs the Mitochondrial Network, Leading to Type I Interferon Production through the RNA Polymerase III/RIG-I Pathway. mBio, 12(6), e0255721.

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Ms Brittany John

The National Hospital for Neurology & Neurosurgery, UK

Cognitive rehabilitation in individuals with encephalitis; the impact on occupational therapy practice

Brittany John, MSc Occupational Therapy, is a specialist occupational therapist currently at The National Hospital for Neurology & Neurosurgery with clinical experience in neurology across both public and private healthcare sectors. With a strong foundation in evidence-based practice, she has worked extensively with patients recovering from complex neurological conditions, including encephalitis, stroke, spinal cord injury, and progressive neurodegenerative diseases. She has held clinical and leadership roles in multidisciplinary teams in tertiary hospitals and private neurorehabilitation centres, where she has been instrumental in delivering patient-centred interventions that support cognitive, sensory, and functional recovery. Brittany collaborates closely with physiotherapists, neurologists, neuropsychologists, and other allied health professionals to optimize outcomes across the continuum of care—from acute inpatient management to community services.

NHS University College London Hospitals NHS Foundation Trust

uclh

Cognitive Rehabilitation in Individuals with Encephalitis; The Impact on Occupational Therapy Practice

Brittany John & Susannah Callow, National Hospital for Neurology & Neurosurgery (NHNN)

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Introduction

Individuals with encephalitis often experience cognitive changes which may impact on engagement in activities of daily living[1]. Existing guidance highlights the role of occupational therapy in rehabilitation; however, it does not specify how to structure cognitive rehabilitation programmes. Cognitive rehabilitation may improve long-term functional outcomes as well as reducing overall care needs[2]. At The National Hospital for Neurology & Neurosurgery (NHNN) Occupational Therapy (OT) is part of the multi-disciplinary team involved in the recovery of acute patients with encephalitis. Functional assessment of the impact of cognitive changes on activities of daily living is a key part of the OT role and essential to facilitate a safe discharge and appropriate community follow-up for individuals with encephalitis.

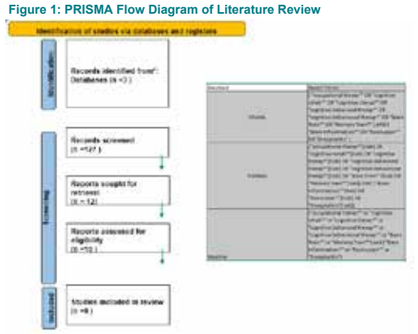
Objective

To explore the literature around cognitive rehabilitation in individuals with encephalitis and compare this with occupational therapy interventions delivered acutely at the National Hospital for Neurology and Neurosurgery (NHNN).

Method

A literature review was conducted to identify cognitive rehabilitation interventions, focused highlighting functional outcomes. Articles focused on interventions within the occupational therapy scope of practice. A PRISMA flow diagram was created to structure how studies were identified. Studies were reviewed using the Critical Appraisal Skills Programme (CASP). Key implications for occupational therapy practice were then collated. Data was collected on acute encephalitis patients at NHNN between August 2024 and March 2025 and evaluated against the findings of the literature review.

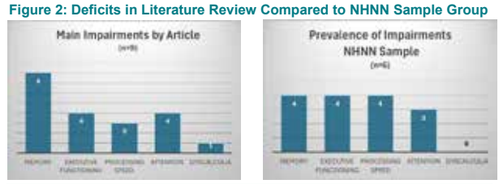
Figure 1: PRISMA Flow Diagram of Literature Review



Results

127 articles were screened and 9 were included for final review. Results indicate while cognitive assessments are frequently conducted, there is limited high quality evidence for cognitive rehab. The most common cognitive impairments are attention, processing speed, memory and executive function; however, interventions vary and details are not well-reported. Between August 2024-March 2025, there were eight encephalitis inpatients at NHNN. Two critical care patients were excluded from the data as not appropriate for cognitive assessment. 6/6 patients were assessed as having at least one of the impairments identified in the review. Acute interventions included multiple errands tests, kitchen assessments, community access and functional task practice.

Figure 2: Deficits in Literature Review Compared to NHNN Sample Group



Discussion

Memory impairments were the most reported deficit across the studies identified. 55.9% of participants in one study[3] experienced deficits in episodic memory and 38.2% in working memory. Executive function and attention were jointly the second most reported deficits. Neuropsychological assessment (NPA) were the primary means of assessing cognition. Specifics of cognitive rehabilitation were not detailed, however interventions mentioned function and activities of daily living. Key indicators of cognitive improvement were level of dependency post intervention and the impact on overall function long-term[2].

The NHNN group, who were assessed in function, had cognitive deficits and rates comparable to the literature review. All the patients included had at least one of the impairments, but none of them had all four impairments. While inference is limited by the small sample size, it does reflect some findings from the literature review such as the types of cognitive deficits and impact on function.

Additionally, there are population differences as the NHNN group only included adults in the acute stage. While NPA may be helpful for identifying impairments, it is not conclusive that they are a predictor of long-term functional outcomes in other neurological populations[4]. To improve independence in ADLs, function should be the focus of assessment and intervention, and this can be delivered through occupational therapy[5], although further studies are needed to identify the best interventions for this population.

Recommendations for Practice

Conclusion

- Cognitive assessment should be routinely offered and prioritise attention, memory, processing speed and executive functioning.
- The NHNN group demonstrated cognitive deficits comparable to the literature review despite differences in the populations compared.
- Within the acute setting, interventions delivered should be function-focused and adapted to their deficits.
- Acute interventions may include multiple errands tests, kitchen assessments, community access and functional task practice.
- There is limited high quality evidence for the use of cognitive rehabilitation in encephalitis.
- Further research is required to identify the best interventions for occupational therapists working with individuals with encephalitis.

References

1. Chen, W. et al. (2021) 'Neurofunctional outcomes in patients with anti-leucine-rich glioma inactivated 1 encephalitis', Acta Neurologica Scandinavica, 144(6), pp. 632–639. doi:10.1111/ane.13503.
2. Howarth RA, Vova J, Blackwell LS. Early Functional Outcomes for Pediatric Patients Diagnosed with Anti-N-Methyl-D-Aspartate Receptor Encephalitis during Inpatient Rehabilitation. Am J Phys Med Rehabil. 2019 Jul;98(7):529-535.
3. McKeon GL, Robinson GA, Ryan AE, Blum S, Gillis D, Finke C, Scott JG. Cognitive Outcomes Following Anti-N-methyl-D-Aspartate Receptor Encephalitis: A Systematic Review. J Clin Exp Neuropsychol. 2018 Apr;40(3):234-252.
4. Revet, M., Immerzeel, J., Voogt, L., & Paulis, W. (2019). Patients with neuropsychological disorders short after stroke have worse functional outcome: a systematic review and meta-analysis. Disability and Rehabilitation, 43(16), 2233–2252. https://doi.org/10.1080/09638288.2019.1693642
5. Steultjens EM, Dekker J, Bouter LM, Leemrijse CJ, van den Ende CH. Evidence of the efficacy of occupational therapy in different conditions: an overview of systematic reviews. Clinical Rehabilitation. 2005;19(3):247-254. doi:10.1191/0269215505cr870oa

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Dr Celia Greenlaw

Boston Children's Hospital USA

Neurologic complications in pediatric patients with influenza

Dr Celia Greenlaw is a Pediatric Neuroimmunology fellow at Boston Children's Hospital. Dr. Greenlaw graduated from Emory University with a major in Neuroscience & Behavioral Biology and a minor in French Studies. She completed medical school at Boston University School of Medicine and then completed pediatrics and child neurology residency at Boston Children's Hospital.

Neurologic Complications in Pediatric Patients with Influenza

Boston Children's Hospital
Where the world comes for answers

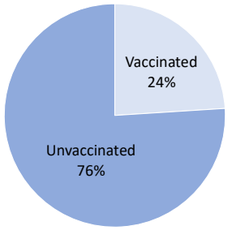
Celia Greenlaw MD, Christine Shrock MD, Rachel Walsh MD , Molly Wilson-Murphy MD
Boston Children's Hospital, Department of Neurology

Background & Methods

- Influenza-associated neurologic complications in children are a major cause of illness and hospitalization
- The 2024-25 flu season was historically severe across the US
- We performed retrospective chart review of children at a single pediatric hospital with influenza-associated neurologic complications during the 2024-25 flu season
- Exclusions: Exacerbations of pre-existing conditions, and simple febrile seizures

Patient Characteristics

	n = 18
Age: median years (range)	7 (8mo – 17y)
Sex: % female	50
Days to neurologic symptom onset: median	5
Encephalopathy: %	88
Seizure: %	33
Ataxia: %	33
Abnormal MRI: %	50
Abnormal EEG: %	55
Abnormal CSF: %	22
Therapy received: %	72
Anti-viral	56
Steroids	33
IVIg	22
Other	44
Length of hospitalization: median days (SD)	4.5 (13)



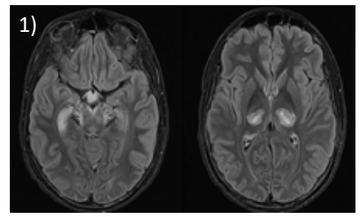
Compared to the 2024-25 national pediatric vaccination rate (49%) and MA state rate (69%), this group had lower vaccination uptake (CDC)

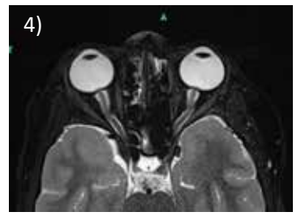
Final Diagnoses & Outcomes

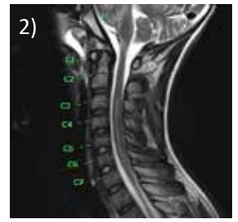
- Acute necrotizing encephalitis (1)
- Influenza associated encephalopathy (14)
- Cytotoxic lesion of the corpus callosum (2)
- Acute cerebellar ataxia (2)
- Idiopathic intracranial hypertension (1)

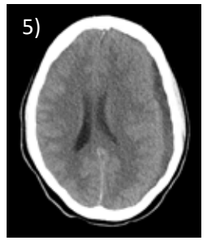
- One third of patients received ICU level care
- 3/18 patients required rehab

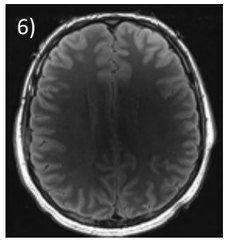
Neuroimaging

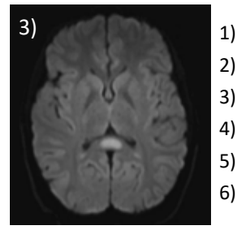












1) Axial MR T2 Flair- Acute necrotizing encephalitis
2) Sagittal MR T2 – Transverse myelitis in patient with ANE
3) Axial MR DWI – Cytotoxic lesion of the corpus callosum
4) Axial MR orbits – Bilateral papilledema
5) Axial CT Head – empyema and cerebral edema
6) Axial MR T2 Flair – Diffuse leptomeningeal enhancement

Conclusions

- These findings highlight the need for vigilant surveillance and counseling for patients diagnosed with influenza
- Low vaccination rate in this cohort suggests the importance of immunization to reduce the risk of neurologic complications

For more information about how to talk with patients & families about vaccinations and vaccine-preventable neurologic illnesses, scan the QR code above

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Dr Charles Coughlan

Jigme Dorji Wangchuck National Referral Hospital, Bhutan & Imperial College London, UK & Hammersmith Hospital, Imperial College Healthcare NHS Trust, UK

HSV-1 encephalitis in Bhutan: diagnostic and management challenges

Dr Charles Coughlan is an NIHR Academic Clinical Fellow and Specialty Registrar in Infectious Diseases and General (Internal) Medicine at Imperial College London, UK. He has recently completed an MSc in Tropical Medicine and International Health at the London School of Hygiene and Tropical Medicine and has postgraduate clinical experience in India, the Philippines and Bhutan. He has clinical and research interests in neurological infection, particularly in resource-constrained settings.

HSV-1 Encephalitis in Bhutan: diagnostic and management challenges

Dr Charles Coughlan, Dr Deki Wangmo, Dr Susmita Rai, Dr Nim Lham, Dr Sonam Zangmo
Jigme Dorji Wangchuck National Referral Hospital, Thimphu, Bhutan

Background

Bhutan is a small, landlocked South Asian country, home to 750,000 people (Figure 1). Despite its size, the country's climate and geography are hugely varied; just 100 miles separates subtropical rainforests from the high Himalayas. Bhutanese citizens enjoy universal access to Western and traditional healthcare, free at the point of use. However, as in other low-middle income countries, there is limited access to specialist expertise, diagnostic tests and treatment.[1]

Neurological infection is common, but the pathogen mix remains poorly understood. At the time of writing, there is one Infectious Diseases physician, but no neurologist, neurophysiologist or microbiologist working in Bhutan. Five centres provide computed tomography (CT) imaging, and just one – the Jigme Dorji Wangchuck National Referral Hospital in Thimphu – offers magnetic resonance imaging (MRI). Basic cerebrospinal fluid (CSF) analyses are available at most district hospitals, but samples must be sent to a partner Indian laboratory – at significant cost and with prolonged diagnostic delays – for uni-plex and multiplex polymerase chain reaction, fungal culture, and auto-antibody testing. We describe the challenges of making the first virologically-confirmed diagnosis of Herpes Simplex Virus-1 (HSV-1) encephalitis in a Bhutanese adult who developed para-infectious neurogenic diabetes insipidus and experienced clinical relapse.

Figure 1: Bhutan is a landlocked South Asian country that lies between India and China. Many of its 750,000 citizens live in remote Himalayan valleys.

LP Analysis Parameter	Result	Normal range
Opening pressure	Not available	10 - 20cm H2O
White cell count	**110** (99% lymphocytes)	<5 cells/µl
CSF protein	**0.62**	0.15 – 0.40 g/L
CSF glucose	3.45 (plasma glucose 4.4)	2.5 – 3.5 mmol/l
Gram stain	Negative	N/A
CSF TB PCR	Negative	N/A

Table 1: Lumbar puncture results

Clinical Case

- 42-year-old female farmer from Southern Bhutan
- 1 week history of fever and apathy
- No associated headache, confusion, or localizing symptoms
- No focal neurological deficit or eschar of scrub typhus
- Relevant investigations
  - Haemoglobin 9g/dL (NR 12 – 16g/dl)
  - White cell count 7 x 10^9/L (NR 4 – 11 x 10^9/L)
  - Platelet count 157 x 10^9/L (NR 150-400 x 10^9/L)
  - CRP 2mg/L (NR <5 mg/L)
  - HIV serology – non-reactive
  - Renal and liver function – unremarkable
  - Chest X-ray – normal cardiac silhouette, clear lung fields

She went on to have further tests for fever of unknown origin, including transthoracic echocardiography (given the presence of a systolic murmur and the high national prevalence of rheumatic heart disease) and ultrasonography of the abdomen. These were unremarkable. Her sister reported that her ongoing apathy was very out of character and this prompted us to perform a lumbar puncture (Table 1).

She was found to have reactive, lymphocytic CSF, concerning for viral encephalitis. She was started on intravenous ceftriaxone and aciclovir and oral doxycycline (to cover rickettsial infection). The patient became confused the day after starting treatment. Further history from the patient's mother revealed that she had experienced two generalized tonic-clonic seizures prior to hospital admission, which were not disclosed due to concerns around stigma, and which prompted an initial visit to a monk for a two-day puja. However, she responded well to aciclovir and her confusion resolved over the next 4-5 days.

Magnetic resonance imaging (Figure 2) was initially reported as showing an ischaemic stroke, but after direct discussion with radiologist colleagues, this was revised to probable HSV encephalitis. A CSF sample was sent to India for HSV-1 PCR. The positive HSV-1 PCR was communicated to our team over one week later.

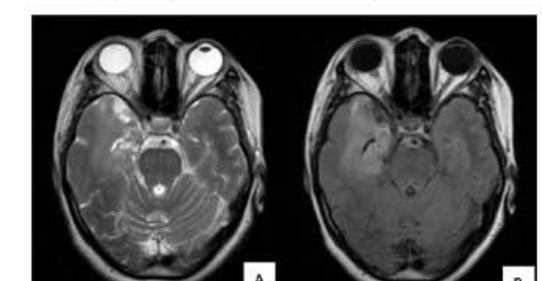

Figure 2: (A) Axial T2-weighted and (B) fluid-attenuated inversion recovery (FLAIR) MRI sequences reveal bilateral hyperintense signal change accompanied by gyral thickening within the mesial temporal lobes, more pronounced on the right. Diffusion weighted imaging (DWI) and apparent diffusion coefficient (ADC) maps (not shown) were reported as showing subtle diffusion restriction in the right mesial temporal lobe. This was initially interpreted as ischaemic stroke.

Progress and Outcome

Almost two weeks into treatment, our patient developed polyuria with unchanged glomerular filtration rate. Her urine output exceeded 7L/24h but this fell to 2L/24h following a therapeutic trial of desmopressin for suspected neurogenic diabetes insipidus, a reported complication of HSV encephalitis.[2] She completed 21 days of aciclovir and was discharged home having made a good clinical recovery.

Two weeks later, she re-presented with rebound confusion. There were no signs of systemic infection and blood tests were unremarkable. We suspected relapse due to virological persistence or post-herpetic NMDAR autoimmune encephalitis.[3] Aciclovir was restarted and repeat lumbar puncture performed. HSV-1 PCR and NMDAR autoantibody testing were negative. She improved clinically and was discharged home after a further fortnight of aciclovir.

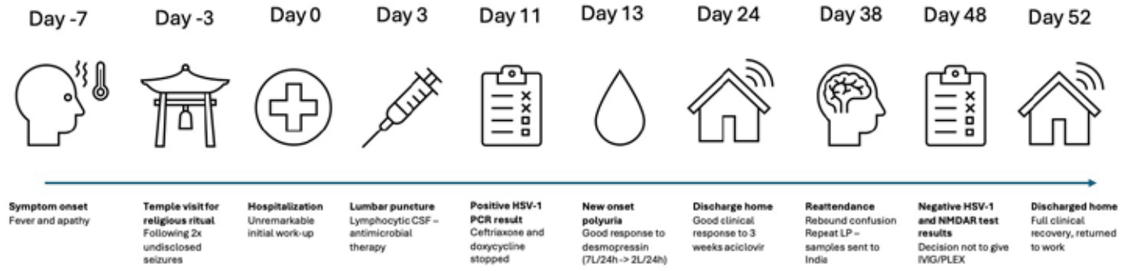

Figure 3: Timeline of key events

Learning Points

- A personal or collateral history of seizures (a key diagnostic feature in encephalitis) may not be disclosed due to concerns regarding stigma
- Alternative care-seeking behaviours (e.g. consulting a local monk for a puja in Bhutan) may influence the timing of clinical presentation and clinical outcomes
- In resource-constrained health systems, treatment is usually prioritised over diagnosis
  - Unclear epidemiology and pathogen mix often leads clinicians to adopt a blunderbuss approach, which is expensive and often toxic
- The investigation of relapsed encephalitis is made more difficult in resource-constrained settings by lack of access to validated encephalitis panels

References

1. Coughlan C, Dhakal GP, Yangchen Y. Neurological letter from Bhutan: Land of the Thunder Dragon. *Pract Neurol* 2025; doi: 10.1136/pn-2025-004561
2. Canton A, Simo R, Mesa J, et al. Central diabetes insipidus: a complication of herpes simplex encephalitis. *J Neurol Neurosurg Psychiatr* 1996;61:325-326
3. Armanague T, Moris G, Cantarin-Extremera V, et al. Autoimmune post-herpes simplex encephalitis of adults and teenagers. Neurology 2015;85(20):1736-1743

ENCEPHALITIS CONFERENCE 2025

Dr Cordelia Dunai

CIMI, IVES, University of Liverpool, UK

Immunophenotyping of HSV-1 encephalitis cases

Dr Cordelia Dunai is a postdoc research associate in Professor Benedict Michael's Infection Neuroscience lab. She is part of the Biomarkers and ImmunologyWorking Group of the COVID-CNS study and the Liverpool Brain Infection and Inflammation Group. She earned her Ph.D. in immunology in 2021 in the lab of Professor William J. Murphy at UC Davis. Her interests include: immunology, virology, cancer biology, translational research, and scientific outreach.

Immunophenotyping of HSV-1 Encephalitis cases

Dunai C.[1,2], Osborne, L. Egbe N.F.[1], Hetherington, C. D.[1], Boardman S.A.[1], Facer, B., da Silva Braga, A.C. [1], Michael B.D. [1,2], and Ellul, M.A.[1,2]

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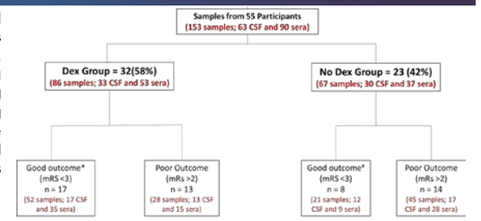
INTRODUCTION

Herpes simplex virus-1 (HSV-1) is the major cause of infectious encephalitis in the U.K. and although it is rare, it has a very significant impact on health[1]. The immune response and subsequent regulation of inflammation is thought to play a major role in neurological complications and outcomes from this normally asymptomatic viral infection. The immunosuppressant dexamethasone was tested in a recent multicentre, randomised controlled trial (DexEnceph) as this treatment is under investigation for being able to reduce brain inflammation. We aim to understand differences in immune cells from blood samples from patients with HSV-1 encephalitis from the DexEnceph trial and compare to HSV-1 negative and positive control samples. Using Standard Biotools Maxpar Direct Immune Profiling Assay with Mass CyTOF which enables phenotyping of 37 immune cell types, we analysed the peripheral blood mononuclear cells (PBMCs). The hypothesis is that specific activated T cells would be protective during viral infection and be associated with good outcomes. However, the anti-viral immune response is complex and pro-inflammatory cytokines detected in the cerebrospinal fluid are associated with a worse prognosis[2-3].
The Maxpar Mass CyTOF enables quantification of immune cells including NK cells, monocytes, and T cell and B cell subsets.

METHODOLOGY

We measured frozen, then thawed PBMCs from participants with Herpes Simplex Virus encephalitis enrolled in the DexEnceph clinical trial[4]; using the Standard Biotools Maxpar Direct Immune Profiling assay with Mass CyTOF. Briefly, cells were thawed and the cells were stained with antibodies for monocytes, NK cells, T cells, and B cells. Cells were then analysed on a Helios Mass CyTOF. A healthy control sample was run during each batch for normalisation. We also measured T cell function in a separate flow cytometry assay, staining for intracellular IL-2, TNF, and IFN-gamma following stimulation with a HSV-1 peptide pool and retaining cytokines with Brefeldin A. The clinical severity of participants was assessed using the Glasgow Coma Scale score (GCS) at admission and the outcome measures were modified Rankin Score (mRS), and Liverpool Outcome Score; magnetic resonance imaging(MRI)-based temporal lobe volumes were also quantified. This will be used to stratify the data in the next step.



RESULTS

White blood cells in controls and cases

Marker	Target Cell(s) / Use
CD45	Pan-leukocyte marker; identifies all white blood cells.
CD196	A chemokine receptor expressed on Th17 cells, some T regulatory cells, and B cells; involved in cell trafficking.
CD123	Marker for plasmacytoid dendritic cells (pDCs).
CD19	Identifies B cells.
CD4	Identifies T helper cells.
CD8a	Identifies cytotoxic T cells.
CD11c	Identifies myeloid cells, including dendritic cells and monocytes.
CD16	Identifies NK cells and some monocyte subsets.
CD45RO	Identifies memory T cells.
CD45RA	Identifies naive and some effector memory T cells.
CD161	Marker for mucosal-associated invariant T (MAIT) cells, NK cells, and some T cell subsets.
CD194	A chemokine receptor expressed on Th2 cells and regulatory T cells; involved in skin homing.
CD25	IL-2 receptor alpha chain; a marker for activated T cells and regulatory T cells (Tregs).
CD27	Defines T and B cell memory subsets; a co-stimulatory molecule.
CD57	Identifies terminally differentiated, senescent T cells with limited proliferative capacity.
CD183	A chemokine receptor expressed on Th1 cells and cytotoxic T cells; involved in homing to inflamed tissues.
CD185	A chemokine receptor expressed on T follicular helper (Tfh) cells and B cells; involved in homing to lymphoid follicles.
CD28	A key co-stimulatory molecule for T cell activation.
CD38	An activation/differentiation marker on T cells, B cells, and other leukocytes.
CD56	Identifies NK cells and is also expressed on some T cells.
TCRγδ	Identifies gamma-delta T cells.
CD294	A chemoattractant receptor expressed on Th2 cells.
CD197	A chemokine receptor that differentiates central memory from effector memory T cells.
CD14	Identifies monocytes.
CD3	Identifies T cells.
CD20	Identifies B cells.
CD66b	A marker for neutrophils.
HLA-DR	A class II MHC molecule that is a marker of activation on various immune cells.
IgD	Identifies naive B cells.
CD127	The IL-7 receptor alpha chain; low expression is characteristic of regulatory T cells.

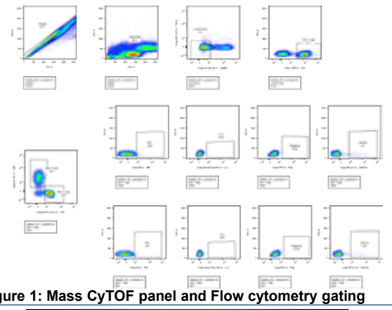


Figure 1: Mass CyTOF panel and Flow cytometry gating

Intracellular staining for T cell function

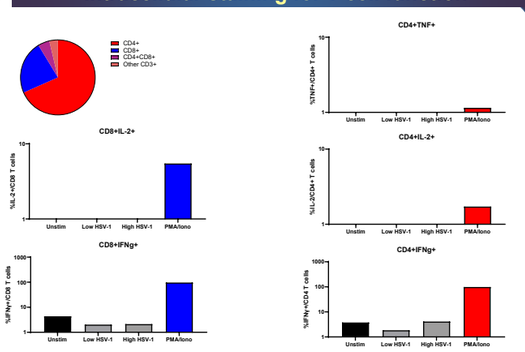


Fig. 2: Intracellular cytokine production in response to HSV-1 peptide

HSV-1 alters the immunophenotype

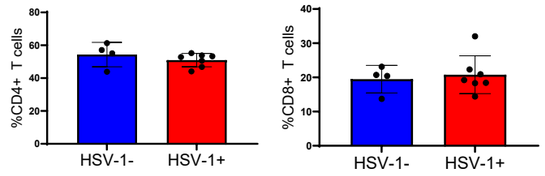


Fig. 3: HSV-1- vs. HSV-1+ T cell subsets

Conclusions

By comparing the immunophenotypes associated with controls and encephalitis cases with a range of HSV-1 status and clinical outcomes, we aim to discover an immune signature predictive of better responses in order to elucidate potential therapeutic pathways.
The inflammatory response is important to protect against viruses, however, too much inflammation can lead to immune-mediated tissue damage. Specific immune modulation could be protective in HSV-1 encephalitis

References

1. Defres S, Tharmaratnam K, Michael BD, Ellul M, Easton A, et al. Clinical predictors of encephalitis in UK adults-A multi-centre prospective observational cohort study. PloS One. 2023;18(8):e0282645.
2. Michael BD, Griffiths MJ, Granerod J, Brown D, et al. The Interleukin-1 Balance During Encephalitis Is Associated With Clinical Severity, Blood-Brain Barrier Permeability, Neuroimaging Changes, and Disease Outcome. J Infect Dis. 2016 May 15;213(10):1651–60
3. Michael BD, Griffiths MJ, Granerod J, Brown D, et al. Characteristic Cytokine and Chemokine Profiles in Encephalitis of Infectious, Immune-Mediated, and Unknown Aetiology. PLOS ONE. 2016 Jan 25;11(1):e0146288.
4. Whitfield T, Fernandez C, Davies K, Defres S, Solomon, T. et al. Protocol for DexEnceph: a randomised controlled trial of dexamethasone therapy in adults with herpes simplex virus encephalitis. BMJ Open. 2021 Jul;11(7):e041808.

Acknowledgements

This research was supported by the National Institute for Health Research Efficacy, Mechanism and Evaluation Programme (NIHR EME number: 12/205/28) and the Medical Research Council [MR/V007181/1].

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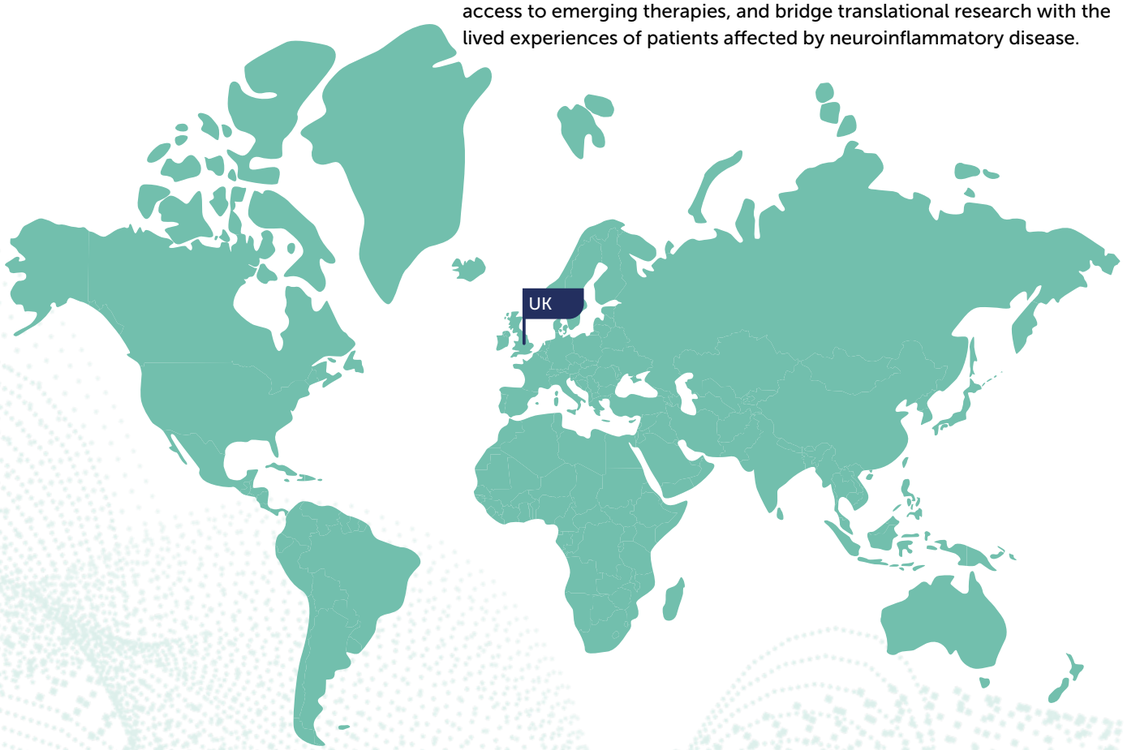
Dr Crystal Teoh

Nottingham University Hospital trust, UK

Applying the 2016 autoimmune encephalitis criteria: diagnostic and outcome insights from a seronegative cohort at a tertiary neuroscience centre

Dr Crystal Teoh is a neurology registrar with robust clinical expertise and academic foundation. Her interests include advancing the understanding and treatment of autoimmune neurology disorders, including autoimmune encephalitis, autoimmune epilepsy, autoimmune neuropathies, multiple sclerosis, NMOSD, MOGAD, and neuromuscular junction disorders.
She is an active member of the Nottingham University Hospital (NUH) Autoimmune Encephalitis (AE) Special Interest Group (SIG), where she leads the design and execution of several retrospective studies based on real-world AE cases. She co-led a local clinical governance submission to include tocilizumab in the trust formulary for the treatment of refractory autoimmune encephalitis, based on clinical audit findings and real-world case analysis. She has contributed as first and co-author to several peer-reviewed publications, including the recent article "Rethinking Corticosteroid Therapy in Autoimmune Neurology", co-authored with Dr Adam Handel (Head, Oxford Autoimmune Neurology Group) and Dr Shirish Dubey. As Lead Registrar for Education and Development in the East Midlands neurology training programme, she initiated and coordinated a regional teaching series for specialty trainees. This included inviting local experts and national speakers to deliver sessions on clinically relevant topics. Her work seeks to advance understanding, promote equitable access to emerging therapies, and bridge translational research with the lived experiences of patients affected by neuroinflammatory disease.



Applying the 2016 Autoimmune Encephalitis Criteria: Diagnosis and Outcome from a Seronegative Cohort at a Tertiary Neuroscience Centre

Afa Ibrahim, Beili Shao, Crystal Teoh, Radu Tanasescu

1 INTRODUCTION

Seronegative autoimmune encephalitis (AE), defined by the absence of detectable pathogenic antibodies, includes limbic encephalitis (LE), acute disseminated encephalomyelitis (ADEM), and antibody-negative probable AE (ANPRA). Diagnosis remains challenging, often delaying treatment. The 2016 Graus criteria offer a structured framework for AE diagnosis. We conducted a retrospective study to evaluate the real-world application of these criteria, focusing on implications for management.

2 METHODS

We reviewed patients with suspected AE and negative initial antibody testing at a UK tertiary care centre (2013–2024). Cases were classified using the 2016 criteria into possible AE, probable AE (ANPRA), definite AE (e.g., LE, ADEM), or alternate diagnosis. Clinical and paraclinical features, immunotherapy use, and outcomes (CASE, mRS, RAPID score) were analysed.

3 RESULTS

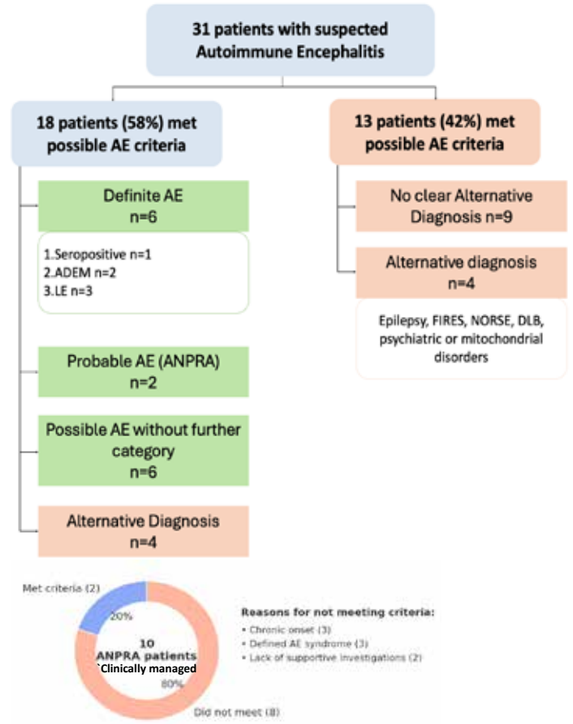
31 patients were included. Eighteen patients (58%) met possible AE criteria; thirteen (42%) did not. The most common reason for non-fulfilment was failure to meet clinical criteria (62%). Among those who met criteria, subacute onset, altered mental status, and inflammatory CSF were more frequent.

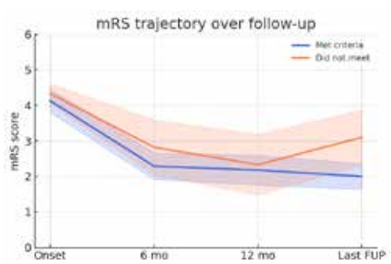
Of the 18 who met possible AE criteria, 6 were later classified as definite AE (1 seropositive, 2 ADEM, 3 LE), 2 as probable (ANPRA), and 6 remained as possible AE without further classification. Four were re-diagnosed with alternative conditions.

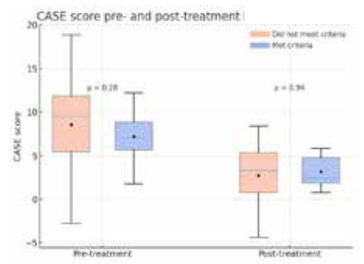
In contrast, 9 of 13 patients in the non-met group were given alternative diagnoses including epilepsy, FIRES, NORSE, DLB, psychiatric or mitochondrial disorders. Four had no clear alternate diagnosis; three of these were treated as AE and two improved with immunotherapy.

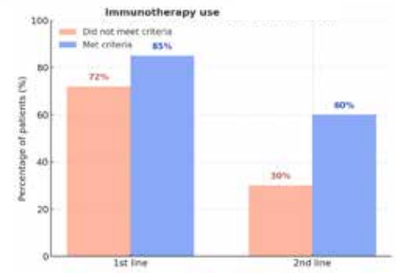
Among 10 patients managed clinically as ANPRA, only 2 met full criteria. The remainder failed due to chronic onset, presence of a defined AE syndrome, or lack of supportive investigations—likely impacted by incomplete CSF testing (oligoclonal bands, IgG index).

First-line immunotherapy was initiated in both groups (72% v 85%) and second line immunotherapy was more frequently used in the met-criteria-group. Treatment delay was longer in the non-met group (median 74 vs 32 days). Outcomes were comparable and favourable outcomes mRS ≤2 were achieved in both groups (64% vs 50%) at last follow-up. CASE score and RAPID score were similar.









4 CONCLUSION

Misdiagnosis of AE remains a challenge. The 2016 criteria aid in distinguishing AE from mimics but may lack sensitivity in seronegative cases, especially ANPRA. Clinical judgment is crucial, and further work is needed to refine diagnostic tools without compromising specificity.

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ENCEPHALITIS CONFERENCE 2025

Mr David Petrosian

Vilnius University, Lithuania

Establishing a novel scoring approach to accurately identify GFAP astrocytopathy over infectious encephalitis using clinical-radiological data

As a researcher passionate about neuroimmunology—particularly autoimmune encephalitis— Mr David Petrosian combines clinical medicine with computational approaches to develop data-driven diagnostic solutions. His research focuses on creating novel machine learning algorithms that improve the real-time detection and differentiation of autoimmune encephalitis, enabling faster and more accurate clinical decision-making. Collaborating closely with clinicians and data scientists, he works to translate computational models into practical tools that address diagnostic challenges in neuroimmunology. By incorporating multimodal data (e.g., clinical, serological, and imaging biomarkers), he builds robust, interpretable models to reduce diagnostic delays and improve outcomes in autoimmune encephalitis—ensuring reliability at every step.

ESTABLISHING A NOVEL SCORING APPROACH TO ACCURATELY IDENTIFY GFAP ASTROCYTOPATHY OVER INFECTIOUS ENCEPHALITIS USING CLINICAL-RADIOLOGICAL DATA

David Petrosian[1], Deimante Roliciute[1], Vera Taluntiene[2], Natasa Giedraitiene[2], Mantas Vaisvilas[2]

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Vilnius University

BACKGROUND AND AIMS

Glial Fibrillary Acid Protein (GFAP) astrocytopathy is a relatively recent and severe form of autoimmune encephalomyelitis that exhibits responsiveness to steroid treatment. First described in 2016, its hallmark features include widespread involvement of the nervous system at presentation, a distinctive linear periradial contrast enhancement pattern visible on cranial imaging, and a positive response to steroids. Considering GFAP encephalitis can present with clinical features that strongly resemble those of an underlying infectious process, and there is no commercially available test to confirm GFAP, we aimed to develop a novel scoring system assisting in the differentiation of GFAP astrocytopathy from infectious encephalitis based on clinical-radiological data.

METHODS

A systematic search was conducted to select articles from PubMed and Web of Science databases published from 2016 to 2024 along with the retrospective review of infectious encephalitis cases from Vilnius University Hospital Santaros Klinikos during the same time interval to gather clinical and MRI data related to respective diseases. Univariate logistic regression analysis was performed to identify variables potentially appropriate for multivariate modelling. Variables with a p-value < 0.05 were included in a stepwise logistic regression model. The results of the multivariate logistic regression were used to develop the scoring system.

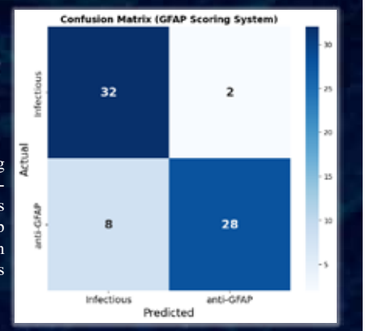
RESULTS

We included a total of 183 patients diagnosed with GFAP encephalitis and 170 patients with infectious encephalitis in our analysis. Our multivariate analysis demonstrated that patients with encephalomyelitis, abnormalities in the basal ganglia or thalamus, leptomeningeal enhancement, and radial linear enhancement patterns are more likely to have GFAP antibody mediated encephalitis, while restricted diffusion on cranial MRI imaging is more associated with infectious aetiology. Our model demonstrated strong discriminatory power with accuracy, sensitivity, specificity, precision, and F1 score values of 85.7%, 77.8%, 94.1%, 93.3%, and 84.9% respectively.

Fig. 1 Graphical schematic of GFAP radiological imaging features.
In the cerebrum (**A**), areas shown in red are most commonly affected. Symmetrical involvement of the basal ganglia and the thalamic structures is shown. White matter lesions may be periventricular, follow a leukodystrophic pattern or resemble demyelinating lesions. Splenium corpus callosum lesion is shown as one of the remarkable patterns seen on imaging. In the spinal cord (**B**), lesions commonly involve multiple spinal segments (<2).
Contrast enhancement patterns are shown in pictures C and D. Cranial contrast enhancement on MRI (**C**) follows either the leptomeningeal or linear perivascular pattern. Spinal cord contrast enhancement (**D**) is most commonly leptomeningeal. Occasionally, nerve root enhancement may be present

Fig. 2 GFAP score-based probability and risk categories for GFAP encephalitis

Fig. 3 Differentiating performance of anti-GFAP vs. infectious encephalitis: heatmap of classification outcomes



CONCLUSIONS

A straightforward clinical-radiological five-variable scoring system to predict GFAP encephalitis that is based on MRI imaging at disease onset has been established demonstrating robust performance metrics following internal validation. This proposed scoring system is designed to identify patients at high risk for GFAP more effectively, facilitating timely antibody testing, diagnosis, and treatment. External validation is in process to confirm its effectiveness in real-world settings.

ENCEPHALITIS CONFERENCE 2025

Mr David Petrosian

Vilnius University, Lithuania

Development of a machine learning approach to distinguish autoimmune limbic encephalitis from herpetic encephalitis using clinical, EEG, imaging, and laboratory data

As a researcher passionate about neuroimmunology—particularly autoimmune encephalitis— Mr David Petrosian combines clinical medicine with computational approaches to develop data-driven diagnostic solutions. His research focuses on creating novel machine learning algorithms that improve the real-time detection and differentiation of autoimmune encephalitis, enabling faster and more accurate clinical decision-making. Collaborating closely with clinicians and data scientists, he works to translate computational models into practical tools that address diagnostic challenges in neuroimmunology. By incorporating multimodal data (e.g., clinical, serological, and imaging biomarkers), he builds robust, interpretable models to reduce diagnostic delays and improve outcomes in autoimmune encephalitis—ensuring reliability at every step.

DEVELOPMENT OF A MACHINE LEARNING APPROACH TO DISTINGUISH AUTOIMMUNE LIMBIC ENCEPHALITIS FROM HERPETIC ENCEPHALITIS USING CLINICAL, EEG, IMAGING, AND LABORATORY DATA

David Petrosian[1], Natasa Giedraitiene[2], Mantas Vaisvilas[2]

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[2]Vilnius University, Clinic of Neurology and Neurosurgery, Institute of Clinical Medicine, Vilnius, Lithuania

Vilnius University

BACKGROUND AND AIMS

The two most common forms of limbic encephalitis are autoimmune limbic encephalitis (ALE) and infectious encephalitis (IE), which is often caused by herpes viruses (HE). An accurate diagnosis is crucial, as the prognosis and response to treatment for both conditions depend on timely intervention. Additionally, the radiological and clinical features of these two conditions may overlap in the early stages of the disease, while confirmatory testing can be time-consuming. Artificial intelligence has rarely been used as a tool for differential diagnosis in this context. Our objective is to develop a machine learning approach to enhance the accurate differentiation of ALE.

METHODS

We retrospectively collected demographic, clinical symptoms, electroencephalography, radiological, and laboratory data from patients diagnosed with ALE and HE at our center. Our dataset was split into 70% for training and 30% for testing. The LASSO method was used to identify the most important factors included in the training process. XGBoost machine learning classifier was employed to build the differentiating model. The overfitting problem was addressed through the implementation of cross-validation.

RESULTS

The study included 45 cases of ALE, with anti-LGI1 (24/45, 53.3%) being the most prevalent, followed by anti-NMDAR (9/45, 20.0%), along with 41 cases of HE. SHAP analysis revealed that fewer cells in the cerebral spinal fluid (CSF), lower protein concentration in the CSF, along with symptoms of seizures and memory impairments, were strong predictors of ALE, whereas diffusion restriction on MRI shifted the prediction toward IE. Internal validation yielded accuracy, sensitivity, specificity, precision, F1-score, and AUC values of 92.3%, 91.7%, 92.9%, 91.7%, 91.7%, and 94.1%, respectively.

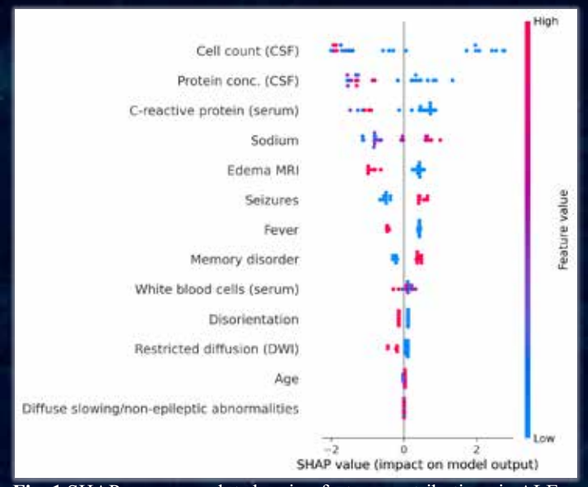
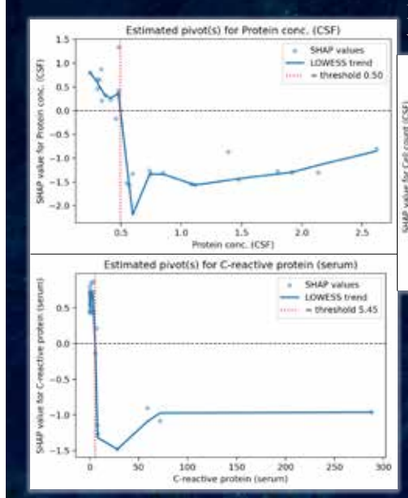


Fig. 1 SHAP summary plot showing feature contributions in ALE



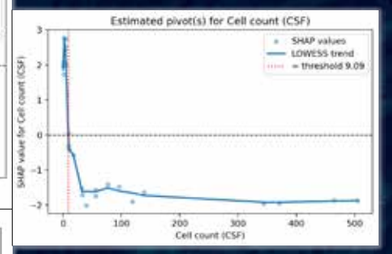
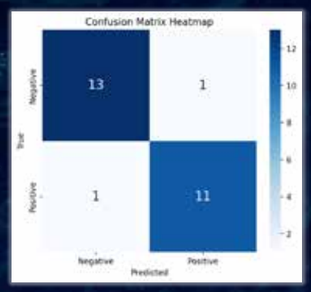


Fig. 2 Model-derived cutoff values for ALE

Fig. 3 Confusion matrix of model predictions



CONCLUSIONS

This data demonstrates that an artificial intelligence-based model capable of differentiating between the two most common causes of limbic encephalitis, using easily accessible clinical information, is feasible. External validation is currently in progress to evaluate its applicability in real-world clinical settings.

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Dr Dulmini Weerathunga

District General Hospital Chilaw, Sri Lanka

Development and validation of a clinical score to differentiate autoimmune from infectious encephalitis based on early presentation and investigations

Dr Dulmini Weerathunga is a consultant neurologist with a special interest on autoimmune and infectious encephalitis. Currently, she practices at a general hospital in Sri Lanka, where she frequently manages cases involving both infection related and autoimmune encephalitis. She graduated from the Faculty of Medicine, University of Colombo Sri Lanka, and hold MBBS, Doctor of Medicine (MD), and MRCP (UK). With over eight years of experience in the field of neurology, she has worked in various teaching hospitals in Sri Lanka as well as at King's College Hospital in London. As a neurologist operating in a resource limited setting, she is dedicated to enhancing awareness, improving diagnostic services, and advancing the management of encephalitis in Sri Lanka

Development and validation of a clinical score for early differentiation of autoimmune from infectious encephalitis based on clinical presentation and investigations

Dulmini Weerathunga (District General Hospital Chilaw, Sri Lanka)

Abstract

A clinical scoring system was developed and validated for early differentiation of autoimmune encephalitis (NMDARE) from infectious encephalitis (HSVE). Based on 15 years of published data, the score was tested on 100 synthetic HSVE and 100 NMDARE cases. Analising the total score ranging from -12 to +18, it showed cutoffs of ≥ +1 suggested NMDARE (88% sensitivity, 100% specificity), while ≤ -4 indicated HSVE (97% sensitivity, 98% specificity). The ROC AUC was 0.9984. This promising, practical tool requires validation with real-world data.

Introduction

Autoimmune encephalitis, particularly anti-NMDAR encephalitis (NMDARE), and infectious encephalitis, most notably herpes simplex virus encephalitis (HSVE), often present with overlapping early features. Prompt differentiation of NMDARE and HSVE is crucial for appropriate treatment. In settings without advanced diagnostics, a clinical tool based on early features is essential. This study aimed to create and validate such an evidence-based scoring system using a synthetic patient dataset.

Methods

The NMDARE vs HSVE Early clinical score was developed based on a systematic review of literature over past 15 years. Clinical features and early investigation parameters (e.g., onset, fever, psychiatric symptoms, CSF, MRI/EEG findings) were identified. Each variable was assigned a weight based on its relative frequency and diagnostic value. Synthetic datasets (100 HSVE, 100 NMDARE cases) were generated reflecting realistic symptom frequencies and demographics. Each case received a total score and performance was assessed via confusion matrix, sensitivity, specificity, and ROC area under the curve (AUC).

Results

The score ranges from -12 (favoring HSVE) to +18 (favoring NMDARE). Mean scores were +5.16 (NMDARE) and -9.80 (HSVE). A threshold of ≥ +1 indicated NMDARE (88% sensitivity, 100% specificity). A score ≤ -4 predicted HSVE (97% sensitivity, 98% specificity). Scores between -3 and 0 represented an indeterminate zone.(table 2, 3) Diagnostic accuracy was high, with an ROC AUC of 0.998.

Feature		Clinical Criteria	Score
1.	**Onset speed**	1.1. subacute (3–30 days)	1
		1.2. hyperacute (<3 days)	-2
2.	**Fever**	body temperature ≥38°C	-2
3.	**Psychiatric symptoms**	3.1. Prominent early psychosis/agitation	2
		3.2. confusion, drawsiness, delirium	-1
4.	**Movement disorder**	4.1 chorea, catatonia	2
		4.2. orofacial dyskinesia	3
5.	**Autonomic dysfunction**		2
6.	**Early seizures (<5days)**	Focal or generalized seizures	-1
7.	**Early memory dysfunction**		1
8.	**Focal neurology**	Focal motor, focal sensory, cranial nerve defects	-2
9.	**CSF WBC count**	>100 cells/mm³	-2
10.	**CSF Protein**	CSF Protein ≥75 mg/dL	-2
11.	**MRI / CT findings**	Unilateral temporal lobe only	-1
12.	**EEG findings**	12.1. Extreme delta brush	3
		12.2. Focal temporal slowing or PLEDs	-2
13.	**Past History of NMDAR Encephalitis**	Past anti-NMDAR Encephalitis	3
14.	**Past History of HSV Encephalitis**	Past HSV <6 weeks ago	1
		Past HSV >6 months ago	-1
		Past HSV unknown timing or 6 weeks - 6months	0

Table 1 - NMDARE vs HSVE Early clinical score

HSVE

Cutoff value	Sensitivity	Sepecificity	PPV	NPV	Acuracy
≤ -1	99%	90%	90.83%	98.90%	94.50%
≤ -2	99%	93%	93.40%	98.94%	96%
≤ -3	99%	97%	97.06%	98.98%	98%
≤ -4	97%	98%	97.98%	97.03%	97.50%

NMDARE

Cutoff value	Sensitivity	Sepecificity	PPV	NPV	Acuracy
≥ 1	88%	100%	100%	89.29%	94.00%
≥ 2	84%	100%	100%	86.21%	92%
≥ 3	78%	100%	100%	81.97%	89%
≥ 4	70%	100%	100%	76.97%	85%

Discussion and Conclusion

The NMDARE vs HSVE Early clinical score demonstrates strong discriminatory power between NMDARE and HSVE using routine findings. Its promising performance in synthetic data suggests it can guide early treatment, particularly where definitive testing is delayed or unavailable. However, the primary limitation is reliance on synthetic data, necessitating real-world validation. Applicability to other encephalitis subtypes also requires exploration.

References:

1. Graus F, et al. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol. 2016.
2. Dalmau J, et al. Anti-NMDA-receptor encephalitis: case series and analysis. Lancet Neurol. 2008.
3. Granerod J, et al. Causes of encephalitis in England: a prospective study. Lancet Infect Dis. 2010.
4. Armangue T, et al. Pediatric anti-NMDAR encephalitis: analysis of 20 cases. Neurology. 2015.
5. Venkatesan A, et al. Encephalitis diagnosis: consensus statement. Lancet Neurol. 2013.
6. Irani SR, et al. NMDAR antibody encephalitis: clinical progression. Brain. 2010.
7. Schmitt SE, et al. Extreme delta brush in anti-NMDA receptor encephalitis. JAMA Neurol. 2012.
8. Whitley RJ, et al. Acyclovir therapy for HSV encephalitis. N Engl J Med. 1986.
9. Gaspard N, et al. Autoimmune epilepsy and immunotherapy. Neurology. 2015.

ENCEPHALITIS CONFERENCE 2025

Dr Fraser Kenny

Kings College Hospital, UK

HHV6 Dilemma: treat the case or treat just in case?

Dr Fraser Kenny is a CT3 Anaesthetic Trainee in South East London. He graduated from Brighton and Sussex Medical School in 2020, having also completed a BSc in Neuroscience at the University of Leeds. He undertook his foundation training at the Royal United Hospital in Bath, followed by a clinical fellow post in intensive care before beginning his anaesthetic training. He plans to go on to continue his training in both anaesthetics and intensive care medicine.

HHV Encephalitis: To treat the case, or treat just in case?

NHS King's College Hospital NHS Foundation Trust

King's Critical Care

1. Fraser Kenny, 1. Sylwia Setla, 1. Masumi Tanaka, 1. Tharuka Kalhari Sikuradipathi, 2. Anjaneya Bapat, 3. Thomas Booth, 1. Despoina Koulenti (1. Critical Care Department, King's College Hospital NHS Foundation Trust, 2. Microbiology Department, King's College Hospital NHS Foundation Trust, 3. Radiology department, King's College Hospital NHS Foundation Trust)

Introduction

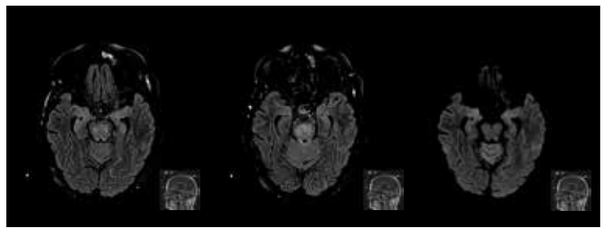
Human herpesvirus 6 (HHV-6) is a common cause of a mild viral illness in children, which can then remain latent in the host. It has been implicated as a rare cause of meningoencephalitis, typically in significantly immunocompromised patients, either as a primary infection or as a reactivation (1).

We present the case of a female in her 60s who presented with non-specific symptoms and subsequently experienced a drop in GCS without a clear cause. The only positive microbiological result obtained was HHV-6 following lumbar puncture. She was known to have Cushing's disease and was awaiting possible resection of her adrenal adenoma. Given her immunocompromised state and the absence of any other identified cause, she was treated with foscarnet therapy and demonstrated rapid neurological improvement.

This case highlights some of the diagnostic challenges surrounding viral encephalitis, particularly those caused by atypical or rare pathogens such as HHV-6. With the increasing availability of viral PCR assays, cases previously labelled as idiopathic encephalitis are now more likely to have potential causative pathogens identified (2). The key question remains whether such findings represent true pathogenic infection or incidental viral detection.

Timeline of Admission

Day	Key Events & Findings	Interventions / Outcomes
0	• Patient presented from rehab facility with malaise, fever, SOB • Tachycardic, febrile, ↑ CRP, GCS 15	• Broad-spectrum antibiotics started (infection of unknown source) • Admitted under medical team
1-15	• Recurrent fevers, no localising signs • Negative blood & urine cultures • CXR clear	• Multiple antibiotic courses
16	• Deterioration: febrile, confused (GCS 11), ↑ O_2 requirement • CT head: nil acute • **LP: mild ↑ protein, no WCC, Gram stain -ve**	• CNS antimicrobials started • Renal replacement therapy for AKI • Admission to ITU
17-19	• CTPA: no PE, no infection • GCS declined → 4 despite CRP normalization	• Aciclovir stopped • CNS antibiotics continued
20	• LP PCR results: **HHV-6 positive, all other viruses tested negative**	• **Foscarnet commenced**
21–24	• CT angio/venous: nil acute • GCS improved → 14 • Residual left-sided weakness • MRI brain/spine: small embolic events	• Care transferred under stroke team
25–30	• Neurology improving • TOE: no endocarditis • Repeat LP: unchanged	• Physiotherapy and ward based medical care continuing
31-107	• Discharged home after prolonged stay • Holter monitor showed sinus rhythm • Several further infective episodes, no new / further neurological decline	• Function on discharge: standing with assist ×2, dependent for ADLs, deconditioned



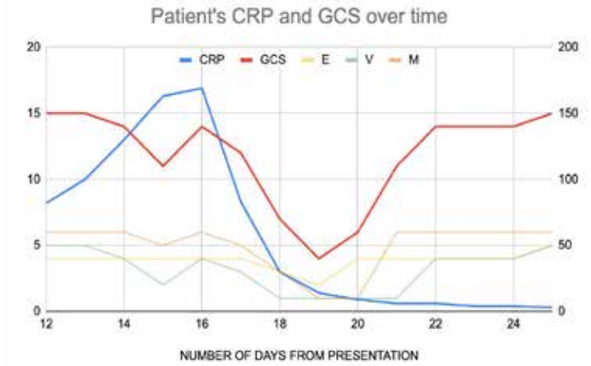
Images 1-3 left to right:
A - MRI T2 flair showing inflammation in the limbic system
B - MRI T2 flair, showing inflammation of the brainstem / pons
C - Diffusion weighted scan showing increased signal from the limbic system

References

1. Pellett PE, Ablashi DV, Ambros PF, et al. Chromosomally integrated human herpesvirus 6 (ciHHV-6). *Rev Med Virol*. 2012;22(3):144–155. PMID: 22052666
2. Green DA, Pereira M, Miko B, Radmard S, Whittier S, Thakur K. Clinical significance of human herpesvirus 6 positivity on the FilmArray meningitis/encephalitis panel. *Clin Infect Dis*. 2018;67(7):1125–1128. PMID: 29635334
3. Madan RP, McNeil K, et al. Human herpesvirus 6, 7, and 8 in solid organ transplantation: a review. *Transpl Infect Dis*. 2019;21(3):e13058. PMID: 30844089
4. Leveque N, et al. Human herpesvirus 6 infection of the central nervous system in immunocompetent adults: a case report and literature review. *J Med Virol*. 2020;92(10):2963–2970. PMID: 32329003
5. Human herpesvirus 6 encephalitis in immunocompetent and immunocompromised hosts: diagnostic and clinical features. *J Clin Virol*. 2021;139:104819. PMID: 33587722
6. A review of reported cases of human herpesvirus 6 encephalitis in immunocompetent adults. *Open Forum Infect Dis*. 2024;11(9):ofae501. PMID: 39301106
7. Miura H, et al. Inherited chromosomally integrated HHV-6: diagnosis and clinical implications. *Viruses*. 2025;17(1):122. PMID: 40472254

Learning Objectives

- To recognise the potential role of HHV-6 as a rare cause of meningoencephalitis in immunocompromised adults.
- To discuss the diagnostic and therapeutic challenges in distinguishing pathogenic infection from viral reactivation or incidental finding.



Discussion

The increasing availability of PCR assays has enhanced the detection of viruses, including HHV-6, in cerebrospinal fluid (CSF). HHV-6 is highly prevalent in the general population, establishing latency following primary infection in childhood (3). Distinguishing between an active infection that causes disease and an asymptomatic viral detection remains difficult and creates a therapeutic dilemma as to whether to treat with antiviral agents or not. The decision to treat carries a risk whichever way it is considered as there is a risk of not treating a true pathogen but also the potential to expose patients to unnecessary treatment. As yet, there are no definitive diagnostic criteria or singular sensitive and specific test that can determine pathogenicity.

Quantitative PCR does offer a potential means of differentiation. High CSF viral loads, particularly when exceeding thresholds established in transplant or immunosuppressed cohorts, may support HHV-6 as a causative pathogen (5). However, these thresholds are not well validated, and values may overlap between incidental and pathogenic states (5,6). Furthermore, chromosomally integrated HHV-6, in which viral DNA is inherited within the host genome, can produce persistently high PCR signals without active replication, leading to potential diagnostic confusion. Testing both serum and CSF can help identify such cases, as similar viral loads in both compartments favour chromosomal integration rather than active infection (7).

In this case, the CSF result was qualitative and the serum result quantitative, making direct comparison difficult and limiting conclusions about HHV-6 as the cause of the patient's symptoms. Qualitative PCR remains useful for broad viral screening but must be interpreted alongside clinical, biochemical, and radiological findings (5).

Although characteristic MRI findings for HHV-6 encephalitis have been described, these are based on limited case series and therefore their diagnostic reliability remains uncertain. In this case, such imaging changes were observed but occurred alongside other potential confounders, complicating interpretation. The absence of CSF pleocytosis or classic MRI features does not exclude viral encephalitis; however, these factors should prompt caution before attributing causality to HHV-6 (2,5,6).

While advances in PCR technology have improved the detection of HHV-6 in CNS samples, establishing its pathogenic significance remains challenging. Interpretation requires careful integration of quantitative viral load data, comparison between CSF and blood compartments, radiological investigations, and close clinical correlation. Further multicentre studies are essential to define validated viral load thresholds and better delineate the neuropathogenic potential of HHV-6 in immunocompetent adults (5,6).

Future work

Further research is required to clarify the clinical significance of HHV-6 detection in cerebrospinal fluid, and to define criteria that reliably distinguish true pathogenic infection from latent or chromosomally integrated virus. Establishing validated quantitative thresholds through multicentre studies would help determine when viral load supports causality, rather than incidental detection. Standardisation of PCR methodologies across laboratories is essential to ensure comparability of results and improve diagnostic confidence.

Integration of clinical, biochemical, and radiological features will be key in producing diagnostic algorithms and guiding management decisions. Finally, prospective studies assessing the impact of antiviral treatment in confirmed HHV-6 meningoencephalitis are needed to balance therapeutic benefit against drug-related toxicity. A better understanding of the relationship between viral activity, host immune status, and neurological outcome will ultimately aid clinicians in navigating the diagnostic and therapeutic uncertainty that currently surrounds this condition.

ENCEPHALITIS CONFERENCE 2025

Dr Hanalise V. Huff

National Institute of Neurological Diseases and Stroke, USA

Is Ebola virus encephalitis under-recognized in children? Evidence of long-term neurologic, cognitive and psychiatric sequelae in Liberian pediatric Ebola survivors

Dr. Hanalise Huff is a child neurologist and currently a clinical research fellow at the NIH in the section of infections of the nervous system. She received her neurology training at Harvard, her masters of public health training at Tulane University and her bachelors from the University of California, Berkeley.

Long-term Neurologic, Cognitive, and Psychiatric Sequelae of Ebola in Liberian Pediatric Survivors

Hanalise V Huff, MD, MPH[1]; John Tweh[2]; Princess Lobbo[2]; Victor Taryor, MHA[2]; Emmanuel Lansana[2]; Joseph Dorbor, NA[2]; Rebecca Aba Slewion, NA[2]; Gina Norato[1]; Richa Duggirala, MS[4]; Leroy Yankae, MD[3]; Avindra Nath, MD[1]; Dehkontee Dennis, MD[2]; Kumblytee Johnson, MD[2]; Jeanne Billioux, MD[1]

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Background:

- The 2014 West Africa Ebola virus (EBOV) epidemic resulted in over 28,000 people infected, mostly in the countries of Liberia, Guinea, and Sierra Leone.
- Prior to this outbreak, knowledge of central nervous system (CNS) complications of Ebola Virus Disease (EVD) was limited.
- An observational cohort study in Liberia of all age groups found headaches, joint pain, memory loss, muscle pain and fatigue were more common in survivors when compared with controls at 12 months post-EVD.
- Adult Liberian EVD survivors in the five years after the outbreak were found to have a higher rate of headaches, memory loss, muscle soreness, depressive symptoms, trouble with concentration, lack of motivation, sexual dysfunction, and sensory changes when compared to controls.
- Pediatric Liberian survivors seen at ~18 months after EVD reported significantly more often than controls arm/leg weakness, fecal incontinence, and problems with sitting, standing, walking, seeing, understanding speech, and motivation. They also had more physical disability and executive function issues.
- The long term neurologic and neurocognitive sequelae following Ebola Virus Disease in children is otherwise not well described in the literature.
- Confirmation of direct viral invasion of the CNS is complicated by the highly contagious nature of the virus, limited access to neurologic specialist, and scarcity of healthcare resources in outbreak settings.
- We hypothesize that EBOV may cause subtle low-grade encephalitis acutely, leaving survivors with long-term neurologic, cognitive and psychiatric sequelae.
- This is the largest cohort of pediatric survivors of EVD studied specifically for neurologic effects known of at this time.

Methodology:

- Design: Single center, single visit case-control cross-sectional observational cohort.
- Protocol: Under Liberia-U.S. Partnership for Research on Vaccines and Infectious Diseases in Liberia (PREVAIL)
- Location: John F. Kennedy Hospital in Monrovia, Liberia.
- Enrollment Period: February-September 2025, ~10 years after EVD infection.
- Inclusion criteria: participants infected with EVD 10 years prior at age <18 (cases) and their family members/household close contacts (also of pediatric age) (controls) previously enrolled through PREVAIL III Ebola Natural History Study.
- Study procedures: 1) questionnaire and 2) psychiatric screening (Patient Health Questionnaire-9 [PHQ-9]) administered by a Liberian Physician/Physician Assistant in Liberian Simple English and 3) neurologic exam and 4) neurocognitive tests (International Cognitive Assessment-Pediatrics [ICA-P], and NIHToolbox Cognitive Battery [NIHTB-CB]) conducted by NINDS Neurologists (Drs. Huff and Billioux)
- Statistical Analysis: Symptom prevalence between survivors and controls were compared using Fisher's exact tests. Scores on NIHTB-CB were compared using multiple linear regression, controlling for sex and education. PHQ-9 was compared using Poisson regression controlling for sex, age, and education. ICA-P and its subdomains were compared using simple Wilcoxon rank sum tests.

Results:

- 153 survivors (cases) and 175 close contacts (controls) were enrolled.
- 94% reported no running water in the home, 35% no electricity, 62% had trouble finding food, and 91% reported less than 3 meals a day.
- Poisson regression of PHQ-9 showed that group did not significantly predict depression, after controlling for sex, age, and education (β = 0.08, SE= 0.17, p=0.65).

Table 1: Demographic data of cases and controls

Demographic Characteristics	Cases (N=153)	Controls (N=175)	Overall (N=328)
Age, *median [Min, Max]*	20 [10, 27]	19 [9, 26]	20 [9, 27]
Sex, *(%)*			
Male	45%	45%	45%
Female	55%	55%	55%
Education			
Years completed, *median [Min, Max]*	10 [0, 17]	10 [0, 20]	10 [0, 20]
Farthest school milestone			
No school	4%	1%	2%
Primary school	16%	22%	20%
Middle school	23%	25%	24%
High school	47%	44%	45%
Vocational school	3%	5%	4%
University	7%	3%	5%

Figure 2: ICA by cognitive domain

Cognitive Domain	Cases	Controls	Overall	p-value
mean (SD)	*(N=153)*	*(N=175)*	*(N=328)*	
Language	6.22 (1.08)	6.4 (0.744)	6.32 (0.918)	0.226
Visual/Construction Skills	3.33 (0.795)	3.23 (0.865)	3.28 (0.834)	0.299
Attention/Working Memory	6.76 (2.01)	6.58 (1.93)	6.66 (1.97)	0.331
Executive Function	1.69 (0.567)	1.68 (0.503)	1.68 (0.533)	0.55
Delayed Memory/Recall	5.85 (1.38)	6.03 (1.05)	5.95 (1.22)	0.452
Total Score	23.8 (4.55)	23.9 (3.66)	23.9 (4.09)	0.468

Figure 1: Neurologic Symptoms reported after EVD

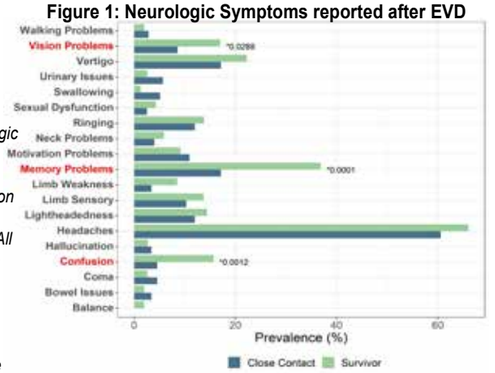
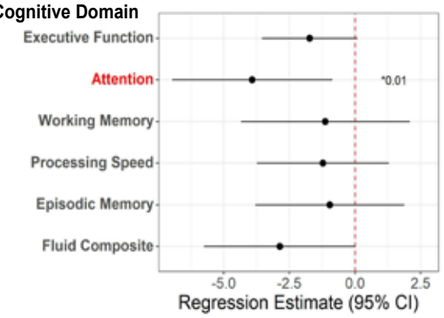


Figure 1 (top right): *On neurologic symptom questionnaire, vision problems (p=0.0288), memory problems (p<0.001), and confusion (p=0.0012) were reported significantly more than controls. All other neurologic symptoms were not determined to be statistically significant.*
**Neurologic symptoms were reported based on participant or parental recall. Of note, there are no pediatric neurologists in the country of Liberia.*
Figure 2 (bottom left): *On International Cognitive Assessment-Pediatrics, there were no significant differences between cases or controls in all cognitive domans.*
Figure 3 (bottom right): *On NIHToolbox, attention was significantly worse for cases than controls. There were no other significant difference between cases and controls.*
**scores were adjusted for age, sex and education.*

Figure 3: NIH Toolbox-Cognitive Battery Performance by Cognitive Domain



Conclusions:

- At ~10 years following infection, pediatric EVD survivors have significantly higher prevalence of memory problems, confusion, and vision issues when compared to controls.
- On cognitive testing, attention was found to be significantly worse in cases than controls, all other domains had no difference between groups.
- There was no significant difference between groups on depression screening.

References:

Schieffelin JS, Shaffer JG, Goba A,et al. Clinical illness and outcomes in patients with Ebola in Sierra Leone. *N Engl J Med*. 2014 Nov 27;371(22):2092-100. doi: 10.1056/NEJMoa1411680. Epub 2014 Oct 29.
PREVAIL III Study Group, Sneller MC, Reilly C, et al. A Longitudinal Study of Ebola Sequelae in Liberia. *N Engl J Med*. 2019;380(10):924-934.
Amuzu C, James PB, Bah AJ, Bayoh AVS, Singer SR. Post-Ebola sequelae among Ebola child survivors in Sierra Leone. *BMC Pediatr*. 2021 Oct 30;21(1):482.
Huff HV, Van Ryn C, Reilly C, Nath A, Billioux BJ, Terfeh-Burnette HD, Johnson KL, Bearden DR. Neurologic Sequelae Following Ebola Virus Disease in Children in Liberia: an Observational Cohort Study. *Neurology* 2025 Nov.

ENCEPHALITIS CONFERENCE 2025

Ms Isabela Bettu Bini

Universidade do Planalto Catarinense, Brazil

Long-term cognitive sequelae after encephalitis: a systematic review.

Ms Isabela Bettu Bini is a medical student at UNIPLAC (University of the Qatar Plateau) in Lages, Brazil. She's currently at the second year of medicine and is interested in research, especially in the area of neurology. Isabela has already presented systematic reviews at national congresses and plans to start sending her work to international meetings in order to increase her reach and meet new professionals.

Long-Term Cognitive Sequelae After Encephalitis: A Sistematic Review.

Encephalitis International
The brain inflammation non-profit

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INTRODUCTION

Encephalitis is an inflammatory condition of the brain parenchyma, which may be infectious or non-infectious in origin, characterized by fever, altered consciousness, seizures, and focal neurological deficits[1]. It represents a significant contributor to morbidity, mortality, and long-term neurological disability in both pediatric and adult populations, as cognitive dysfunction frequently persists beyond the acute phase of the illness[2],[3].

OBJECTIVES

This systematic review aims to evaluate the long-term cognitive sequelae in post-encephalitis patients, with particular emphasis on the most frequently impaired cognitive domains, thereby enhancing the understanding of the neurocognitive consequences associated with this condition.

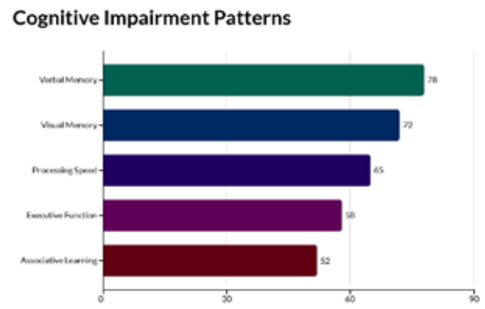
METHODS

A systematic review was conducted in accordance with PRISMA guidelines, utilizing the PubMed database to identify relevant studies published within the last five years. The search strategy employed the MeSH terms ("Encephalitis") AND ("Cognition Disorders") with Boolean operators to optimize study retrieval. An initial pool of 16 articles was identified. Two independent reviewers screened titles and abstracts, applying predefined inclusion and exclusion criteria. Following this process, 10 articles were excluded due to their nature as review articles, irrelevance to the research question, or non-human subject focus, resulting in six studies eligible for final analysis. Any discrepancies between reviewers were resolved through consensus.

REFERENCES

FINDINGS

The six included studies, encompassing over 250 participants, investigated cognitive outcomes across various encephalitis subtypes, with a predominant focus on autoimmune encephalitis, particularly anti-NMDAR encephalitis. Cognitive assessment tools included standardized instruments such as the Wechsler Adult Intelligence Scale, Wechsler Memory Scale, Cambridge Neuropsychological Test Automated Battery, and MATRICS Consensus Cognitive Battery.
The findings consistently demonstrated cognitive impairments, most notably in verbal and visual memory, processing speed, executive function, and associative learning.
Notably, cognitive deficits persisted for up to three years post-diagnosis, even among patients deemed to have achieved favorable functional recovery, with memory and language domains being particularly affected. Furthermore, longitudinal data revealed that approximately one-third of patients failed to resume occupational or academic activities during follow-up.



CONCLLUSION

The present analysis demonstrates that encephalitis, particularly autoimmune variants, is associated with persistent cognitive dysfunction despite clinical recovery. The observed variability in cognitive impairment patterns highlights the imperative for individualized and longitudinal neuropsychological monitoring in this patient population.

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Dr Jeroen Kerstens

Erasmus University Medical Center, The Netherlands

"Unexplained" chorea explained by autoimmune encephalitis: a Dutch cohort study

Dr Jeroen Kerstens is a clinical neurologist with experience in autoimmune neurology and work as an associated neurologist at the neuroimmunology unit of the University Hospital of Antwerp, Belgium. In addition, he is a PhD candidate at the autoimmune encephalitis research group of the Erasmus University Medical Center in Rotterdam, the Netherlands. In 2016, he obtained his medical degree with great distinction at the University of Antwerp. Thereafter, he was trained in neurology in Antwerp and Rotterdam, and completed his five-year neurology residency in August 2021.

"Unexplained" chorea explained by autoimmune encephalitis: a Dutch cohort study

Jeroen Kerstens, j.kerstens@erasmusmc.nl

Jeroen Kerstens, MD[1], Juna de Vries, MD PhD[1], Marleen van Coevorden-Hameete, MD PhD [1], Suzanne Franken, MSc[1], Mariska Nagtzaam, MSc[1], Sharon Veenbergen, PhD[2], Eline Verhagen, MD[3], Susanne de Bot, MD PhD[3], Mayke Oosterloo, MD PhD[4], Peter Sillevis Smitt, MD PhD[1], Agnita Boon, MD PhD[1], Maarten Titulaer, MD PhD[1].

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Introduction

Autoimmune causes of chorea are increasingly recognized and the number of neuronal antibodies associated with this clinical phenotype is growing.

Goal: to identify autoantibodies in patients with unexplained chorea and to describe the prevalence of chorea in a retrospective cohort of Dutch patients with autoimmune encephalitis (AIE) and paraneoplastic neurologic syndromes (PNS).

Conclusions

Neuronal antibody testing has a relevant diagnostic yield (5-14%) in unexplained chorea and should be considered in all chorea patients without a clear structural or genetic cause.

Slow disease progression and absence of CSF pleocytosis or characteristic MRI do not rule out autoimmune causes of chorea and should not preclude a patient from antibody testing.

Most common antibody targets in autoimmune chorea are NMDAR, IgLON5, LGI1 and CV2.

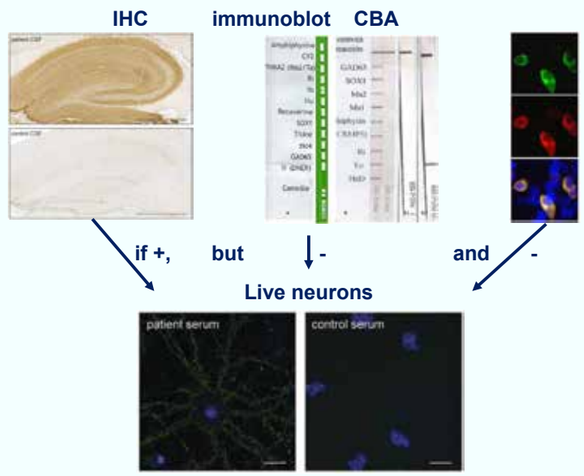
Methodology

We retrospectively tested two cohorts of patients with chorea:
- A: pts with suspicion of autoimmune chorea **(n=86)**
>>> Serum and/or CSF sent to Dutch national referral laboratory for antibody diagnostics
- B: pts without suspicion of autoimmune chorea and negative first-tier diagnostics* **(n=56)**
>>> Referred to three tertiary outpatient movement disorders clinics after
* Brain MRI, routine blood tests, genetic testing for Huntington's disease normal in all

Serum and/or CSF of all pts was tested by immunohistochemistry (IHC), PNS immunoblot and cell-based assays (CBAs). Samples positive on IHC but without identifiable antibodies were further evaluated with live neurons (Figure 1).

Review of nationwide retrospective AIE/PNS cohort (n=1,140) for presence of chorea.

Figure 1: Antibody testing techniques



Results

Cohort A (Figure 2): 12/86 antibody-positive (14%): IgLON5 (n=5), GlyR (n=1), $GABA_BR$ (n=1), unspecified antibodies (n=5; both IHC and live neurons +)

Cohort B (Figure 3): 3/56 antibody-positive (5%): LGI1 (n=1), CV2 (n=1), KLHL11 (n=1)

Nationwide Dutch AIE/PNS cohort: 39/1,140 (3.4%) patients with chorea (including ten newly diagnosed patients from aforementioned cohorts A-B): NMDAR (n=13), LGI1 (n=8), CV2 (n=6), IgLON5 (n=6), GlyR (n=2), Hu (n=2), $GABA_BR$ (n=1), KLHL11 (n=1)

Figure 2: Cohort A (suspicion of autoimmune chorea; n=86)

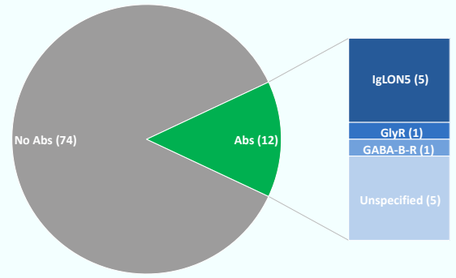


Figure 3: Cohort B (no suspicion of autoimmune chorea; n=56)

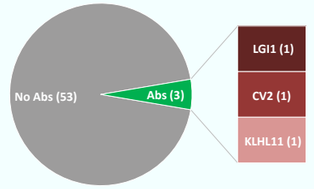


Table 1: Patients without suspicion of autoimmune chorea (cohort B) who turned out to be antibody-positive

Pt	Clinical syndrome	Ancillary tests	Tumor	Antibody testing	Final diagnosis	Treatment and response
F, 80y	>10y of slowly progressive behavioral changes, cognitive decline, apathy and generalized chorea (head, trunk, limbs); no observed seizures	**Brain MRI**: microvascular white matter lesions (Fazekas 3), generalized atrophy **CSF**: wbc 2/µL, nl protein, mirrored OCB	NSCLC (diagnosed 9y before onset; considered unrelated)	**Serum**: CBA anti-LGI1 +, IHC + (anti-LGI1 pattern) **CSF**: CBA anti-LGI1 +, IHC -	Anti-LGI1 encephalitis	Partial improvement of chorea with symptomatic treatment (tetrabenazine); no improvement of chorea or cognition with immunotherapy (three-day course of IVMP, 12y after onset)
F, 72y	3y of slowly progressive generalized chorea (orofacial + limbs R>L); 6y after onset also parkinsonism	**Brain MRI**: normal **CSF**: wbc 0/µL, nl protein, CSF-restricted OCB	NSCLC (diagnosed 4y after onset)	**Serum**: anti-CV2+ (titer 400), IIF + **CSF**: anti-CV2+ (titer 10), IIF +	Anti-CV2-PNS	Partial improvement with symptomatic (tiapride), immunological (IVMP) and later also oncological treatment (chemoradiation)
M, 76y	2y of slowly progressive dysarthria, cognitive decline, behavioral changes, ataxia, dystonia and chorea (orofacial, R upper limb)	**Brain MRI**: minimal microvascular white matter lesions (Fazekas 1), minimal cerebellar atrophy **CSF**: wbc 1/µL, nl protein, no OCB	None	**CSF**: CBA anti-KLHL11 +	Anti-KLHL11 encephalitis	Partial improvement with immunotherapy (IVMP, oral prednisone)

Abbreviations: CBA: cell-based assay, CSF: cerebrospinal fluid, F: female, IHC: immunohistochemistry, IIF: indirect immunofluorescence, IVMP: intravenous methylprednisolone, l: left, M: male, MRI: magnetic resonance imaging, nl: normal, NSCLC: non small-cell lung carcinoma, OCB: oligoclonal bands, PNS: paraneoplastic neurological syndrome, pt: patient, R: right, wbc: white blood cell, y: years

References

1. Balint B, Vincent A, Meinck HM, Irani SR, Bhatia KP. Movement disorders with neuronal antibodies: syndromic approach, genetic parallels and pathophysiology. Brain. 2018 Jan 1;141(1):13-36. doi: 10.1093/brain/awx189.
2. Balint B, Bhatia KP. Autoimmune movement disorders with neuronal antibodies - an update. Curr Opin Neurol. 2021 Aug 1;34(4):565-571. doi: 10.1097/WCO.0000000000000956.

Funding

This work was supported by a Research Mobility Fellowship from the European Joint Programme on Rare Diseases (EJP-RD) and by the Erasmus Trust Fund.

Dr Jakob Theorell

Center for Infectious Medicine, Sweden

Establishing a national registry for autoimmune encephalitides in Sweden

Dr Jakob conducted his PhD studies on human immunodeficiency syndromes affecting lymphocyte cytotoxicity in the Professor Yenan Bryceson research group from 2010 to 2017, in parallel with his clinical training. After obtaining his medical license and PhD in 2017, he became as a registrar in general adult psychiatry at Psychiatry Southwest, Stockholm. In 2018, he took up a postdoctoral researcher position in the Oxford Autoimmune Neurology Group led by Professor Sarosh Irani at the University of Oxford. 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. Jakob 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. In 2022, Jakob joined the Jenny Mjösberg research group at the Center for Infectious Medicine as a team leader, focusing on autoantibody-associated autoimmune encephalitis. He became a registrar in neurology at the Karolinska University Hospital in 2023. He is currently involved in building both national and Scandinavian networks for collaboration for the betterment of patient care and resarch around autoantibody-associated autoimmune encephalitis.

Swedish Neuro Registries

Autoimmune encephalitis registry

The autoimmune encephalitis registry aims to include all pediatric and adult patients with autoantibody-associated autoimmune encephalitis in Sweden. This includes both individuals with a non-paraneoplastic disease, such as Leucine-rich glioma 1-autoantibody encephalitis, classically paraneoplastic disorders, such as patients with Yo antibody-associated disease.

Scope

Given that the autoimmune encephalitides are non-demyelinating and tend to present with combinations of limbic symptoms, rapidly developing cerebellar ataxia, memory deficits and epilepsy, the information that the registry aims to catch covers differs somewhat from the other registries under the MS registry umbrella. However, given the shared treatments as well as overlapping follow-up infrastructure, the aim has been to mirror the registries for demyelinating disorders when possible.

Specifically, the register covers the following areas:
- Date of diagnosis
- Fulfillment of diagnostic criteria
- Radiological examinations
- Symptoms and symptom burden
- Treatments over time
- Disability scores
- Patient reported outcomes
- Inclusion in scientific studies

Current state of the register

- Operational since 2025-06-12
- Currently, ~20 patients are included

Plans ahead

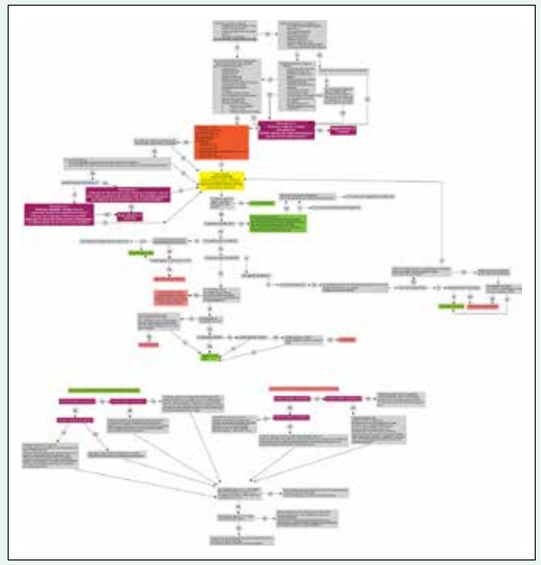
Connecting the registry with the output from the clinical laboratories that report positive antibody tests, so that all individuals that test positive get a basic registration, with feedback to the clinician asking them to fill out the registry, thereby ensuring that a systematic approach to the diagnosis is available in the whole country.

Registry Holder:
Katharina Fink
Responsible for sub-registry: Jakob Theorell

Email: Katarina.fink@ki.se
Jakob.Theorell@ki.se

Interactive diagnostic tool

Autoimmune encephalitis is diagnosed with a complex set of criteria, involving neurological, psychiatric, neuroradiological, neurophysiological and laboratory-based findings. Even as the autoantibodies are a prerequisite for the diagnosis, potential false positive and false negative results on the antibody tests means that systematic, stringent diagnostic procedures are needed. For this reason, the registry includes an interactive diagnostic tool, that follow criteria by Graus *et al(1, 2)* but also extending psychiatric criteria in accordance with Pollak *et al(3)*, as well as incorporating pediatric aspects, based on Cellucci *et al(4)*. With this tool, advice is given on how to interpret constellations of symptoms together with antibodies as well as pointing to the risk for associated malignancies.



Principal internal architecture of the interactive diagnostic tool. The point of entry is the left upper grey box.

References

1. F. Graus, *et al.*, Updated Diagnostic Criteria for Paraneoplastic Neurologic Syndromes. *Neurology - Neuroimmunology Neuroinflammation* **8** (2021).
2. F. Graus, *et al.*, A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol* **15**, 391–404 (2016).
3. T. A. Pollak, *et al.*, Autoimmune psychosis: an international consensus on an approach to the diagnosis and management of psychosis of suspected autoimmune origin. *Lancet Psychiatry* **7**, 93–108 (2020).
4. T. Cellucci, *et al.*, Clinical approach to the diagnosis of autoimmune encephalitis in the pediatric patient. *Neurol Neuroimmunol Neuroinflamm* **7**, e663 (2020).

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Mr. Justin Levinsky

University of Toronto, Canada & University Health Network, Canada.

Time to treatment in patients with autoimmune encephalitis: a single-center cohort study

Justin Levinsky is a Clinical Research Study Assistant and recent graduate of the Master of Health Science program in Medical Physiology at the University of Toronto (Toronto, ON, Canada). His research, conducted at Toronto Western Hospital within the University Health Network, focuses on autoimmune encephalitis, with particular emphasis on treatment timelines and predictors of intensive care unit (ICU) outcomes.

UNIVERSITY OF TORONTO

UHN Krembil Brain Institute

Delays to Immunotherapy in Patients with Autoimmune Encephalitis: Trends and Disparities

Justin Levinsky[1-3], Lana Sladoje[2,3], Mary Jane Lim-Fat[4,5], Alexandra Muccilli[5,6], Gregory S. Day[7], Sarah Lapointe[8], Seth A. Climans[9], Richard A. Wennberg[2,5], David F. Tang-Wai[3,5,10], Julien Hébert[2,3,5]

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Introduction

- Autoimmune Encephalitis (AE) is characterized by the production of autoantibodies targeted at the brain causing seizures, cognitive, and psychiatric symptoms.[1,2]
- Since the first description of anti-NMDAR encephalitis in 2007, multiple antibodies have been identified and linked to specific clinical presentations, presumably enhancing our diagnostic abilities.[3,4]
- Appropriate and early treatment of patients with AE is associated with improved long-term outcomes.[5,6]

Objectives

1. **Ascertain whether time to immunotherapy initiation has decreased in patients with AE since the year 2007.**
2. **Identify demographic and disease factors associated with time to immunotherapy in AE.**

Methods

- Study Design: Retrospective cohort study.
- Inclusion criteria: Probable or definite AE diagnosed between January 1, 2007, and December 31, 2024, at a single tertiary care center AE clinic.
- Primary outcome: Time from symptomatic onset to immunotherapy initiation.
- Statistical analysis:
  - Spearman correlation coefficient of year of symptomatic onset and time to treatment.
  - Wilcoxon rank sum and Fisher's exact tests for disease and clinical factors associated with time to treatment.
  - Multivariate linear regression of log-transformed time to treatment adjusting for age, sex, and factors significant on univariate analysis.

Results

Table 1: Study Cohort and Factors Associated with Time to Treatment

	n (%)
Sample Size, n (%)	91 (100)
Female, n (%)	59 (65)
Age at onset, years, median (range)	33 (11-83)
Received immunotherapy, n (%)	91 (100)
Onset to admission, days, median (range)	45 (0-3316)
White ethnicity, n (%)	39 (43)
Results of Antibody Testing	
Cell-Surface, n (%)	49 (54)
NMDAR, n (%)	26 (29)
LGI1, n (%)	17 (19)
Intracellular, n (%)	16 (18)
GAD65, n (%)	9 (10)
Negative, n (%)	26 (29)
Cerebrospinal Fluid (CSF) Analysis	
CSF Pleocytosis (>5WBC/μL), n (%)	37 (41)
CSF Protein, mg/dL, median (range)	39 (0-733)
EEG and MRI	
Temporal interictal epileptic discharges, n (%)	6 (7)
Temporal focal slowing, n (%)	18 (20)
Mesial temporal T2 hyperintensities, n (%)	16 (18)
Paraneoplastic	
Associated neoplasm, n (%)	9 (10)

Figure 1: Univariate Analysis of Clinical Factors Associated with Time to Immunotherapy

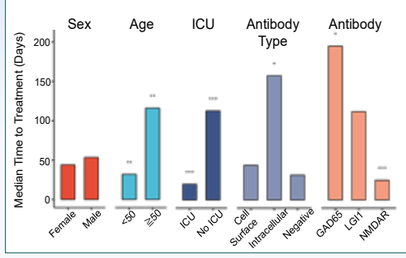
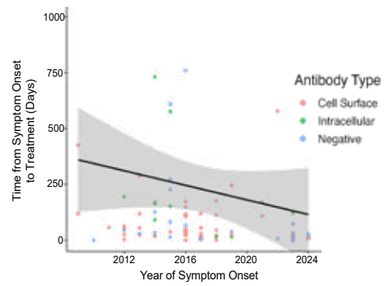


Figure 2: Multivariate Linear Regression of Time to Immunotherapy by Year of Symptomatic Onset

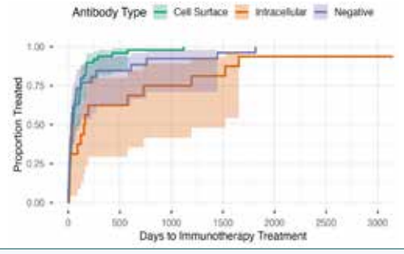


Spearman correlation between year of onset and time to immunotherapy: ρ = −0.34, p = 0.001.

Table 2: Multivariate Linear Regression Results

Variables	β Estimate (95 % CI)	Percent Change in Time to Treatment	p-Value
Year of onset	−0.26 (−0.47 to −0.05)	-23%	**0.019***
Male sex	0.18 (−0.22 to 0.58)	+20%	0.38
Age	0.09 (−0.08 to 0.27)	+9%	0.313
NMDAR	−0.30 (−0.75 to 0.15)	-26%	0.20
GAD65	0.05 (−0.64 to 0.74)	+5%	0.87
Intracellular	1.10 (0.56 to 1.64)	+200%	**<0.001***
ICU Admission	0.85 (0.30 to 1.40)	+133%	**<0.01***

Figure 3: Kaplan-Meier Curve of Delay to Treatment by Antibody Type



Conclusions

- Since its inception as a distinct disease entity in 2007, time to immunotherapy has significantly decreased in AE.
- Patients with NMDAR experienced shorter times to treatment.
- Patients with intracellular antibodies experienced longer delays to treatment but the steepest decrease in delays over the years.

Abbreviations

AE: Autoimmune encephalitis; GAD65: Glutamic Acid Decarboxylase 65; LGI1: Leucine-rich Glioma-Inactivated protein 1; NMDAR: N-Methyl-D-Aspartate Receptor.

References

1. Graus F, Titulaer M, Ramani B, Benseler S, Bien C, Cellucci T, et al. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol. 2016 Apr;15(4):391–404.
2. Hébert J, Muccilli A, Wennberg RA, Tang-Wai DF. Autoimmune Encephalitis and Autoantibodies: A Review of Clinical Implications. The Journal of Applied Laboratory Medicine. 2022 Jan 5;7(1):81–98.
3. Dalmau J. NMDA receptor encephalitis and other antibody-mediated disorders of the synapse: The 2016 Cotzias Lecture. Neurology. 2016 Dec 6;87(23):2471–82.
4. Hahn C, Budhram A, Alikhani K, AlOhaly N, Beecher G, Blevins G, et al. Canadian Consensus Guidelines for the Diagnosis and Treatment of Autoimmune Encephalitis. Can J Neurol Sci. 2024 Feb 5;1–21.
5. Balu R, McCracken L, Lancaster E, Graus F, Dalmau J, MJ. A score that predicts 1-year functional status in patients with anti-NMDA receptor encephalitis. Neurology. 2018 Dec 21.
6. Hébert J, Day GS, Steriade C, Wennberg RA, Tang-Wai DF. Long-Term Cognitive Outcomes in Patients with Autoimmune Encephalitis. Can J Neurol Sci. 2018 Sep;45(5):540–4.

Acknowledgements

- This study was funded by a grant from the University of Toronto Slamen Fast Fund for New Initiatives in Neurology.

ENCEPHALITIS CONFERENCE 2025

Dr Kathryn Holroyd

Columbia University Irving Medical Center, USA

Clinical and diagnostic characteristics of autoimmune, infectious, and cryptogenic central nervous system vasculitis at a tertiary care center

Dr Kathryn (Katie) Holroyd completed medical school at Johns Hopkins University School of Medicine followed by neurology residency at the Harvard Massachusetts General and Brigham and Women's Hospitals, where she was elected chief resident in 2020. Dr. Holroyd then completed a neuroimmunology fellowship at Harvard Massachusetts General Brigham where she further specialized in the care of autoimmune conditions such as multiple sclerosis, neuromyelitis optica, and encephalitis. Subsequently, she spent two years training in global health and neuroinfectious diseases through Yale University School of Medicine and the International Neuro-HIV Cure Consortium, during which she was based full time in Bangkok Thailand studying the neurologic complications of HIV and other infections. She has also participated in clinical work and research in multiple other global settings including the United Arab Emirates and Zambia. She is currently the medical student and residency education director for neuro-infectious disease, and assists in running the post-doctoral neuroinfectious disease clinical research fellowship for LIC and LMIC physician-scientists at Columbia.

COLUMBIA | COLUMBIA UNIVERSITY IRVING MEDICAL CENTER

CLINICAL AND DIAGNOSTIC CHARACTERISTICS OF AUTOIMMUNE, INFECTIOUS, AND CRYPTOGENIC CENTRAL NERVOUS SYSTEM VASCULITIS AT A TERTIARY CARE CENTER

Gerome B. Vallejos[1], Jackson A. Roberts[2], Carla Y. Kim[1], Kiran T. Thakur[1], Kathryn B. Holroyd[1]

Background

- Central nervous system (CNS) vasculitis is a rare, diagnostically challenging disorder
- Differentiating between infectious and autoimmune etiologies of CNS vasculitis is difficult due to nonspecific clinical presentations and limited diagnostic tools

Methods

- Patients admitted to Columbia University Irving Medical Center between 2010 and 2024 with an ICD-9 or ICD-10 diagnosis of CNS vasculitis were included
- Cases were categorized through detailed chart review into definite or probably vasculitis, as well as infectious, autoimmune, or cryptogenic
  - Definite = confirmative histopathologic findings or identification of a causative pathogen
  - Probable = compatible findings on MRI, angiography along with compatible clinical and laboratory findings
- Demographic, neurologic exam, cerebrospinal fluid, neuroimaging, treatment, and outcome data were gathered from detailed chart review
- Immunocompromised state was defined as HIV, asplenia, post-transplantation, and/or use of immunosuppressive medication
- Statistical comparisons across diagnostic subgroups were conduced using nonparametric testing

Results

- 48 cases were reviewed, 43 met criteria for definite (23%) or probable (77%) vasculitis
  - Mean age 45.7 years, 51% male
  - Race: 28% white, 14% black, 7% Asian, 14% other, 34% unknown
  - Ethnicity: 28% non-Hispanic/Latino, 16% Hispanic/Latino, Unknown 51%
  - 44% immunocompromised
- 14% infectious, 30% autoimmune, 56% cryptogenic
- No differences were seen across neurologic presenting symptoms
- No differences were seen across CSF parameters
- Corticosteroids were given to 97% of cases, disease modifying therapy to 25%, and antimicrobials to 16%

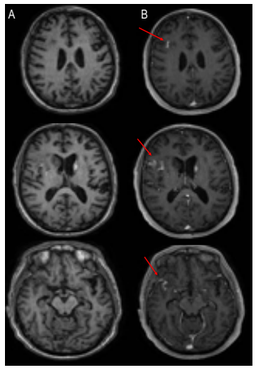
Imaging Results

- More people in the cryptogenic group had narrowing in more than two vessels, as well as parenchymal ischemia, hemorrhage, or FLAIR hyperintensities
- Vessel narrowing was identified in 81% of cases (MCA 44%, ACA 32%, PCA 23%, basilar 11%, vertebral 9%.
- Vessel narrowing was seen more often in infectious than other causes of vasculitis
- Ischemia was seen in 53%, more common in cryptogenic
- Enhancement occurred in 28%, more common in cryptogenic
- Hemorrhage occurred in 40%

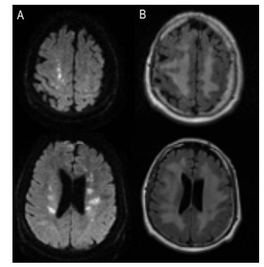
Laboratory, Neuroimaging and Treatment Findings Across Causes of CNS Vasculitis

	Total N=43	Infectious N=6	Autoimmune N=13	Cryptogenic N=24	p value
Meningitis/Encephalitis Panel	11 (25.6%)	2 (33.3%)	4 (30.8%)	5 (20.8%)	0.575
CSF Profile median (IQR)					
CSF Protein	53 (32-83)	104 (58-402)	49 (29-69)	52 (32-69)	0.125
CSF Glucose	79 (66-98)	97 (83-115)	77 (67-105)	72 (62-87)	0.124
CSF RBC	60 (2-598)	1002 (63-2440)	2 (0-52)	64 (11-599)	0.164
CSF WBC	3 (2-27)	4 (1-544)	16 (2-34)	5 (1-13)	0.897
CSF Neutrophil %	2 (0-57)	42 (0-86)	2 (1-42)	3 (0-24)	0.851
CSF Lymphocytes %	85 (60-92)	20 (3-91)	90 (80-94)	83 (65-91)	0.308
CSF Monocyte %	8 (4-14)	9 (3-13)	7 (3-11)	10 (4-17)	0.754
CSF:Serum Glucose ratio	0.63 (0.50-0.74)	0.67 (0.62-0.68)	0.58 (0.49-0.69)	0.64 (0.50-0.74)	0.162
Imaging					
Brain MRI	41 (95.3%)	6 (100%)	12 (92.3%)	23 (95.8%)	0.750
Head and Neck MRA	36 (83.7%)	5 (83.3%)	11 (84.6%)	20 (83.3%)	0.995
CTA	32 (74.4%)	6 (100%)	8 (61.5%)	18 (75%)	0.202
DSA	13 (30.2%)	2 (33.3%)	4 (30.8%)	7 (29.2%)	0.979
Vessel Narrowing					
Total	35 (81.4%)	6 (100%)	9 (69.2%)	20 (83.3%)	0.385
ACA	14 (32.6%)	4 (66.7%)	0 (0%)	10 (41.7%)	**0.004**
PCA	10 (23.3%)	3 (50%)	1 (7.7%)	6 (25%)	**0.014**
MCA	19 (44.2%)	5 (83.3%)	2 (15.4%)	12 (50%)	**0.010**
Basilar	5 (11.6%)	1 (16.7%)	0 (0%)	4 (16.7%)	**0.018**
Vertebral	4 (9.3%)	0 (0%)	1 (7.7%)	3 (12.5%)	**0.025**
Other	3 (7%)	0 (0%)	1 (7.7%)	2 (8.3%)	**0.015**
≥2 Vessel Narrowing	17 (39.5%)	5 (83.3%)	1(7.7%)	11 (45.8%)	**0.005**
Imaging features					
Ischemia	23 (53.5%)	2 (33.3%)	3 (23.1%)	18 (75%)	**<0.001**
Hemorrhage	17 (40.55%)	4 (66.7%)	3 (25%)	10 (41.7%)	0.233
T2 FLAIR Hyperintensities	26 (60.5%)	3 (50%)	5 (38.5%)	18 (75%)	**0.001**
Enhancement	12 (27.9%)	2 (33.3%)	1 (7.7%)	9 (37.5%)	**0.008**
Biopsy	12 (27.9%)	1 (16.7%)	3 (23.1%)	8 (33.3%)	0.644
Definite	3 (27.3%)	0 (0%)	1 (33.3%)	2 (28.6%)	0.804
Treatment					
Steroid	38/39 (97.4%)	5/6 (83.3%)	12/12 (100%)	21/21 (100%)	0.059
Time to steroid, median days (IQR)	2 (1-7)	1 (1-2)	3 (1-6)	4 (1-7)	0.54
DMT	11 (25.6%)	0 (0%)	3 (23%)	8 (33.3%)	0.239
Antibiotics	7 (16.3%)	2 (33.3%)	2 (15.4%)	3 (12.5%)	0.463

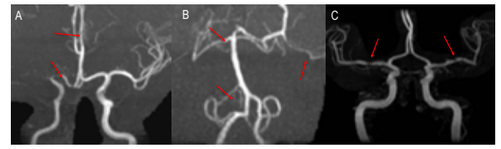
Imaging Results



T1 Pre (A) and Post contrast images from a patient demonstrating both parenchymal enhancement in an area of subacute stroke, along with abnormal leptomeningeal and pachymeningeal enhancement associated with vasculitis



Example DWI (A) and T2FLAIR (B) axial images from the same case demonstrating diffuse, confluent, bilateral T2FLAIR hyperintensities out of proportion to acute ischemic changes.



MRA demonstrating diffuse anterior circulation vessel narrowing and irregularity (A) and bilateral posterior circulation irregularity, stenosis, and beading (B) from the same patient patient with cryptogenic vasculitis. Panel C demonstrates similar multifocal anterior circulation narrowing from a patient with infectious vasculitis

Conclusions and Limitations

- Definitive diagnosis of CNS vasculitis remains difficult, despite use of extensive testing
- We did not identify laboratory or CSF testing to reliably distinguish infectious from inflammatory causes of CNS vasculitis
- Differences in pattern of vessel involvement and neuroimaging features may help distinguish causes of CNS vasculitis
- This study was limited by its retrospective nature and small sample size

ENCEPHALITIS CONFERENCE 2025

Dr Krzysztof Smolik

Hospices Civils de Lyon, France

Cognitive profile of patients with anti-IgLON5 disease

Dr Krzysztof Smolik is a neurologist and PhD student in Neurosciences at University Hospital of Modena in Italy as well as a research fellow at French Reference Center for Paraneoplastic Neurological Syndromes and Autoimmune Encephalitis in Lyon, France. He has a master's degree in Medicine and a bachelor's degree in Computer Engineering. He is a fellow of the European Board of Neurology and a member of the EAN's panels on Neuroimmunology and on Multiple Sclerosis. His main clinical and research interests include neuroimmunology, with a focus on autoimmune encephalitis and multiple sclerosis. In the field of AE, his works focus on IgLON5 and biomarkers. In the field of MS he mainly worked on biomarkers and treatments' safety and efficacy.

Cognitive profile of patients with anti-IgLON5 disease

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BACKGROUND

Anti-IgLON5 disease is a recently described type of autoimmune encephalitis (AE) with multidomain clinical presentation which includes cognitive impairment. Unlike domains such as sleep disorders or movement disorders, cognitive dysfunction has not been well characterized.

OBJECTIVES

- Describe the frequency of cognitive impairment in anti-IgLON5 disease
- Assess the severity of cognitive deficits
- Identify the most frequently affected cognitive domains
- Describe the trajectory of cognitive deficits

METHODS

All patients with anti-IgLON5 disease diagnosed at the French Reference Centre on AE (Feb 2016-Jan 2025) with at least one cognitive screening test (Mini Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Frontal Assessment Battery (FAB), and/or full neuropsychological assessments were included. Data on cognitive tests were retrospectively collected and analysed using z-scores based on age and education-adjusted normative values

RESULTS

We included 44 patients (mean age at diagnosis 69.7±8.7 years, 59% male). The mean diagnostic delay was 36.1±43.9 months; the mean modified Rankin Scale (mRS) at diagnosis was 3.0±1.0 while the mean IgLON5 composite score (ICS) was 16.7±8.0. 4/24 (17%) patients showed a neurodegeneration biomarker profile suggestive of Alzheimer's disease (i.e., A+T+N+). At diagnosis, impairment in general cognitive screening tests (MMSE or MoCA) was present in 14/23 (61%) patients. MoCA scores negatively correlated with mRS at diagnosis (rho=-0.82, p=0.024) while for MMSE there was a nearly significant trend (rho=-0.42, p=0.092). At diagnosis, the lowest z-scores were obtained in RLD (delayed verbal recall), TMT B-A test and TMT B test.

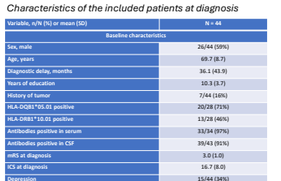
At last follow-up, in patients previously tested at diagnosis (n=11), MMSE scores were significantly lower than at diagnosis (21.9±7.7 vs 25.9±3.4, p=0.0488) and 8/11 (73%) patients worsened. Throughout the whole disease course, the most affected cognitive domains were verbal memory (11/22, 50%), verbal fluency (9/28, 32%) and mental flexibility (5/19, 26%). Contrarily, the least impaired domains were praxis (0/12, 0%) and visuo-constructional abilities (1/19, 5%). Deficits in verbal memory often overlapped with those in verbal fluency, as did impairments in mental flexibility with those in attention. 38% of patients presented impairment in more than 1/3 of tested domains. A marked discrepancy was observed between the proportion of patients exhibiting deficits in free delayed recall and those with impaired total delayed recall (25% vs 42%) suggesting a retrieval deficit potentially associated with frontal lobe dysfunction.

Characteristics of the included patients at diagnosis

Variable, n/N (%) or mean (SD)	N = 44
Baseline characteristics	
Sex, male	26/44 (59%)
Age, years	69.7 (8.7)
Diagnostic delay, months	36.1 (43.9)
Years of education	10.3 (3.7)
History of tumor	7/44 (16%)
HLA-DQB1*05.01 positive	20/28 (71%)
HLA-DRB1*10.01 positive	13/28 (46%)
Antibodies positive in serum	33/34 (97%)
Antibodies positive in CSF	39/43 (91%)
mRS at diagnosis	3.0 (1.0)
ICS at diagnosis	16.7 (8.0)
Depression	15/44 (34%)
Use of psychoactive drugs	11/39 (28%)
Cardiovascular comorbidities	
Arterial hypertension	23/44 (52%)
Dyslipidaemia	14/44 (32%)
Smoker	13/44 (30%)
Diabetes	12/44 (27%)
Ancillary testing	
Any CSF abnormality	29/43 (67%)
WBC elevated (>5 cells)	3/43 (7%)
Total protein elevated (>0.45 mg/dL)	25/43 (58%)
Oligoclonal bands present	6/25 (24%)
MRI	
Any MRI abnormality	21/32 (66%)
Atrophy	13/32 (41%)
Leukoaraiosis	12/32 (38%)
Temporal hyperintensity	2/32 (6%)
EEG	
Any EEG abnormality	7/23 (30%)
Epileptic discharges	0/23 (0%)
Diffuse slow waves	7/23 (30%)

Profile of CSF biomarkers at diagnosis

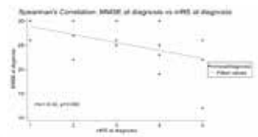
Biomarker	Value, mean (SD)	Cut-off for abnormal values	Abnormal values, n/N (%)
Aβ40 (n=18)	7608 (5731) pg/mL	-	-
Aβ42 (n=23)	794 (423) pg/mL	<550 pg/mL	9/28 (32)
Aβ42/ Aβ40 ratio (n=17)	0.53 (1.61)	<0.10	9/23 (39)
t-tau (n=24)	307 (119) pg/mL	>400 pg/mL	8/29 (28)
p-tau (n=24)	40 (23) pg/mL	>60 pg/mL	5/28 (18)
t-tau/p-tau ratio (n=24)	8.72 (3.05)	>10	4/29 (14)
t-tau/ Aβ40 ratio (n=23)	0.54 (0.45)	>0.52	7/23 (30)



Cognitive performance of patients at diagnosis (n=16)

Cognitive domain; test	No. of patients tested	Patients with significant impairment (z-score<-1.65 or <5 percentile), n/N (%)	Z-score, mean (SD)
Verbal fluency			
Fluency animals	13	1/13 (8)	-0.12 (1.35)
Fluency letters	14	1/14 (7)	-0.23 (1.19)
Mental flexibility			
TMT B-A time	10	1/10 (10)	-0.87 (1.50)
Information processing speed			
TMT A time	12	1/12 (8)	-0.36 (0.91)
Attention			
TMT B time	10	1/10 (10)	-0.83 (1.39)
Verbal memory			
RL1 (free immediate recall)	12	0/12 (0)	-0.39 (0.91)
RL9 (free delayed recall)		5/12 (42)	-1.04 (1.85)
RT1 (free delayed recall)		1/12 (8)	-
RTD (cued delayed recall)		3/12 (25)	-
Working memory			
Digit span forward	15	0/15 (0)	-0.21 (1.42)
Digit span backward		0/15 (0)	-0.25 (0.73)
Visuo-constructional abilities			
Rey's/Taylor's figure copy	7	0/7 (0)	1.25 (0.46)
Visual memory			
Rey's/Taylor's figure delayed recall	5	0/5 (0)	0.50 (1.07)
Praxis			
Mahieux's praxis	9	0/8 (0)	-

Correlation between MMSE and mRS scores at diagnosis (rho=-0.42, p=0.092)

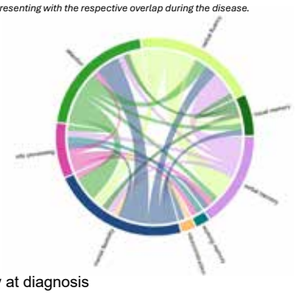


Spider plot showing the percentage of patients with impairment in each of the cognitive domains at baseline and over the disease course.

Longitudinal evolution of cognitive screening tests in patients tested at diagnosis

Cognitive screening test	Score at diagnosis, mean (SD)	Score at last follow-up, mean (SD)	p-value	Changes at individual level
MMSE (/30), n=11	25.9 (3.4)	21.9 (7.7)	0.0488	2/11 (18%) improved, 1/11 (9%) stable, 8/11 (73%) worsened
MoCA (/30), n=3	24.7 (4.0)	25.0 (5.0)	1.0000	1/3 (33%) worsened, 1/3 stable (33%), 1/3 improved (33%)
FAB (/18), n=7	13.3 (2.5)	14.4 (3.0)	0.3750	1/7 (14%) worsened, 3/7 (43%) stable, 3/7 (43%) improved

Overlap of deficits during the disease. The strength of the connection between domains represents the number of patients presenting with the respective overlap during the disease.



CONCLUSIONS

- Over 60% of patients exhibited impaired global cognitive efficiency and deficits in frontal executive functions already at diagnosis
- Cognitive impairment in anti-IgLON5 disease was frequently multi-domain, with verbal memory and verbal fluency being most frequently involved
- Performance on verbal memory sub-tests suggested dysfunction of the fronto-striatal circuit
- Cognitive tests employed in patients with anti-IgLON5 disease were highly heterogenous -> standardized neuropsychological testing needed in all patients

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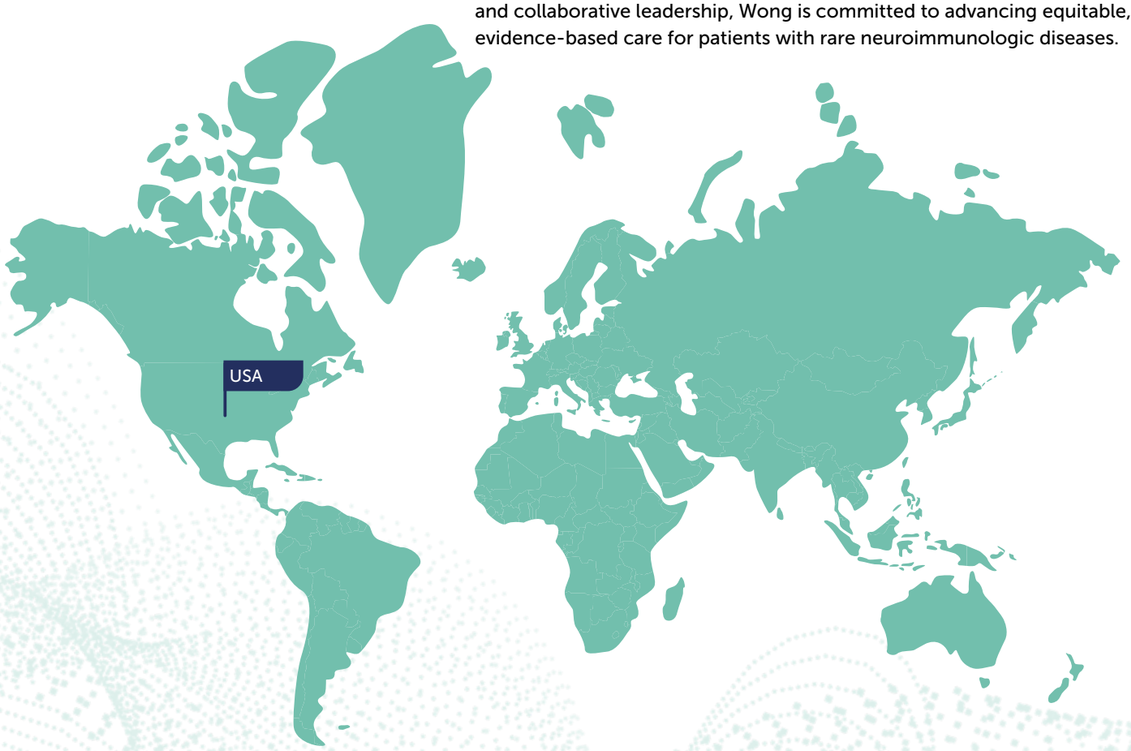
Mr Ka-Ho Wong

University of Utah, USA

The ExTINGUISH Trial: A Phase-2B randomized placebo-controlled trial of inebilizumab in anti-NMDA receptor encephalitis

Ka-Ho Wong, MBA, is a population health scientist and neuroimmunology researcher whose work integrates large-scale data analytics, health-equity investigations, and clinical research operations. He is a PhD student in the Department of Population Health Sciences at the University of Utah and a Research Associate and Administrative Coordinator in the Division of Autoimmune Neurology. His research focuses on social determinants of health, care disparities, and outcomes in rare immune-mediated neurologic disorders, including NMDAR encephalitis, neuromyelitis optica spectrum disorder, transverse myelitis, myasthenia gravis, and stiff person spectrum disorders. A central component of Wong's work is his extensive leadership within ExTINGUISH, the first NIH-funded randomized, placebo-controlled trial for anti-NMDAR encephalitis. Wong plays a critical operational and scientific role in the study, coordinating protocol implementation across international sites, overseeing regulatory processes, managing complex multi-stakeholder communication, and driving key data integrity and trial readiness activities. His contributions have been essential in shaping trial workflows, troubleshooting operational challenges, and supporting the development of ancillary studies such as CAPTIVA-MRI, an NIH-funded stroke sub-study. Recognized for his interdisciplinary expertise and collaborative leadership, Wong is committed to advancing equitable, evidence-based care for patients with rare neuroimmunologic diseases.



The ExTINGUISH Trial

A Phase-2B randomized placebo-controlled trial of inebilizumab in anti-NMDAR encephalitis

K Wong,[1] GS Day,[2] J Torner,[3] M Cudkowicz,[4] C Coffey,[3] S Cho,[5] U Utz,[5] E Klawiter,[4] JR Singleton,[1] D Mitchell, S Cahalan, J Fedler,[3] DJ Ecklund,[3] M Costigan,[3] B Pearson,[3] E Steinhart,[4] C Desir,[4] MJ Titulaer,[6] SL Clardy[1]

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Introduction

Anti-N-methyl-D-aspartate receptor (NMDAR) encep-halitis is a life-threatening antibody-mediated disorder that presents with prominent psychiatric symptoms, alterations in consciousness, seizures, movement disorders, and dysautonomia, for which there are no FDA-approved treatments. The lack of approved therapies has led to substantial variability in the treatment of patients with moderate-to-severe NMDAR encephalitis. Quality data are needed to guide treatment and optimize long-term outcomes in recovering patients.

Objective: Assess the safety and efficacy of inebilizumab in patients with moderate-to-severe NMDAR encephalitis.

clinicaltrials.gov: NCT04372615

Inclusion Criteria
- Age ≥18 years & mRS ≥3 at screening.
- Diagnosis of NMDAR encephalitis, requiring
  - ➢Subacute change in mental status consistent with autoimmune encephalitis and
  - ➢NMDAR IgG Ab confirmed in CSF by a study-specified laboratory.
- Participants received at least 3 days of methylprednisolone 1000 mg IV within 30 d of randomization, and *either,*
  - ➢IVIg (2 g/kg), or
  - ➢PLEX or plasmapheresis (min 5 treatments)
- Participants are willing to forego *other* immunomodulatory therapies.

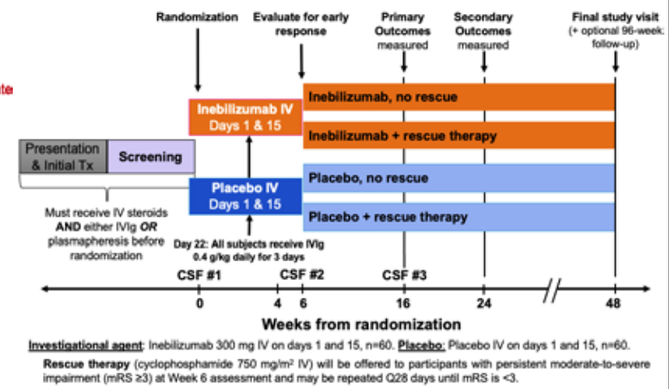
Exclusion Criteria
- Past NMDAR encephalitis within 5 years.
- Untreated NMDAR encephalitis for ≥3 months prior to screening.
- Exposure to a B cell-depleting therapy (e.g., rituximab) within 6-months or randomization.
- Exposure to *other* immunomodulatory therapies within 3 months of randomization (other than steroids, IVIg, PLEX).
- Any condition that would interfere with the evaluation or administration of the investigational agent or study conduct.

Primary endpoints:
- **Change in mRS at 16 weeks** from randomization.
- **Inebilizumab safety**, measured by the number of treatment-emergent adverse events and treatment-emergent serious adverse events.

Secondary / Exploratory Outcomes:
- Disease-specific outcomes: e.g., requirement for rescue therapy, relapse rate, CASE.
- Changes in blood and CSF biofluid biomarkers.
- Cognitive outcomes were assessed using comprehensive neuropsychological tests and bedside screening tools.
- Quality of life measures (patient and caregiver).
- Health care utilization measures (e.g., length of stay, requirement for ICU admission).

Trial Design

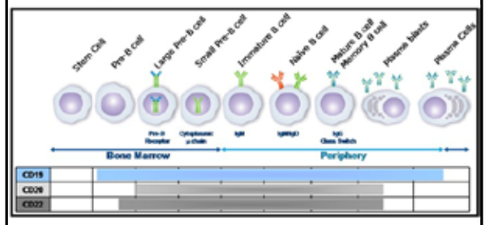
The ExTINGUISH trial will randomize 120 patients with moderate-to-severe NMDAR encephalitis (mRS ≥3) to receive inebilizumab or placebo across 37 US and **2 European sites (Barcelona, Spain; Rotterdam, Netherlands)**.



Investigational agent: Inebilizumab 300 mg IV on days 1 and 15, n=60. **Placebo:** Placebo IV on days 1 and 15, n=60.

Rescue therapy (cyclophosphamide 750 mg/m² IV) will be offered to participants with persistent moderate-to-severe impairment (mRS ≥3) at Week 6 assessment and may be repeated Q28 days until mRS is <3.

Inebilizumab



- Inebilizumab (Uplinza®) is a humanized IgG1 kappa monoclonal antibody (mAb) that binds to the B cell-specific surface antigen, CD19, resulting in the depletion of CD19+ B cells.
- CD19 is present on a broader spectrum of B cells than CD20, including plasmablasts and subsets of CD20-plasma cells, and *may* be more efficacious in the treatment of NMDAR encephalitis than off-label therapies (e.g., rituximab).
- Inebilizumab is FDA-approved for the treatment of neuromyelitis optica associated with antibodies against aquaporin-4, with a favorable safety profile (Cree. 2019-*Lancet*).

Key Points

1. **NMDAR encephalitis is a neurologic emergency**. Do not wait for antibody test results to return to begin first-line treatments in patients with suspected NMDAR encephalitis.
2. **ExTINGUISH will focus on patients with moderate-to-severe NMDARE**. All patients must receive first-line treatment before enrolling in ExTINGUISH.
3. **Do you have an eligible patient**? Reach out to your local ExTINGUISH Site PI or contact the Study Team via the 24-hour ExTINGUISH hotline: **1-844-4BRAIN5 (1-844-427-2465)**.

Conclusions:

ExTINGUISH Trial results will influence patient care while informing the design and implementation of future clinical trials in autoimmune encephalitis.

Acknowledgments and Funding

The ExTINGUISH Trial is funded by NINDS U01NS120901, with additional support from Horizon Therapeutics plc. The NeuroNEXT Network is supported by NINDS (Clinical Coordinating Center: U01NS077179, Data Coordinating Center: U01NS077352)

Questions/comments?
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HORIZON THE ExTINGUISH NMDAR ENCEPHALITIS TRIAL

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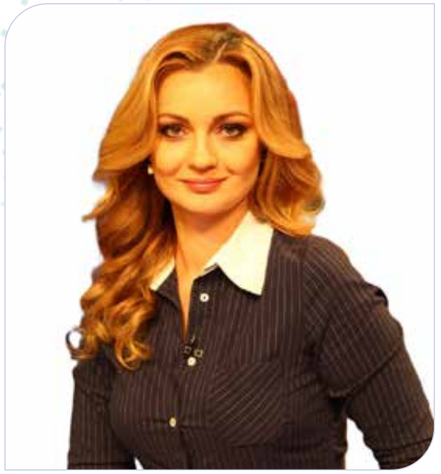

Dr Katerina Divakova

Belarusian State Medical University, Belarus

HHV-7 encephalitis

After graduation from the Medical University, Dr Katerina Divakova worked as a pediatrician at the Pediatric Infectious Diseases Hospital in Minsk for several years. After becoming a Pediatric Infectious Diseases specialist, she continued working at the same hospital and at the Department of Pediatric Infectious Diseases of Belarussian State Medical University. Currently, she is a PhD researcher on HHV-6/HHV-7 infections in children.

Human Herpesvirus-7 encephalitis

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Prof. Oxana Romanova, MD, PhD[1]; Natalia Rybak, MD, PhD[1]
[1]Belarusian State Medical University

Introduction

Human herpesvirus 7 (HHV-7) is a virus that infects children and is accompanied by lifelong latency. Even though the clinical manifestation of the encephalitis caused by HHV-7 is uncommon in immunocompetent person, the HHV-7 infection should not be neglected for encephalitis for unknown reasons.

Case Description

- A 3-year-old previously healthy and fully vaccinated boy presented with low-grade fever (38,0ºC), accompanied by behavioral disorders, gait disturbances and tonic-clonic seizures, which lead to status epilepticus that had necessitated intubation for 5 days.
- CSF sample was colorless, and routine analysis indicated total cells are 7/mm^3, total protein and glucose levels were 1.5 g/L and 3.1 mmol/L.
- Normal findings were obtained from the autoimmune encephalitis examination. Detail screening didn't evaluate any tumors. Results of an extensive investigation for infectious agents were positive only for HHV-7 in CSF by PCR.
- Cranial MRI revealed peri-ictal changes: visible diffusion restriction and reduced apparent diffusion coefficient in both hippocampi.
- EEG expressed irregular activity with epileptiform discharge in the right temporal area.
- After confirmation of HHV-7 etiology, empirical acyclovir was switched to ganciclovir in addition to intravenous immunoglobulin therapy (2 g/kg/course) with pulse dose of methylprednisolone 1.5 mg/kg/day for 4 days.
- MRI performed 2 weeks later, revealed bilateral (mostly on the right) damage to the cortex and juxta of the cortical white matter of the cerebral hemispheres: on the right in the parietal, occipital and temporal lobes (including the hippocampus), on the left - in the parietal and temporal (hippocampus) lobes, in the form of slight swelling of the cortex and an increase in the signal in T2/FLAIR, an increase in the signal in DWI (Figure 1)

Clinical Course / Timeline

- T 38.0°C; Tonic-clonic seizures; Behavioral disorders; Gait disturbances
- Day +3: T 38.0°C; New-onset refractory status epilepticus; Empirical Treatment for Encephalitis
- Days +4, +5: IVIG 2g/kg/course
- Day +7: HHV-7 DNA (CSF) - positive; Autoimmune Encephalitis Panel Test – negative; Methylprednisolone 1.5 mg/kg/day for 4 days; Ganciclovir 10 mg/kg/day twice daily for 14 days
- Day +21: HHV-7 DNA (CSF) - negative; Cortical blindness; Neurological deficit; Routine anticonvulsant therapy

Learning Points/Discussion

- The HHV-7 rarely causes encephalitis, especially in immunocompetent patients. In a study conducted in Toronto, 57 (1.9%) out of 2,972 children were detected positive with HHV-7 DNA in their CSF, including 8 patients with meningitis and 7 patients with encephalitis. Clinical presentations of HHV-7 infection in the neurological system include a gradual loss of strength and weakness in the limbs, disorientation and confusion, flaccid paraplegia, localized anesthesia and hypoesthesia for pain and light touch, urinary retention, and constipation. These symptoms are similar to other encephalitis.
- Conventional diagnostic methods including culture and serology are not ideal for the detection of HHV-7. In this case report, HHV-7 was successfully identified by PCR in CSF. The limitation of PCR in this patient is that the HHV-7 DNA detection could not discriminate whether it is a primary infection or a latent reactivation, and it is complex to interpret the result.

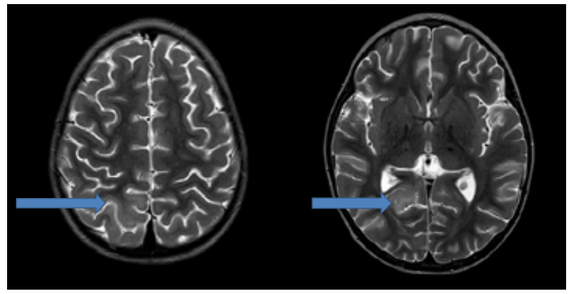

Figure 1. Cranial MRI on 18th day of the disease.

Conclusions

- The case indicates clinicians should memorize HHV-7 as an unusual etiology of encephalitis to make an early diagnosis and therapy.
- The treatment of encephalitis associated with the human herpesvirus-7 infection is still limited and unclear.

Contact

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References

1. Foiadelli T, Rossi V, Paoluzzi S, Rovida F, Novazzi F, Orsini A, Brambilla I, Marseglia GL, Baldanti F, Savasta S. Human Herpes Virus 7-related encephalopathy in children. Acta Biomed. 2022 Mar 21;92(S4):e2021415. doi: 10.23750/abm.v92i54.12664. PMID: 35441609; PMCID: PMC9179060.
2. Christou E, Mastrogianni S, Bourousis E, Bachou T, Tsikrikas T, Mouskou S, Voudris K, Delis D. A case of seronegative autoimmune encephalitis associated with human herpesvirus-7 (HHV-7). J Med Virol. 2022 Feb;94(2):795-798. doi: 10.1002/jmv.27411. Epub 2021 Oct 27. PMID: 34676889.
3. Divakova, K. The First Case of Human Herpesvirus 7-Related Epilepsy in the Republic of Belarus / K. Divakova, E. Kishkurno, T. Amvrosieva, O. Romanova, S. Belaya, I. Zaitsau, Y. Shilova // Journal of Pharmacy and Pharmacology. – 2020. – Vol. 8, № 3. – P. 73-76. https://doi.org/10.17265/2328-2150/2020.03.001
4. Lynch M, Nedjat-Haiem M, Abeson K, Chang C. Limbic Encephalitis Associated with Human Herpesvirus-7 Infection in an Immunocompetent Adolescent. Child Neurol Open. 2023 Oct 10;10:2329048X231206935. doi: 10.1177/2329048X231206935. PMID: 37829673; PMCID: PMC10566268.
5. Schwartz KL, Richardson SE, Ward KN, Donaldson C, MacGregor D, Banwell B, et al. Delayed primary HHV-7 infection and neurologic disease. *Pediatrics*. (2014) 133:e1541–7. doi: 10.1542/peds.2013-3344

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Dr Lærke Storgaard Duerlund

Aalborg University Hospital, Denmark

Early vs late diagnosis in infectious encephalitis: a population-based cohort study

Dr Lærke Storgaard Duerlund is a PhD student at the Department of Infectious Diseases, Aalborg University Hospital, Denmark. Her research focuses on primarily on infectious encephalitis. She is affiliated with the Danish Study Group for Infections of the Brain (DASGIB), a national cohort study of CNS infections. Currently, she is completing a one-year research stay at the Johns Hopkins Encephalitis Center in the Department of Neurology, where she is collaborating on projects related to encephalitis epidemiology. Her work focuses on clinical data and register-based research.

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Early vs late diagnosis in Infectious encephalitis: A population-based cohort study

Lærke Storgaard Duerlund[1,2] • Henrik Nielsen[1,2] • Jacob Bodilsen[1,2] • The DASGIB Study Group
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[2]Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

Background

Encephalitis is a life-threatening condition leaving many survivors with debilitating sequalae. Delay in treatment is a suggested modifiable risk factors. However, factors associated with delay of diagnosis remain unknown. This study examined the clinical characteristics and outcomes of patients with early versus late diagnosis of infectious encephalitis in Denmark.

Methods

Nationwide, prospective, population-based cohort study utilizing the Danish study group for infections of the brain (DASGIB) database to include all adults (≥18 years) diagnosed with infectious encephalitis in Denmark (2015-2023). Case definition in alignment with International encephalitis criteria. Early diagnosis defined as lumbar puncture or acyclovir treatment initiated withing six hours of hospitalization. Extended Glasgow outcome scale used as outcome measurement.

Conclusion

Late diagnosis of infectious encephalitis was common and was associated with older age (>65) and absence of altered mental status (GCS>12) at admission. Moreover, 30-day mortality was higher compared with those with an early diagnosis. Diagnosis retrieved later than 24 hours after admission was associated with higher risk of mortality at 6-month follow-up
Clinical strategies to support timely recognition and management of encephalitis are needed.

Results

Table 1: Demographics, clinical characteristics, treatment, and outcome

	n/N (%) or median (IQR)		
	Early diagnosis N=183	Late diagnosis N=312	P-value
Age	65 (43-75)	72 (61-79)	<0.001
Females	89/183 (49)	151/312 (48)	0.951
Immunocompromise	61/183 (33)	117/195 (38)	0.351
Duration of symptoms	4 (1-7)	3.0 (1-7)	
Referral diagnosis			
Confusion/altered mental status	39/183 (21)	198/312 (32)	
Stroke	30/183 (16)	63/312 (20)	
CNS infection	59/183 (32)	14/312 (4)	
Seizures	9/183 (5)	14/312 (4)	
Infection (non-specified)	24/183 (13)	51/312 (16)	
Other	22/183 (12)	72/312 (23)	
Time of admission			0.29
Weekdays, daytime (0-23)	125/183 (68)	209/312 (67)	
Weekdays, nighttime (23-08)	8/183 (4)	31/312 (10)	
Weekends (0-24)	50/183 (27)	72/312 (23)	
Symptoms and signs at admission			
Confusion	156/179 (87)	235/309 (76)	0.003
Headache	98/146 (67)	136/251 (54)	0.011
Seizures	28/172 (16)	47/285 (16)	0.953
Focal neurological deficits	21/157 (13)	42/274 (15)	0.581
GCS <12	30/182 (16)	19/309 (6)	<0.001
Fever	97/179 (54)	133/301 (44)	0.029
Laboratory results			
C-reactive protein (mg/L)	5 (1-16)	5 (2-16)	0.99
B-leukocytes (10^9/L)	9.2 (6.9-11.9)	9 (6.8-11.4)	0.64
B-creatinine (mmol/L)	78 (64-94)	78 (61-97)	0.85
Imaging before lumbar puncture	127/182 (70)	277/311 (89)	<0.001
Imaging before acyclovir treatment	124/179 (69)	251/292 (89)	<0.001

Figure 1: Time to diagnosis since admission of 495 patients with infectious encephalitis in Denmark from 2015-2023

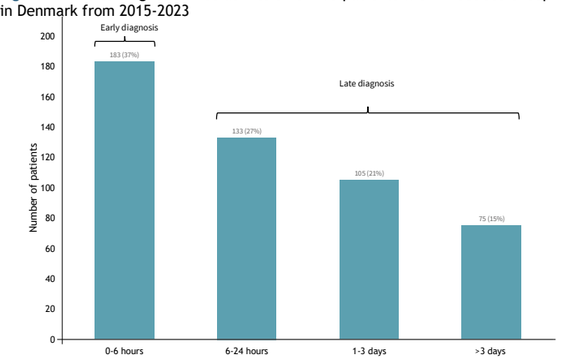


Figure 2: Extended Glasgow Outcome Scores of patients with infectious encephalitis stratified by late and early diagnosis. Estimated at discharge, 30-day, 90-day and 180-days of follow-up

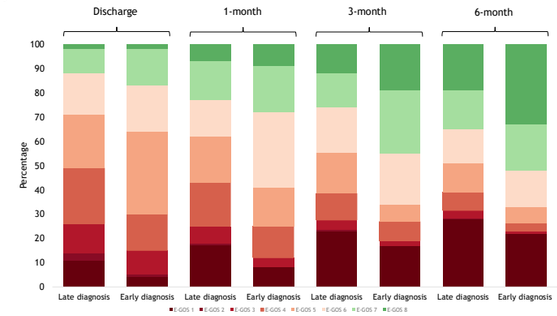
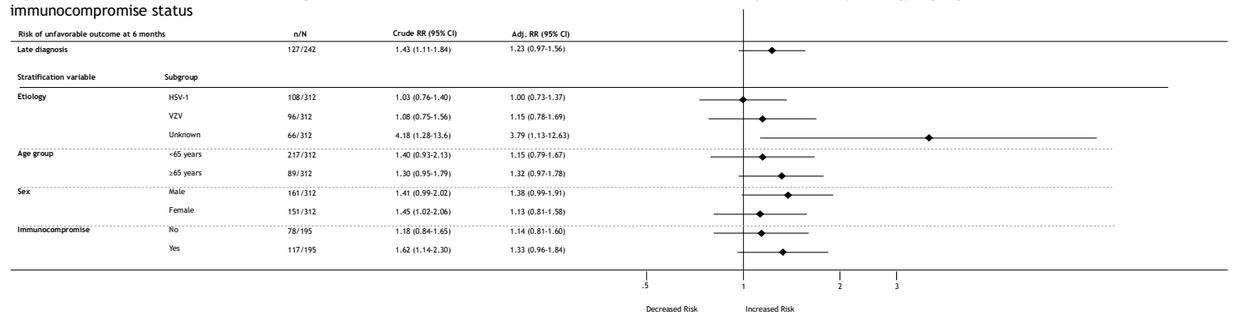


Figure 3: The association between late diagnosis and the risk of unfavorable outcome at six months follow-up stratified by etiology, age, gender, and immunocompromise status



DASGIB: Danish Study Group of Infections of the Brain. DASGIB members are: Lykke Larsen, Merete Storgaard, Helene Mens, Lothar Wiese, Micha Phill Grønholm Jepsen, Birgitte Rønde Hansen, Christian Østergaard Andersen, Hans Rudolf von Lüttichau, Jacob Bodilsen, Henrik Nielsen.

Contact
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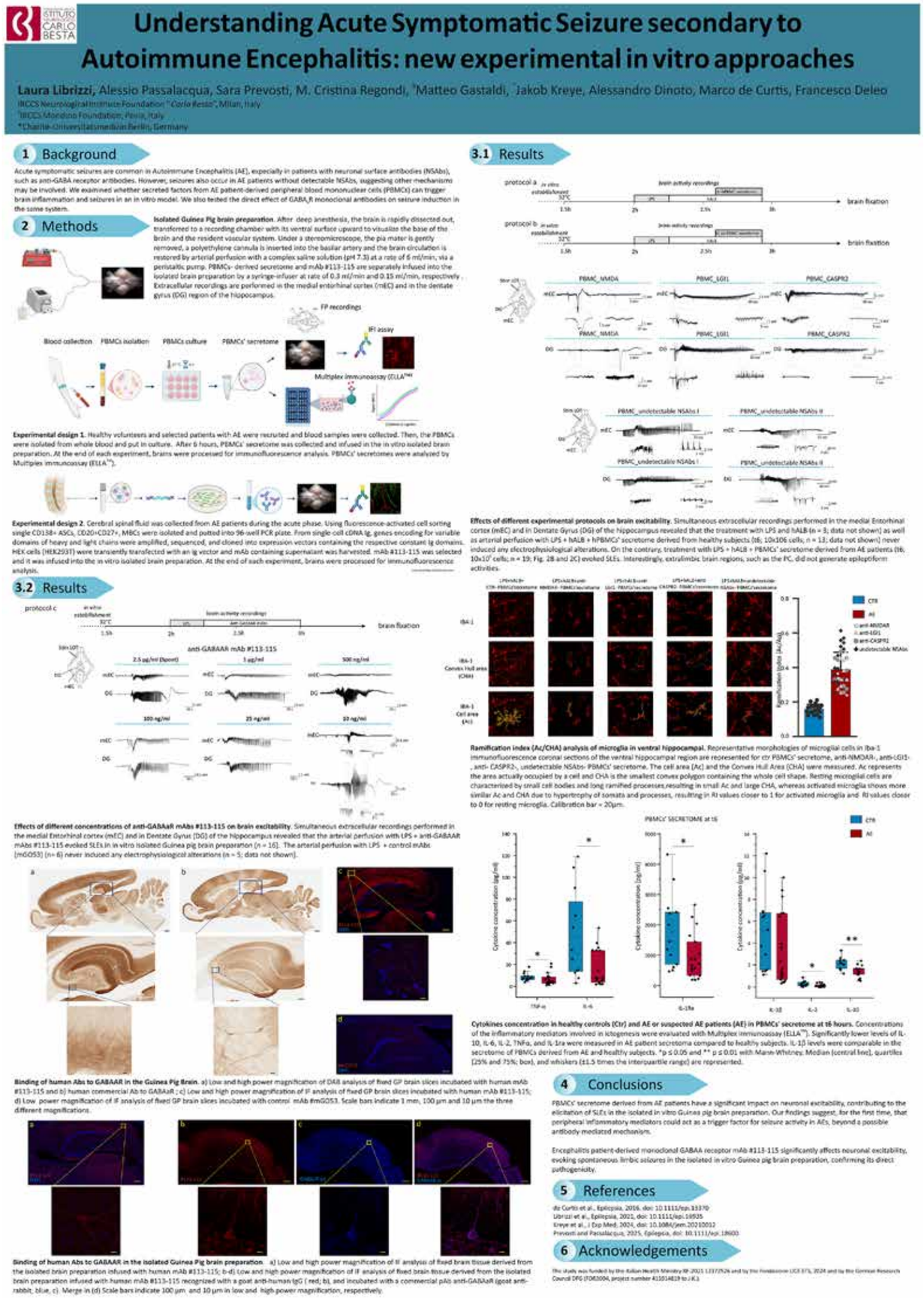
Dr Laura Librizzi

Fondazione IRCCS Istituto Neurologico “Carlo Besta”, Italy

Understanding acute symptomatic seizure secondary to autoimmune encephalitis: new experimental in vitro approaches

Dr Laura Librizzi is a biologist and a senior researcher at the Epilepsy Unit of the Fondazione IRCCS Istituto Neurologico Carlo Besta in Milan, Italy. She has a solid background in neuroscience and practice in experimental neurophysiology. Since her Master’s degree thesis in Biological Sciences, she was interested in the study of the inflammatory processes taking place in the CNS. During her PhD period spent between the Department of Pharmacological Sciences at the University of Milan and the Epilepsy Unit at the Neurological Institute she acquired the technique for isolating and maintaining in in vitro condition the guinea pig brain. Her PhD thesis focused on the evaluation of the morphological and functional preservation of the cerebral endothelium and blood brain barrier (BBB) in the in vitro isolated brain preparation with the future aim to study the interactions between neuronal, extracellular and vascular compartments during ictogenesis. Over the last years, her research has focused on investigating inflammatory processes involved in seizure initiation and recurrence, BBB impairment, GABAergic transmission and alterations in extracellular potassium dynamics during during the transition to seizures. In the last few years her research focused on the study of the pathogenic mechanisms leading to seizure occurrence in autoimmune-mediated epilepsy.



ENCEPHALITIS CONFERENCE 2025

Dr Laura Stokes

The Francis Crick Institute, UK & National institute of mental health and Neuro Sciences (NIMHANS), India

Strengthening research capacity for neurological flavivirus diagnostics in India: NeuroFlaviDx

Dr Laura Stokes is a physician based in the UK. She has just completed a MSc in Tropical Medicine and International Health at the London School of Hygiene and Tropical Medicine. She is now working as a Clinical Research Fellow with the Oxford Vaccine Group, University of Oxford.

Strengthening research capacity for neurological flavivirus diagnostics in India: NeuroFlaviDx

Laura Stokes, Dorcas Anane-Amponsah, Vijay Bondre, Tina Damodar, Sabine Dittrich, Audrey Dubot-Pérès, Ava Easton, Lonika Lodha, Lucky Sangal, Ashwini Shetty, Bhagteshwar Singh, Tom Solomon, Lance Turtle, NeuroFlaviDx consortium, Reeta Manf and Tehmina Bharucha#
 # These authors contributed equally to this work.

Background

The recent WHO encephalitis technical brief highlights persistent gaps in global surveillance, diagnostics, and coordinated research. Japanese encephalitis (JE), a neurotropic flavivirus infection causing substantial morbidity and mortality, remains a major public health burden in India, particularly in northern and eastern states such as Uttar Pradesh. However, our current epidemiological insight is constrained by limited specificity of current diagnostic assays, especially when testing serum. The National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, acts as the WHO Regional Reference Laboratory, underscoring its central role in improving diagnostic accuracy and strengthening surveillance across the region. Against this backdrop, the NeuroFlaviDx conference, co-hosted by the Francis Crick Institute and NIMHANS in October 2025, sought to address these challenges and build sustainable research networks.

Meeting Overview

- Two-day hybrid meeting in Bangalore, India, 6-7th October 2025.
- 35 participants with clinical, laboratory, research, public health and industry backgrounds.
- The Programme featured an array of presentations, participatory talks, breakout sessions for networking and collaborative planning, and thematic roundtable discussions.

Aims and Objectives

1. Set up a flavivirus research network with focus on neurotropic infections, using JE as an exemplar
2. Formalise scope and governance structure for a network of key sites across JE-endemic areas in India including scientists and clinicians.
3. Establish clinical experiences, diagnostic challenges and laboratory capacity in neurological flavivirus diagnostics for each site, to produce a living document of local training needs and strategies for capacity building.
4. Explore interdisciplinary research opportunities with proteomics experts for verification of novel diagnostic biomarkers; establish how this will fit into a grant application.
5. Liaise with local commercial groups to define the practicalities of developing and testing a prototype JE rapid diagnostic test.
6. Agree on a timeline for development and publication of a research protocol.
7. Identify funding applications and future routes for the research.

Key Findings/Discussion Themes

Diagnostic challenges

- **Non-specific presentation**: acute encephalitis syndrome (AES) has multiple aetiologies
- **Serological cross-reactivity** among co-circulating flaviviruses and with prior vaccination
- High proportion of **asymptomatic infections**
- Sample constraints: cerebrospinal fluid (CSF) offers higher specificity but is **invasive** and often unavailable.
- Technical limitations: PRNT and other seroneutralisation assays are limited by **cost, complexity and turnaround time**, challenging to interpret in endemic areas
- Temporal factors: transient viraemia and rapid IgM-to-IgG switching in secondary infections
- Surveillance gaps: **non-uniform reporting** and evolving encephalitis epidemiology

Collaboration & Capacity Building

- Collaboration between laboratories, clinicians, and public health authorities
- Strengthen **national laboratory and reference networks** with shared clinical biobanks, quality-assured reference panels, and standardised reporting systems
- Roundtable discussions consolidated a **promising research network**, with opportunities for future collaboration identified.
- **Public-private partnerships** to drive research innovation, funding and scalability

Research Priorities

- **Real-time diagnostics** that support patient management (acknowledging that any diagnostic for this purpose will inform public health surveillance).
- **Point-of-care tests** appropriate for primary/district-level care
- Further refinement of NS1, EDIII, monoclonal-based assays, and fusion-loop antigen designs
- AES syndromic diagnostics
- **Region-specific multiplex panels**: JEV and other high-priority AES pathogens
- **Tiered diagnostic testing algorithms**: initial flavivirus-positive → targeted confirmatory testing.
- Evaluate alternative sample types (urine, throat swabs, whole blood) & optimal sampling windows

Emerging Diagnostic Tools & Approaches

- **Luminex** multiplex serology
- Engineered E-protein antigens (fusion-loop mutations)
- Rapid cell-free protein expression & bead-based screening
- Deep mutational scanning & structural stability prediction
- Sequencing-based serology (PhIP-Seq/NIPSA)
- Proteomic / host-response biomarkers
- **Pseudovirus neutralisation assays**
- ELISA and lateral-flow device translation
- Syndromic AES panels and routine metagenomic sequencing
- **Expansion from VRDLs to IRDLs** to strengthen multi-pathogen diagnostic capacity.

Conclusions & Future Directions

The conference identified a significant gap in current knowledge surrounding neurotropic flavivirus infections, amidst a changing landscape of encephalitis. Discussions emphasised the urgent need for improved diagnostic tools to improve clinical care, enhance public health surveillance efforts, and guide the development of novel treatments. Addressing these challenges requires coordinated, multidisciplinary approaches within a sustained research network. The network is co-ordinating further work to evaluate and implement novel tests.

NeuroFlaviDx consortia: Nivedita Gupta, Kaveri Krishnasamy, Priscilla Rupali, Asha Abraham, Shobha Mammen, Angel Miraclin, Adrian Keith Noronha, Labanya Mukhopadhyay, Siraj Ahmed Khan, Kavitha Saravu, Krishna Srinavasan, Shruti Radeea, Aparna Sonowal, Partha Pratim Das, Rahul Dhodapkar, Ashleigh Otter, Ravi Vasanthapuram, Vykunta Raju, Uddhav Kinhal, Ashok Munivenkatappa, Sakib Akther, Manjunatha NV, Ashwin YB
Funding: The work was supported by an Academy of Medical Sciences Networking Grant (NGR2\10551) funded by the Department for Science, Innovation and Technology (DSIT) through the International Science Partnerships Fund (ISPF). TB is supported by The Francis Crick Institute through a Crick Postdoctoral Career Development Fellowship for Clinicians. RM is supported by NIMHANS as Head of the Department of Virology.

ENCEPHALITIS CONFERENCE 2025

Dr Lindt Camille O. Alba

University of the East Ramon Magsaysay Memorial Medical Center, Philippines

Dual Positivity for HHV-6 and anti-NMDAR antibodies in an immunocompetent adult with encephalitis: a case report

Dr Lindt Camille O. Alba is currently serving as a fourth-year neurology resident at the University of the East Ramon Magsaysay Memorial Medical Center and Cardinal Santos Medical Center (UERM–CSMC) in the Philippines. Her clinical and research interests include autoimmune and infectious encephalitides, neuroimmunology, and neurodegenerative care. She has presented at local conferences and is actively engaged in academic and research activities aimed at improving neurologic care in low-resource settings. She aspires to pursue further specialization in neuroimmunology and dementia to help bridge diagnostic and therapeutic gaps in underserved populations.

DUAL POSITIVITY FOR HHV-6 AND ANTI-NMDAR ANTIBODIES IN AN IMMUNOCOMPETENT ADULT WITH ENCEPHALITIS

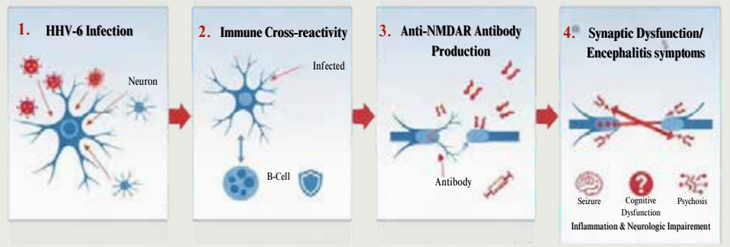
AUTHORS **Lindt Camille O. Alba, MD** [1,2]
Stephanie Patricia J. Badillo, MD [1,2]

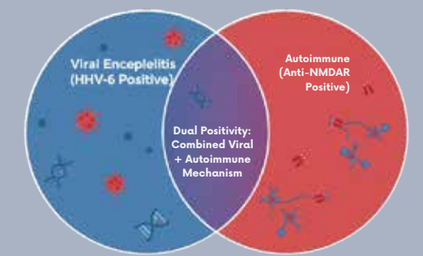
1 DEPARTMENT OF CLINICAL NEUROSCIENCES, UNIVERSITY OF THE EAST RAMON MAGSAYSAY MEMORIAL MEDICAL CENTER, QUEZON CITY, PHILIPPINES
2 SECTION OF NEUROLOGY, DEPARTMENT OF INTERNAL MEDICINE, CARDINAL SANTOS MEDICAL CENTER, SAN JUAN CITY, PHILIPPINES

INTRODUCTION

AUTOIMMUNE ENCEPHALITIS (AE) IS AN IMMUNE-MEDIATED INFLAMMATION OF THE BRAIN CAUSED BY ANTIBODIES AGAINST NEURONAL SURFACE ANTIGENS, MOST COMMONLY THE NMDA RECEPTOR. ALTHOUGH MANY CASES ARE IDIOPATHIC, VIRAL INFECTIONS CAN SERVE AS TRIGGERS. HUMAN HERPESVIRUS 6 (HHV-6) HAS BEEN IMPLICATED THROUGH MOLECULAR MIMICRY AND IMMUNE ACTIVATION. THE CO-OCCURRENCE OF HHV-6 REACTIVATION AND ANTI-NMDAR ANTIBODY–MEDIATED ENCEPHALITIS IS EXCEPTIONALLY RARE, POSING UNIQUE DIAGNOSTIC AND THERAPEUTIC CHALLENGES. RECOGNIZING THIS DUAL PATHOLOGY IS CRUCIAL, AS OPTIMAL MANAGEMENT REQUIRES COMBINED ANTIVIRAL AND IMMUNOMODULATORY THERAPY TO ADDRESS BOTH THE INFECTIOUS AND AUTOIMMUNE COMPONENTS.

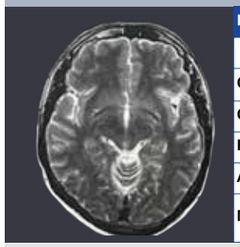
PATHOPHYSIOLOGY





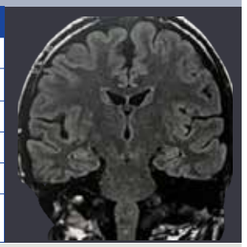
CASE PRESENTATION

A 21-YEAR-OLD PREVIOUSLY HEALTHY MALE PRESENTED WITH ACUTE BEHAVIORAL CHANGES, HALLUCINATIONS, AND SEIZURES FOLLOWING A FEBRILE ILLNESS. BRAIN MRI REVEALED NONSPECIFIC T2/FLAIR HYPERINTENSITIES IN THE DORSAL MIDBRAIN; EEG SHOWED DIFFUSE SLOWING WITH INTERMITTENT EPILEPTIFORM DISCHARGES. CSF ANALYSIS DEMONSTRATED LYMPHOCYTIC PLEOCYTOSIS.

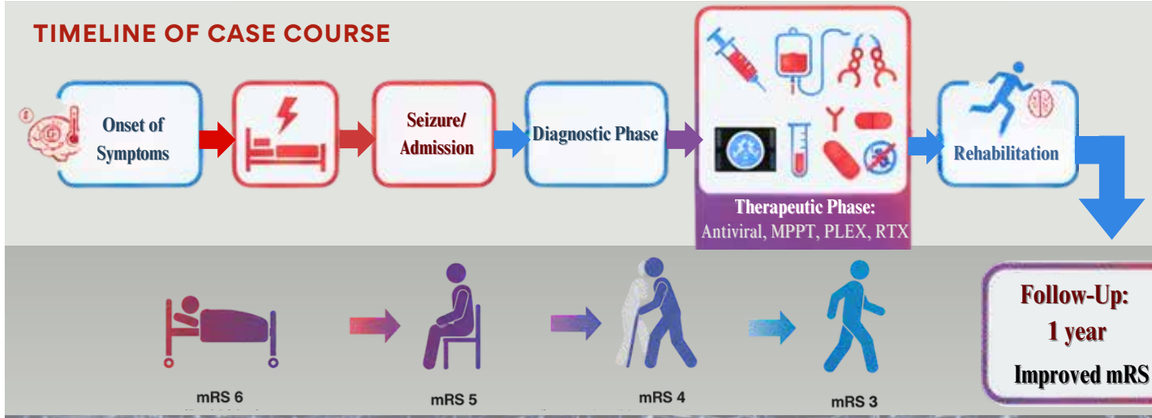


Laboratory & Imaging Summary

Test	Result	Interpretation
CSF Cell Count	40 cells/mm³ (90 % lymphs)	Autoimmune/viral
CSF Protein	65 mg/dL	Mild ↑
HHV-6 PCR	Positive	Viral reactivation
Anti-NMDAR IgG	Positive	Autoimmune
MRI	right paramidline dorsal midbrain T2 hyperintensity	probably gliosis



TIMELINE OF CASE COURSE



REFERENCES:

SHIMOHAMA S, LIZUKA T, TAKIZAWA T, WATANABE N, TEZUKA T, MATSUDA K, YAMANOI K, KANAZAWA N, KAWAMURA Y, YOSHIKAWA T, SUZUKI T, TAKAO M, NAKAHARA J, IZAWA Y. ANTI-N-METHYL-D-ASPARTATE RECEPTOR ENCEPHALITIS WITH CONCURRENT HUMAN HERPES VIRUS-6A DEOXYRIBONUCLEIC ACID DETECTION: AN AUTOPSY CASE. NEUROPATHOLOGY. 2023 JUN;43(3):257-261. DOI: 10.1111/NEUP.12881. EPUB 2022 NOV 8. PMID: 36349409.

ATTENDANCE AT THIS CONFERENCE WAS SUPPORTED BY AN ENCEPHALITIS INTERNATIONAL

ENCEPHALITIS CONFERENCE 2025

Dr Martijn van Duijn

Erasmus MC, The Netherlands

Transcriptomic and proteomic analysis of intrathecal immunity in IgLON5 disease

Dr Martijn van Duijn was trained in biochemistry and biophysics. After working on therapeutic antibodies in the biotechnology sector, research work continued at the Department of Neurology at the Erasmus MC in Rotterdam. In this department, work has focused on antibody-mediated disease, in particular through the use of LC-MS based proteomics. More recently, the work has integrated (single cell) transcriptomics data as well as other proteomics platforms in the study of disease processes, in particular auto-immune encephalitis.

A multi-omic analysis of cellular and serological responses in IgLON5 disease

Martijn van Duijn[1], Daniela Esser[2], Christoph Stingl[1], Yvette Crijnen[1], Eric Bindels[1], Sumanta Barman[3], Saskia Räuber[3], Nico Melzer[3], Katharina Eisenhut[4], Franziska Thaler[4], Manuela Paunovic[1], Julie de Houwer[1], Elise Dopper[1], Gerd Meyer zu Hörste, Harro Seelaar[1], Norbert Goebels[3], Frank Leypoldt[2], Maarten Titulaer[1]

1) Erasmus University Medical Center, Rotterdam, The Netherlands; 2) University Hospital Schleswig Holstein, Kiel, Germany; 3) Heinrich Heine Univerity Düsseldorf, Germany; 4) Ludwig Maximilians University, München, Germany; 5) University of Münster, Münster, Germany

Introduction and cohort description

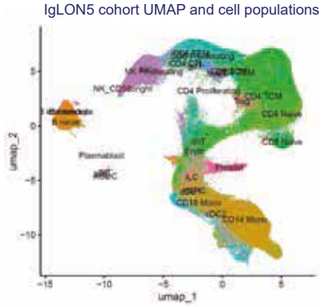
IgLON5 disease is an auto-immune condition characterized by antibody reactivity to the IgLON5 antigen. Patients suffer from neurodegeneration which may manifest in various ways such as sleeping disorders or cognitive decline. Affected areas of the brain may shown deposition of tau protein, indicating pathologic similarity to tauopathies like Frontotemporal Lobar Degeneration.

From untreated IgLON5 patients, cerebrospinal fluid and peripheral blood samples were collected. Lymphocytes were collected from both samples and single cell RNA sequencing was performed on the 10x genomics platform. For samples acquired with 5' kits, BCR and TCR data was collected as well. As controls, material collected from patients with a idiopathic intracranial hypertension (IIH) was used.

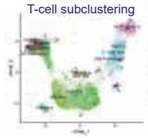
	CSF scSeq	PBMC scSeq	Olink
IgLON5 patients	10 (10×5' kit)	9 (9×5' kit)	43
IIH Controls	22 (8×5' kit)	11 (8×5' kit)	28

Clustering and cell populations

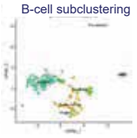
IgLON5 cohort UMAP and cell populations



T-cell subclustering



B-cell subclustering

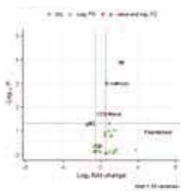


Single cell data was integrated and clustered. Shown are UMAP plots for all samples combined, as well as subcluster analysis of B and T-lymphocytes.

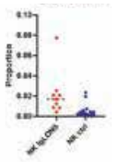
The proportion of NK cells was increased in the CSF of IgLON5 patients as indicated in the Volcano plot. Plasmablasts were uniquely seen in the CSF of IgLON$_5$ patients and not in controls.

In a differential gene expression analysis, CSF B-cells expressed increased amounts of IgG$_2$ and IgG$_4$. In the PBMC of some patients, B-cells with enhanced expression of TBX21 (Tbet) were seen, a B-cell subtype associated with auto-immunity. In the elevated NK cells, no significant differential genes were found.

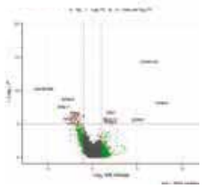
Volcano plot CSF cells IgLON5 vs Controls



Proportion of NK cells in CSF



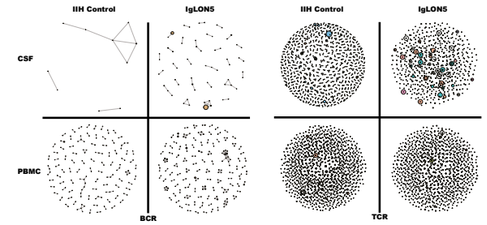
Gene expression in B-cells IgLON5 vs Controls



Acknowledgements

The work was supported by ERARE UltraAIE, Dioraphte and Erasmus MC Trustfonds

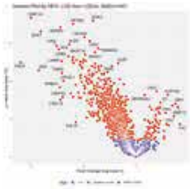
Clonality analysis

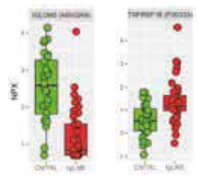


Clonal relations between adaptive immune receptors were investigated. In the B-cell receptors (BCR, antibodies) evidence for modest clonal expansion was seen for IgLON5 patients in the number of clones related in their sequence. This was also visible as a reduction in diversity metrics (not shown). A similar pattern emerged in CSF T-cell receptor (TCR) data. In a comparable published dataset on LGI1/CASPR2 encephalitis*, a much more robust clonal expansion could be observed.

*) 10.1093/brain/awaf096

Proteome analysis





In a larger cohort, CSF samples were analyzed on the Olink Explore 3072 platform. Differential abundance of proteins was summarized in a volcano plot (above). Interestingly, IgLON5 -the target antigen in these patients- was found at a lower concentration in patients. Among the fewer upregulated proteins, inflammation-related soluble TNF receptor and macrophage-related matrix metalloproteinase were found.

Three antibody clones derived from CSF lymphocytes of one of the IgLON5 patients were expressed recombinantly. Specific binding to IgLON5 antigen could be confirmed in affinity testing. With targeted LC-MS, the presence of these clones as endogenously expressed antibodies in the CSF was explored. Although clonotypic peptides of the recombinant reference samples were readily detected, no endogenous expression could be shown, suggesting a low abundance of specific IgG circulating free in the CSF.

Discussion

We present a multi-omic dataset on IgLON5 disease samples from untreated patients. Single cell RNA sequencing showed an increase in NK cells in the CSF of patients, suggesting a role of the innate immune system. However, patient CSF also contained plasmablasts that can produce antibodies. Cloning and expression studies confirmed IgLON5-specific antibodies, but their presence in the patients CSF could not be demonstrated, indicating their free abundance is low. Possibly, they are sequestered on IgLON5-expressing tissues.

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Dr Michael Eyre

King's College London, UK & Evelina London Children's Hospital at Guy's and St Thomas' NHS Foundation Trust, UK

Microstructural and metabolic brain changes predictive of long-term outcome in children and young people at early recovery from NMDAR-antibody encephalitis: A 7-Tesla MR study

Dr Michael Eyre studied Natural Sciences (Experimental Psychology) at the University of Cambridge and Medicine at King's College London. He underwent specialty training in Paediatrics followed by subspecialty training in Paediatric Neurology at Great Ormond Street Hospital for Children and Evelina London Children's Hospital. His research fellowships include an NIHR BRC Senior Clinical Training Fellowship in Translational Research at the Centre for the Developing Brain (King's College London) and an Action Medical Research and British Paediatric Neurology Association Research Training Fellowship at the School of Biomedical Engineering & Imaging Sciences (King's College London). He works as a Consultant Paediatric Neurologist with an interest in Neuroinflammation at Evelina London Children's Hospital. He is co-director of the British Paediatric Neurology Association Acute Neurology course. He has an MRes in Clinical Research and is currently a PhD candidate in Biomedical Engineering at King's College London.

Microstructural and metabolic brain changes predictive of long-term outcome in children and young people at early recovery from NMDA receptor antibody encephalitis: A 7-Tesla MR study

michael.eyre@kcl.ac.uk

Michael Eyre, Pip Bridgen, Chiara Casella, Ayse Sila Dokumaci, Kathleen Colford, Sarah Rudebeck, Yael Hacohen, Cheryl Hemingway, Tom Rossor, Sukhvir Wright, Jon Cleary, Ata Siddiqui, Anthony Price, Lucilio Cordero-Grande, Rui Pedro Teixeira, Shaihan Malik, Joseph V Hajnal, Mike Zandi, Sarosh Irani, Ava Easton, Jonathan O'Muircheartaigh, Enrico De Vita, Ming Lim, David W Carmichael

School of Biomedical Engineering & Imaging Sciences, King's College London | Evelina London Children's Hospital | London Collaborative Ultra high field System (LoCUS)

BACKGROUND

NMDARE causes cognitive-psychiatric symptoms with protracted recovery; the post-acute features have been compared to chronic schizophrenia[1]. **We used ultra-high field neuroimaging, ^{1}H MR spectroscopy (MRS) and quantitative relaxometry to investigate this disease phase in children and young people, aiming to develop prognostic biomarkers for long-term outcome.**

METHODS

Patients with definite NMDARE[2] and healthy controls (ages 8-24 years) were prospectively recruited. **7T scan:** STEAM MRS (left medial temporal lobe [MTL] 25x20x16mm, prefrontal cortex 20x20x20mm) and high-resolution structural MRI (T1w 0.65mm^3, T2w 0.55mm^3). **3T scan:** quantitative T2 maps fitted with joint system relaxometry[3]. **Neuropsychological assessment 12 months post scan:** memory (Doors & People, RAVLT), full-scale IQ, parent-reported behavioural measures (Conners, BRIEF), psychiatric symptom scores (PHQ-9 [depression], GAD-7 [anxiety], PQ-B [psychotic symptoms]). **Analysis:** Linear models compared GABA and glutamate concentrations, qT2 maps (voxelwise in white matter, vertexwise in cortex) and regional subcortical qT2 between groups with age/sex covariates. Relationships between early MRI/MRS and 12-month outcomes (hippocampal qT2 and MTL metabolites with recall memory; prefrontal qT2/metabolites with behavioural-psychiatric measures and IQ) were tested with Pearson's correlation.

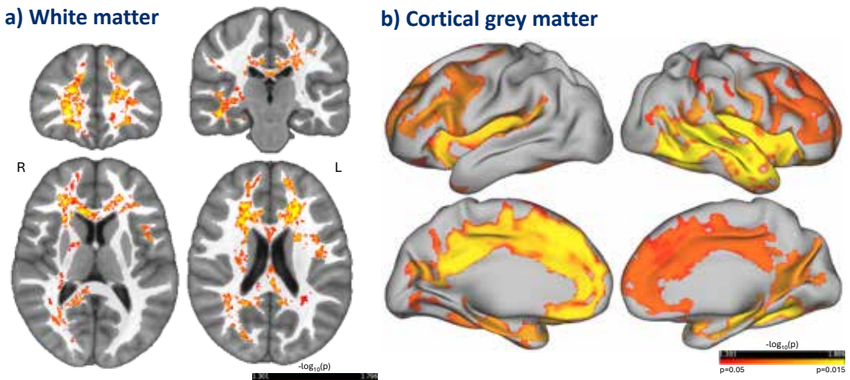
Study hypotheses were pre-registered: clinicaltrials.gov/study/NCT05280600

RESULTS

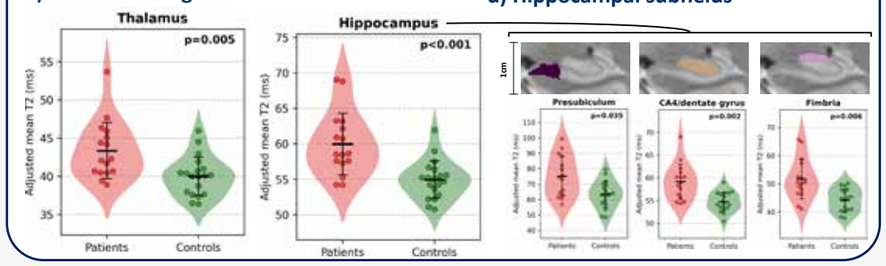
(1) Increased quantitative T2 in patients vs. controls

Parameter maps revealed widespread qT2 prolongation in patients, most prominent in bifrontal white matter **(a)** and frontotemporal/medial parietal cortices **(b)**. Patients had increased hippocampal (60.0 vs 54.9ms) and thalamic (43.4 vs 40.0ms) qT2 **(c)** and reduced hippocampal volumes (5.8 vs 6.3cm^3, p=0.01). The most affected hippocampal subfields were CA4/dentate gyrus, fimbria and presubiculum **(d)** (Bonferroni-corrected p-values).

a) White matter **b) Cortical grey matter**



c) Subcortical regions **d) Hippocampal subfields**

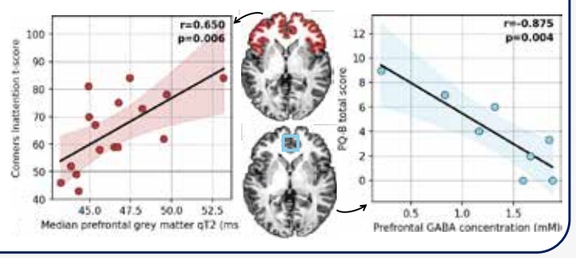


(3) Associations with long-term outcome (12 months post scan)

In 18 patients followed up so far:

- Hippocampal qT2 was inversely correlated with recall memory (r=-0.59, p=0.02).
- Prefrontal grey matter qT2 was correlated with inattention **(a)** and executive dysfunction (r=0.50, p=0.049) and inversely correlated with full-scale IQ (r=-0.51, p=0.04).
- Prefrontal white matter qT2 was correlated with inattention (r=0.53, p=0.04) and hyperactivity/impulsivity (r=0.53, p=0.04).
- Prefrontal GABA was inversely correlated with psychotic symptoms **(b)**.

a) Prefrontal grey matter qT2 versus inattention score **b) Prefrontal GABA versus psychotic symptom score**



Participants

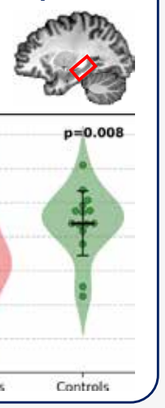
20 NMDARE patients Mean age 15.7y

20 healthy controls Mean age 15.7y

→ **Median 7.4 months from symptom onset (IQR 5.4-10.9)**

(2) Reduced medial temporal lobe glutamate in patients

Patients had reduced MTL glutamate (7.1 vs 7.7mM)



CONCLUSIONS

- **Patients at early recovery from NMDARE had prefrontal microstructural changes predictive of long-term cognitive-behavioural dysregulation and hippocampal changes predictive of memory dysfunction.**
- **The hypoglutamatergic state parallels some findings in chronic schizophrenia[4].**
- **qT2 is a promising microstructural biomarker for predicting long-term neuropsychological outcome in autoimmune encephalitis.**

ME was supported by Action Medical Research [GN2835] and the BPNA. With thanks to LoCUS, Encephalitis International and referring clinicians.

[1] Guasp et al. 2022, *Lancet Neurology* 21(10): 899–910. [2] Graus et al. 2016, *Lancet Neurology* 15(4): 391–404. [3] Teixeira et al. 2018, *MRM* 79(1): 234-245. [4] Merritt et al. 2023, *Molecular Psychiatry* 28(5):2039-48.

ENCEPHALITIS CONFERENCE 2025

Dr Mirriam Munthali

Queen Elizabeth Central Hospital, Malawi

A man with unusual presentation of neurocysticercosis: racemose neurocysticercosis

Dr Mirriam Munthali is a female medical doctor from the northern part of Malawi. She is currently in her third year of internal medicine training under the Kamuzu College of Health sciences (KUHES) as well as the East Central and southern African college of Physicians (ECSACOP). She is a professional member of Encephalitis International and an associate member of the Royal College of Physicians. Furthermore, she is passionate about infectious diseases with an interest in neurological Infectious diseases and Encephalitis. In 2023, she presented a poster presentation at the Neurological Infectious Disease Course held in Liverpool, on a scholarship as an international scholar and in 2024 she was part of the Organizing team of the 2024 Neurological Infectious Diseases Course held in Blantyre, Malawi in July. She hopes to Specialize in Infectious diseases once done with her masters in Internal medicine training.

A man with unusual presentation of Neurocysticercosis: Racemose Neurocysticercosis

Mirriam Munthali[1], Omega Mbewe[2], Chisomo Kadam'manja[1], Karen Chetcuti[1], Sithembile Chimaliro[2], Patrick Kamalo[2], Yohane Gadama[1], Johnstone Kumwenda[1]
[1]Kamuzu University of Health Sciences, School of Medicine and Oral Health
[2]Queen Elizabeth Central Hospital, Malawi

CASE DESCRIPTION

- A 53-year-old male presented with a 3-month history of headache, described as pressure-like and located in the occipital region.
- Two weeks prior to presentation, he started vomiting and developed tonic-clonic seizures.
- He also noted that he had difficulties expressing himself.
- His past medical history was notable for HIV infection since 2022 and he was on Antiretroviral Therapy
- His HIV control was uncertain as there were no recent recorded CD4 count or viral load results.
- He neither smoked cigarettes nor drunk alcohol and worked as a freelance electrician.
- The only abnormality on examination was Anomic Aphasia.
- The differential diagnosis was an HIV associated space-occupying lesion or Central Nervous System (CNS) Infection

RESULTS

- Routine blood tests like FBC and RFT were unremarkable
- His CD4 cell count was 207c/UL and his serum cryptococcal antigen test was negative
- With the strong impression of raised intracranial pressure, a lumbar puncture was deferred.

PROGRESS IN THE MEDICAL WARD

- The patient's headache worsened and he became completely aphasic.
- At this point, A CT scan of the brain was done and the images are shown in Figure 1 below. MRI was not available at the hospital.

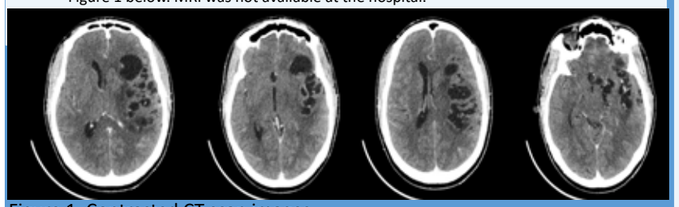


Figure 1. Contrasted CT scan images

RADILOGIST CT REPORT

- Appearances are of a left supratentorial sulcal and cisternal multicystic abnormality for which intracranial cryptococcosis versus malignancy are thought as strong differentials

NEUROSURGICAL INTERVENTION

- He was reviewed by the neurosurgical team and transferred to their ward.
- While in the surgical ward, he developed right sided weakness and was started on Dexamethasone 4mg IV three times a day and Omeprazole 20mg twice daily.
- Day 36 post admission, a stereotactic biopsy was done, where solid and cystic samples were taken for histology.

HISTOLOGY RESULTS

- His histology results revealed that he had neurocysticercosis.

MANAGEMENT

- He was started on Albendazole 400mg twice daily to take for a month, and his Dexamethasone dose was tapered down to 3mg four times a day.
- The patient made a full recovery on this treatment

DISCUSSION

- While we are accustomed to diagnosing and managing parenchymal Neurocysticercosis, which predominantly manifests with seizures, this patient exhibited a distinct clinical course.
- Despite a history of seizures, there were no observed seizure episodes during hospitalization, even in the absence of antiepileptic therapy.
- Additionally, the patient demonstrated a vasculitis process manifested by hemiparesis and aphasia.
- These evolving neurological deficits prompted consideration of alternative space-occupying lesions, rather than typical Neurocysticercosis.
- Neuroimaging further complicated the diagnosis, as multiple large cystic lesions visualized on CT brain imaging were inconsistent with the classical appearance of parenchymal Neurocysticercosis.
- This case highlights the importance of multidisciplinary approach and histopathological confirmation in complex neurological presentation

LARNING POINTS

- 1.Racemose Neurocysticercosis presents atypically and should be considered as differential in patients presenting with any neurological symptoms and signs, especially in endemic areas.
- 2.CT brain has limitations in diagnosing Racemose Neurocysticercosis, MRI Brain is imperative
- 3.Complex neurological cases benefit from a multidisciplinary collaboration to refine diagnosis and guide management
- 4.In cases with uncertain imaging findings, tissue biopsy remains crucial for a definitive diagnosis and appropriate treatment planning

REFERENCES

- 1.Saini AG, Vyas S, Singhi P. Racemose neurocysticercosis. Journal of Infection and Public Health. 2017 Nov;10(6):884–5.
- 2.Rabiela Cervantes MT, Rivas-Hernandez A, Rodrigues-Ibarra J, CastilloMedina S, Cancino FM. Anatomopathological aspects of human brain cysticercosis. In: Flisser A, Sillms K, Laclette JP, Larralde C, editors.
- 3.Mahale RR, Mehta A, Rangasetty S. Extraparenchymal (Racemose) Neurocysticercosis and Its Multitude Manifestations: A Comprehensive Review. J Clin Neurol. 2015;11(3):203

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ENCEPHALITIS CONFERENCE 2025

Dr Molly Wilson-Murphy

Boston Children's Hospital, USA

Influenza-associated acute necrotizing encephalopathy in U.S. children: characteristics and outcomes

Dr Molly Wilson-Murphy is a pediatric neurologist dual fellowship trained in neuroimmunology and neuroinfectious disease. Her areas of expertise include infectious, post-infectious, and autoimmune encephalitis, meningoencephalitis, and myelitis and well as other neuroinfectious and neuroinflammatory diseases and disorders. Her research has involved describing emerging neuroinfectious and neuroinflammatory conditions in children. She has particular interest in arboviral encephalitis including Powassan virus, as well as neurologic and psychiatric symptoms of post-acute sequelae of COVID-19, influenza associated encephalitis and encephalopathy, and acute necrotizing encephalopathy. She is also currently working with basic scientists in translational research surrounding acute necrotizing encephalopathy.

Influenza-Associated Acute Necrotizing Encephalopathy in U.S. Children: Characteristics and Outcomes

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Objective

To elucidate clinical presentation, interventions, and outcomes among US children diagnosed with influenza-associated acute necrotizing encephalopathy

Background

The 2024-25 influenza season was characterized by significant morbidity and mortality comparable to the 2009 H1N1 pandemic. Neurologic complications have been unusually high. ANE is a rare, but severe neurologic complication associated with influenza and other viral infections, for which epidemiologic and management data remain limited.

Methods

- Following anecdotal reports of increased influenza-associated ANE in children, we issued a call for cases via academic societies, public health agencies, and by directly contacting pediatric specialists at 76 US academic centers.
- Inclusion criteria included: (1) age ≦ 18; (2) hospitalized in the US between October 1, 2023 and May 1, 2025; (3) laboratory-confirmed influenza infection and (4) suspected diagnosis of ANE (acute onset of encephalopathy and/or seizure with characteristic imaging findings and relevant serum markers).

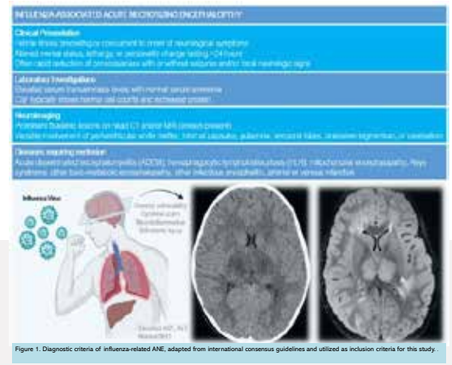


Figure 1. Diagnostic criteria of influenza-related ANE, adapted from international consensus guidelines and utilized as inclusion criteria for this study.

Results

Demographics	Survivors (N=30)	Non-survivors (N=11)
Age (years)		
N	30	11
Mean (SD)	6.4 (4.14)	4.5 (5.30)
Median (IQR)	5.5 (3.0, 8.0)	1.8 (1.3, 7.0)
Range	1.3, 17.0	0.6, 16.0
Sex, n (%)		
Female	15 (50%)	8 (73%)
Male	15 (50%)	3 (27%)
Race, n (%)		
Asian	5 (17%)	3 (27%)
Black	2 (7%)	0 (0%)
Multiracial	1 (3%)	0 (0%)
Native Hawaiian or Pacific Islander	1 (3%)	0 (0%)
White	17 (57%)	7 (64%)
Ethnicity, n (%)		
Hispanic	15 (50%)	3 (27%)
Not Hispanic	12 (40%)	7 (64%)
Medical History, n (%)		
None	23 (77%)	8 (73%)
Systemic lupus erythematous	0 (0%)	1 (9%)
RYR1/Myopathy	0 (0%)	1 (9%)
Craniofacial microsomia, Erb's palsy	0 (0%)	1 (9%)
Juvenile idiopathic arthritis	1 (3%)	0 (0%)
History of ANE	1 (3%)	0 (0%)
History of febrile seizures	1 (3%)	0 (0%)
History of viral encephalitis	1 (3%)	0 (0%)
Tuberous sclerosis complex, epilepsy	1 (3%)	0 (0%)
Obesity	1 (3%)	0 (0%)
Autism spectrum disorder	1 (3%)	0 (0%)
BMI Z-score		
N	26	8
Mean (SD)	1.9 (2.85)	0.1 (2.42)
Median (IQR)	2.2 (-0.3, 4.3)	0.5 (-1.0, 1.7)
Range	-4.1, 8.2	-4.5, 3.3
Vaccinated for seasonal influenza, n/N (%)	5/28 (18%)	1/10 (10%)
Tmax (Celsius)		
N	26	7
Mean (SD)	39.4 (1.10)	40.4 (1.14)
Median (IQR)	39.4 (38.7, 40.0)	40.2 (39.4, 41.7)
Range	36.7, 41.5	39.3, 41.9
GCS at nadir		
N	29	11
Mean (SD)	6.6 (3.04)	3.7 (1.27)
Median (IQR)	6.0 (4.0, 9.0)	3.0 (3.0, 4.0)
Range	2.0, 13.0	3.0, 6.0
Triaminar lesion, n/N (%)	12/28 (43%)	5/6 (83%)
Brainstem involvement, n/N (%)	25/30 (83%)	11/11 (100%)
ANE Severity Score		
N	30	11
Mean (SD)	4.8 (1.86)	6.0 (2.19)
Median (IQR)	5.0 (4.0, 5.0)	6.0 (5.0, 7.0)

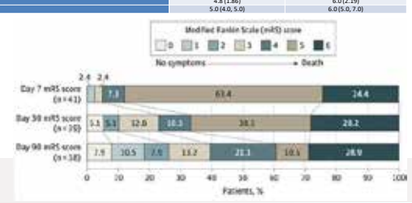


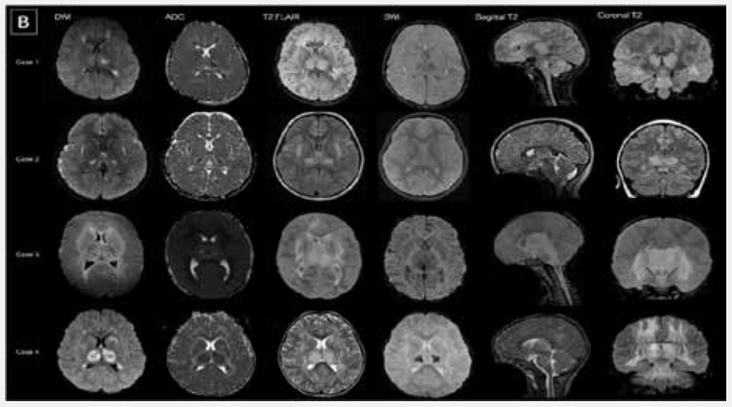
Figure 2. Longitudinal Outcomes

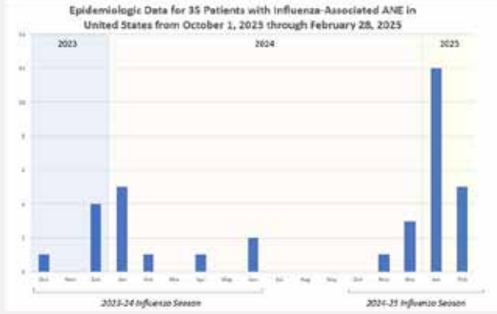
Conclusion

- Influenza-associated ANE carried a high morbidity and mortality in this cohort of predominantly young and previously healthy children. Low vaccination rates among affected children highlight a critical prevention opportunity, while the identification of *RANBP2* and other genetic variants underscores the complex interplay between viral triggers and host genetic susceptibility.

Table 3. Immunotherapies administered.

Immunotherapy	Total, No. (%)
Intravenous methylprednisolone	19 (73)
Intravenous immunoglobulin	17 (68)
Tocilizumab	21 (53)
Plasmapheresis	13 (50)
Intrathecal methylprednisolone	7 (35)
Anakinra	2 (9)





Key Findings

- In this multicenter case series of 41 children from 23 US hospitals, influenza-associated ANE carried a 27% mortality rate despite multimodal therapy.
- Clinical presentation included fever (93%) and encephalopathy (100%), and seizures in 28 (68%); most patients had no medical history, despite the high rate of genetic risk alleles for ANE identified.
- The H1/2009 influenza A strain predominated, and among 38 patients with available vaccination history, only 6 (16%) had received age-appropriate seasonal influenza vaccination, notably lower than the national pediatric influenza vaccination rates of 48-55% for the corresponding influenza seasons.
- Median ICU and hospital lengths of stay were 11 and 22 days, respectively.
- Eleven patients died a median of 3 days from symptom onset, primarily from cerebral herniation (91%).
- Among the 27 survivors with 90-day follow-up, 63% had at least moderate disability (mRS≥3).

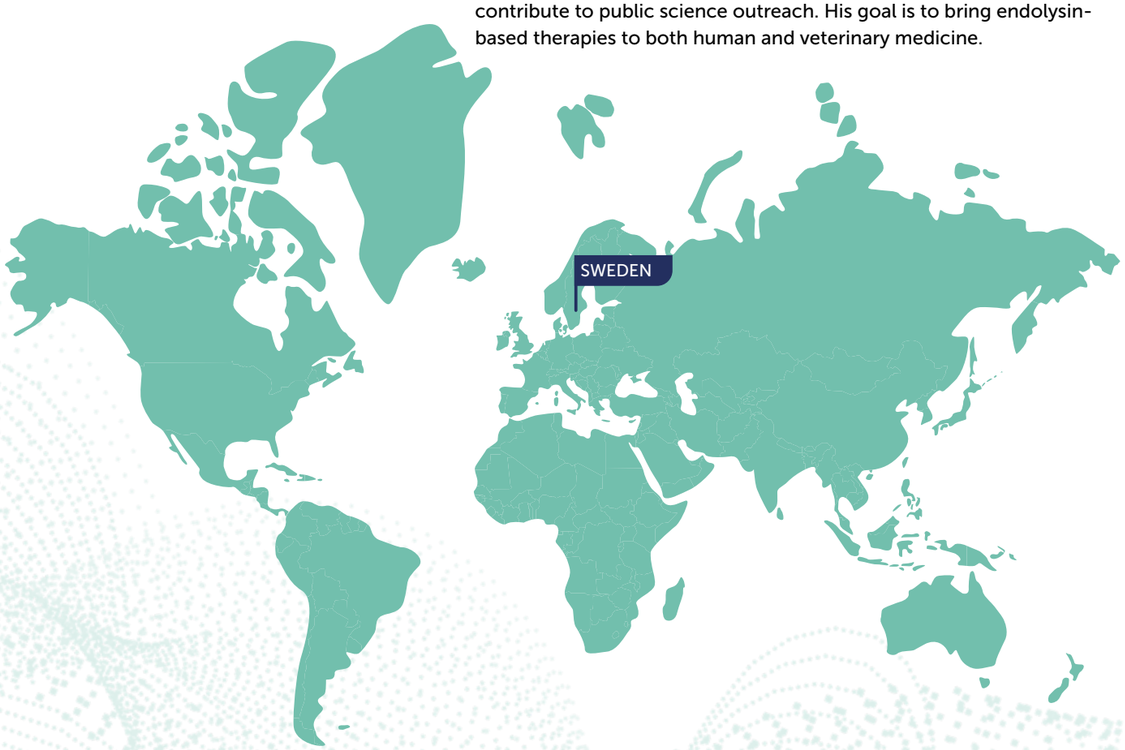
Lab Findings	Survivors (N=30)	Non-survivors (N=11)
Influenza Subtype, n (%)		
Flu A (total)	29 (97%)	10 (91%)
Flu A - H1/2009	9 (30%)	5 (45%)
Flu A - H3	7 (23%)	0 (0%)
Flu A - No typing	13 (43%)	5 (45%)
Flu B - No typing	1 (3%)	1 (9%)
Peak ALT, Median (IQR)	86.0 (49.0, 213.0) [n=28]	596.0 (125.0, 4832.0) [n=11]
Peak AST, Median (IQR)	97.0 (32.0, 303.0) [n=29]	439.0 (69.0, 3024.0) [n=11]
Platelet nadir, Median (IQR)	128.0 (93.0, 201.0) [n=30]	96.0 (48.0, 221.0) [n=11]
ESR, Median (IQR)	23.5 (11.0, 38.0) [n=14]	32.0 (32.0, 32.0) [n=1]
CRP, Median (IQR)	4.3 (2.2, 12.0) [n=22]	2.3 (0.9, 6.4) [n=6]
Ammonia, Median (IQR)	24.0 (19.0, 34.0) [n=18]	37.0 (20.0, 52.0) [n=7]
CSF WBC, Median (IQR)	2.5 (1.5, 7.0) [n=28]	6.0 (3.0, 25.5) [n=4]
CSF Protein, Median (IQR)	77.9 (50.0, 110.5) [n=28]	171.0 (80.5, 327.0) [n=4]
Genetic testing results, n (%)		
No genetic findings identified	10 (33%)	4 (36%)
RANBP2 (heterozygous pathogenic)	6 (20%)	0 (0%)
EAS1P2 (heterozygous VUS)	2 (7%)	3 (27%)
YRF1 (biallelic VUS)	1 (3%)	0 (0%)
TBK1 (homozygous VUS)	1 (3%)	0 (0%)
NEK4/ADK (biallelic pathogenic)	0 (0%)	1 (9%)
OLIG6 (heterozygous likely pathogenic)	0 (0%)	1 (9%)
SETD1A (heterozygous VUS)	0 (0%)	1 (9%)
THOC2 (heterozygous VUS)	1 (3%)	0 (0%)
ACAA2_UFSP2 (heterozygous VUS)	1 (3%)	0 (0%)
TOP3 (heterozygous pathogenic)	1 (3%)	0 (0%)
Not available	7 (23%)	1 (9%)

Dr Niels Vander Elst

Karolinska Institutet, Sweden

Bacteriophage-derived endolysins restore antibiotic susceptibility in β-lactam- and macrolide-resistant Streptococcus pneumoniae infections

Dr Niels Vander Elst has specialized in bacteriophage-derived endolysins—enzymes with strong potential to address antibiotic-resistant infections. Beginning with an internship at Stockholm University and then a dual PhD in Biotechnology and Veterinary Medicine at KU Leuven and Ghent University, supported by the Research Foundation Flanders (FWO). His research focuses on Gram-positive pathogens, particularly Streptococcus and Staphylococcus species. One of his patented endolysins is now in clinical trials for veterinary use, while another was a finalist for the University of Maryland's 2020 'Invention of the Year.' He secured competitive funding across Europe and the U.S., including a BAEF fellowship for research at the Institute for Bioscience and Biotechnology Research (University of Maryland). Currently, he is a postdoctoral researcher at Karolinska Institutet, where he engineers next-generation endolysins to improve efficacy, reduce adverse effects like antigen release, and enhance synergy with antibiotics. A recent study he authored on restoring antibiotic susceptibility in resistant Streptococcus pneumoniae ranked in the top 5% of research outputs by Altmetric. Outside the lab, he serves on the Leadership of the Junior Faculty at Karolinska Institutet and represent it on the Open Science board. He also teaches neurohistology in the medical curriculum and contribute to public science outreach. His goal is to bring endolysin-based therapies to both human and veterinary medicine.



Bacteriophage-derived endolysins restore antibiotic susceptibility in β-lactam- and macrolide-resistant *Streptococcus pneumoniae* infections

Niels Vander Elst[1], Kristine Farmen[1], Lisa Knörr[1,2], Lotte Merlijn[1] and Federico Iovino[1]

[1]Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden.
[2]European Institute for Molecular Imaging (EIMI), Universitätsklinikum Münster, Germany.

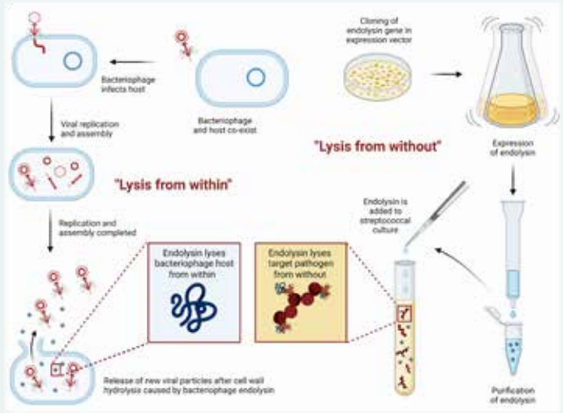
Vander Elst N., *et al.* (2025); Molecular Medicine; https://doi.org/10.1186/s10020-025-01226-1

Take-home messages:

- Endolysins are peptidoglycan hydrolases derived from bacteriophages that are extremely effective in killing antibiotic-resistant pneumococci in blood and CSF.
- Endolysins lower the MIC of antibiotics below clinical resistance breakpoints by synergistic (β-lactams) or additive (macrolides) effects in a combination, mitigating neurotoxicity in infected human neuronal-like cells.
- Endolysins cross the blood-brain barrier and treat penicillin-resistant invasive pneumococcal disease *in vivo*, including pneumococcal meningitis.

Introduction

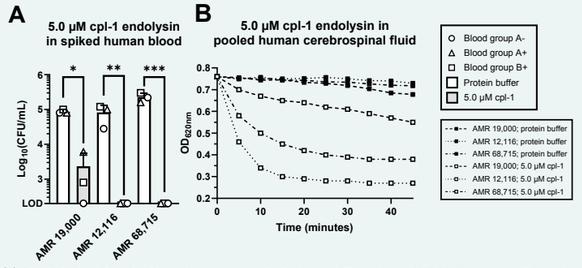
What are endolysins and how can they help?



The action of endolysins in a 'lysis-from-within' *versus* 'lysis-from-without' scenario is demonstrated (from Vander Elst N., 2024). Bacteriophages employ endolysins at the end of their lytic replication cycle to release newly assembled viral particles from the infected host, causing 'lysis-from-within'. In the 'lysis-from-without' scenario, the endolysin gene is cloned in a vector, after which the endolysin is expressed and purified. In the case of Gram-positive pathogens, the purified endolysin retains its functionality when applied externally to the targeted pathogen (created with https://biorender.com/).

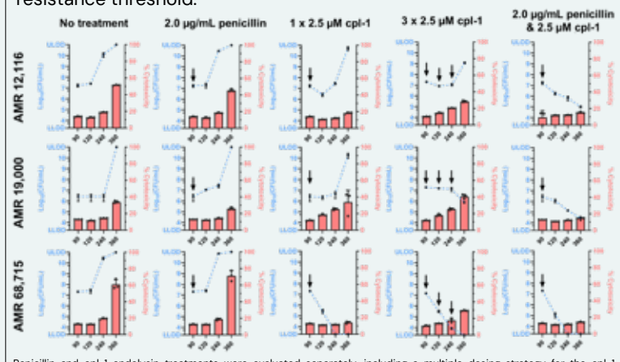
Methods & Results

Endolysins retain killing activity against antibiotic-resistant pneumococci in human blood and cerebrospinal fluid.



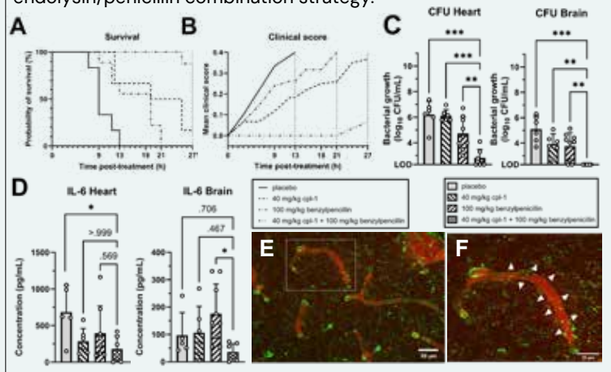
(**A**) Blood obtained from healthy volunteers was spiked with penicillin-resistant AMR 19,000, or penicillin- and erythromycin-resistant AMR 12,116 and AMR 68,715, which was subsequently treated with 5.0 µM endolysin cpl-1 or protein buffer as a negative control. (**B**) Turbidity reduction assay with the same isolates in pooled human cerebrospinal fluid. In A, bars show the mean ± standard deviation of three biological replicates (n=3). In B, datapoints show one biological replicate (n=1) every 5 minutes. Log_{10}(CFU/mL) were analyzed by means of a two-tailed, paired t-test; LOD indicates the limit of detection (200 CFU/mL); * indicates $p < 0.05$, ** indicates $p < 0.01$ and *** indicates $p < 0.001$.

Endolysin supplementation protects human neuronal-like cells from cytotoxicity caused by penicillin-resistant pneumococci by synergistically lowering the penicillin MIC below the clinical resistance threshold.



Penicillin and cpl-1 endolysin treatments were evaluated separately, including a multiple dosing strategy for the cpl-1 endolysin, and together as a combination in human neuronal-like cells infected with the penicillin-resistant pneumococcal clinical isolates AMR 12,116, AMR 19,000, and AMR 68,715. Untreated controls were included for comparison; the blue dotted lines represent bacterial growth in log_{10}(CFU/mL) plotted on the left y-axis, with data points at 90-, 120-, 240-, and 360-minutes post-infection showing the mean ± standard deviation of three biological replicates (n=3). The red bars depict the percentage of cytotoxicity in human neuronal-like cells at these same time points, plotted on the right y-axis, showing three biological replicates (n=3; corresponding to three white circles), alongside bars indicating the mean and an error bar indicating the standard deviation. 2.0 µg/mL is the clinical breakpoints for penicillin resistance (year: 2024). The black arrow indicates administration of treatment. LLOD and ULOD indicate the lower and upper limit of detection of 200 and 10^{11} CFU/mL, respectively.

Endolysins can cross the blood brain barrier and rescue mice from penicillin-resistant invasive pneumococcal disease by following an endolysin/penicillin combination strategy.



(**A**) Kaplan–Meier survival curve and (**B**) mean clinical scores, assessed according to Karolinska Institutet's veterinary protocol for rodent physiological and psychological well-being. A clinical score of 0.0 indicates a fully healthy status, while 0.4 indicates the humane endpoint. (**C**) Bacterial load in the heart and brain. (**D**) Levels of IL-6 in the heart and brain. In C and D, data were analyzed using one-way ANOVA with Bonferroni post-hoc tests after outlier removal via the ROUT method (Q = 5%); Bars represent the mean ± standard deviation of biological replicates (each dot representing one mouse); LOD indicates the limit of detection (200 CFU/mL); * indicates $p < 0.05$, ** indicates $p < 0.01$ and *** indicates $p < 0.001$. (**E**) Confocal images display z-stacks of brain tissue stained for brain microvasculature (green) and cpl-1 endolysin (red); (**F**) brain tissue area within white borders was enlarged to highlight the diffusion (white arrowheads) of the cpl-1 red signal from the vasculature into the brain parenchyma. The scale bars represent either 10.0 or 50.0 µm, as indicated.

Dr. Vander Elst is a postdoctoral researcher affiliated to the Karolinska Institute, Sweden. He specializes in engineering endolysin variants with applications in (veterinary) medicine and beyond. Dr. Vander Elst earned a dual PhD in Biotechnology and Veterinary Medicine that was jointly awarded by Ghent University and KU Leuven, Belgium. During his doctoral research, he spent a significant amount of time working on endolysins at the Institute for Bioscience and Biotechnology Research (IBBR) associated to the University of Maryland, Rockville, MD, USA. Dr. Vander Elst declares pending patent applications regarding endolysins.

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ENCEPHALITIS CONFERENCE 2025

Dr Robin van Steenhoven

Erasmus University Medical Center, The Netherlands

Cytotoxic T cells and acute neuronal damage play a central role in the immunopathology of anti-GABA-B receptor encephalitis.

Dr Robin van Steenhoven is a neurologist and clinical research fellow in neuroimmunology at the Erasmus University Medical Center Rotterdam, the Netherlands. He attended clinical fellowships in both neuroimmunology and neurodegenerative diseases. In his clinical and scientific work, he is focusing on rapidly progressive dementia and autoimmune encephalitis. By studying the neuropathology of autoimmune encephalitis, he aims to identify unknown pathogenic mechanisms, in order to develop targeted treatment regimens.

Immunopathology of anti-GABA$_B$-receptor encephalitis

Robin van Steenhoven[1*], Nina L. Fransen[2*], Annemieke Rozemuller[2], Maarten Titulaer [1]
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* Equal contributions

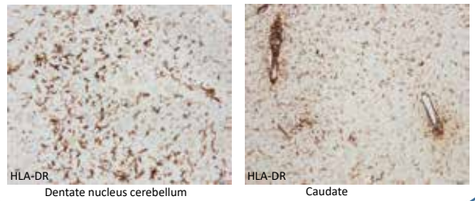
Anti-GABAB receptor (anti-GABA$_B$-R) encephalitis is characterized by rapidly progressive dementia, seizures, and severe neuropsychiatric symptoms (1). The GABA$_B$-R mediates inhibitory signals, suppress high activity states in neuronal networks and is mainly expressed in hippocampus, amygdala, thalamus and cerebellum. Patient with anti-GABA$_B$-R encephalitis usually strongly improve after treatment with immunotherapy. Previously, it has been shown in anti-NMDAR receptor that B cells play an essential role in the pathogenesis of AE with extracellular antibodies (2, 3). However, the immunopathology of GABA-BR encephalitis in human brain and the role of T cells has not been systematically described.

Case identification

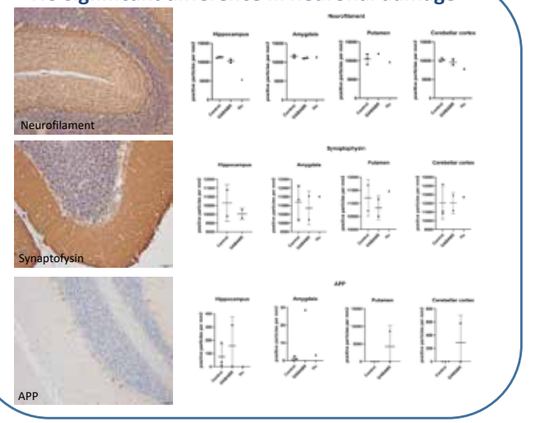
	Anti-GABA-B$_R$ n=4	Anti-Hu n=2	Control n=3
Sex	1 F / 3 M	2 M	2 M / 1 F
Age (years)	69-77	62-71	58-98
Disease duration	2-77 months	2,5 years	
Clinical syndrome	Limbic encephalitis	Encephalomyelitis	
Malignancy	1 possible / 4	1 SCLC / 2	
Treatment	3 untreated, 1 limited treatment	2 treated	

- Standard brain bank procedure for neuropathological diagnostics
- Additional 8 brain regions; hippocampus, amygdala, cerebellum, basal ganglia, frontal, temporal, pons, medulla,
- Immunohistochemistry for microglia (CD68, HLA), T cells (CD3,CD4,CD8, GranB), B and plasma cells (CD20, CD79a, CD138), IgG and neuronal damage (APP, synapto, neurofilament)

Hippocampus, Amygdala, Basal Ganglia and Cerebellum are primarily affected with microglial activation

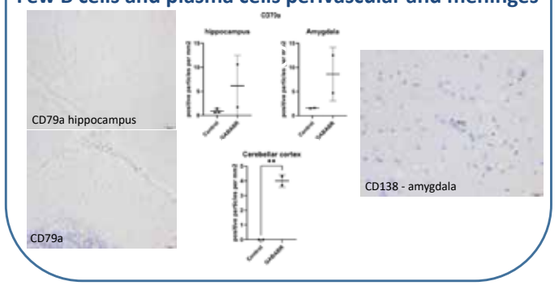


No significant difference in neuronal damage

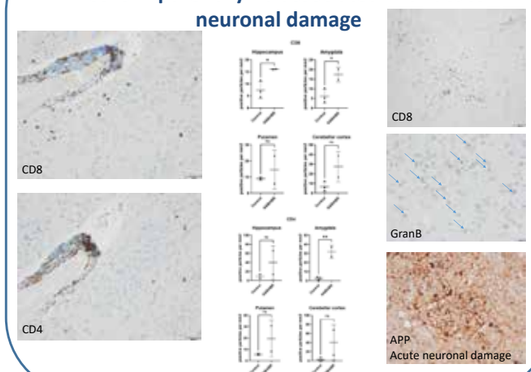


IgG deposition on neurons

Few B cells and plasma cells perivascular and meninges



CD8 and CD4 T cells are increased and CD8 cytotoxic T cells in parenchyma associated with acute neuronal damage



Conclusion

Anti-GABA-B$_R$ encephalitis neuropathology is characterized by limbic encephalitis with involvement of cerebellum and basal ganglia with a prominent cytotoxic T cell response, in addition to IgG deposition, B cells and plasma cells. Perivascular there is accumulation of CD4 T-helper cells with B cells and plasma cells suggesting antibodies are potentially produced within the brain. We show that T cells play a role in this subtype of AE with antibodies against extracellular antigens.

References: 1. Van Coevorden-Hameete&De Bruijn et al, Brain 2019. 2. Bien et al, Brain 2012. 3. Zrzavy et al, Annals of Neurology 2021

ENCEPHALITIS CONFERENCE 2025

Dr Rukesh Yadav

Maharajgunj Medical Campus Institute of Medicine Tribhuvan University, Nepal

Assessing the utility of neutrophil-to-lymphocyte ratio in determining the severity of autoimmune encephalitis: a meta-analysis

Dr Rukesh Yadav is an Internal Medicine resident at Maharajgunj Medical Campus, Institute of Medicine, Tribhuvan University, Nepal. With a strong foundation in clinical medicine and research, he has developed a keen interest in the field of infectious diseases, driven by the diverse and evolving challenges it presents in patient care and public health. He is committed to advancing his clinical expertise and contributing to research and education that can improve outcomes in infectious disease management, particularly in resource-limited settings like Nepal.

Elevated Neutrophil-to-Lymphocyte Ratio Predicts Severity in Autoimmune Encephalitis: A Meta-Analysis

Rukesh Yadav[1]

1. Department of Internal Medicine, Institute of Medicine, Maharajgunj Medical Campus, Tribhuvan University

Introduction & Background

-Autoimmune encephalitis (AE) is a serious neurological disorder characterized by immune-mediated brain inflammation.

-Reliable biomarkers to predict disease severity at early stages are crucial for improving patient outcomes.

-The neutrophil-to-lymphocyte ratio (NLR), a marker of systemic inflammation, has shown prognostic value in various neuroinflammatory disorders.

-This meta-analysis aims to evaluate the utility of NLR in predicting the severity of AE.

-Methods

-Systematic search of PubMed, Embase, Web of Science, and Scopus for studies published up to May 2025 assessing baseline NLR in AE patients.

-Severity stratified using modified Rankin scale (mRS) and Clinical Assessment Scale for Autoimmune Encephalitis (CASE).

-Standardized mean differences (SMDs) pooled using a random-effects model; subgroup analyses performed based on antibody status.

-Included 4 studies with a total of 452 AE patients.

Results

Comparison of NLR by Disease Severity

-Patients with mild to moderate AE (mRS ≤ 3, CASE ≤ 4) showed significantly lower NLR levels compared to severe AE patients (mRS > 3, CASE ≥ 5).

-Pooled standardized mean difference (SMD) = -3.14 (95% CI: -3.43 to -2.85), $p < 0.00001$, with high heterogeneity ($I^2 = 94\%$).

-Subgroup Analysis by Antibody Status

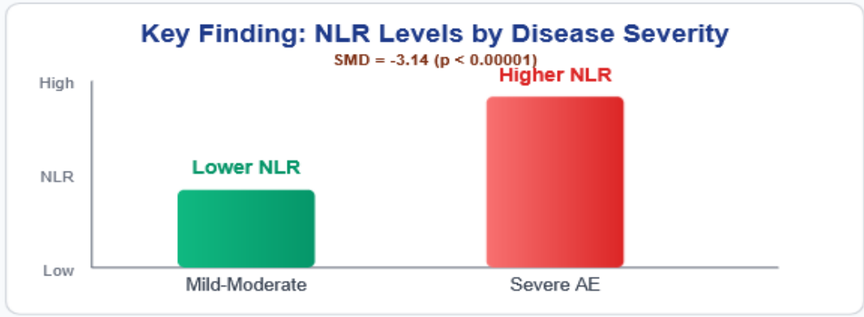
-Subgroup analyses based on antibody status (anti-NMDAR versus others) showed consistent results with main findings.

-NLR remained significantly elevated in severe AE across antibody subtypes.

Association of Elevated NLR with AE Severity

-High NLR was significantly associated with greater disease severity in AE.

-Pooled multivariate odds ratio = 1.48 (95% CI: 1.25 to 1.76), with no observed heterogeneity ($I^2 = 0\%$), $p < 0.00001$.



Statistical Results

Standardized Mean Difference	Odds Ratio for High NLR
-3.14 (95% CI: -3.43 to -2.85)	1.48 (95% CI: 1.25 to 1.76)

Discussion & Implications

-Elevated NLR reflects systemic inflammation correlating with AE severity, supporting its role as a prognostic biomarker.

-This meta-analysis advances understanding in neuroinflammatory biomarker research by consolidating evidence linking NLR with AE severity.

-NLR measurement, being inexpensive and accessible, can enhance early clinical decision-making for AE management.

-Further studies are warranted to validate the clinical utility and to explore longitudinal changes in NLR with treatment.

Funding: None | Acknowledgments: None| Disclosures: None | Contact: rukeshyadav46@gmail.com

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Ms. Sadie Eggmann

University of Colorado Anschutz Medical Campus, USA

Leucine-Rich Glioma Inactivated-1 (LGI1) autoimmune encephalitis: associated biomarkers of inflammation, neuronal and glial injury and associated long-term outcomes

Sadie Eggmann is a neuroscience research professional in the Autoimmune Neurology Program at the University of Colorado Anschutz Medical Campus who works under the supervision with Dr Amanda Piquet, MD, the Céline Dion Foundation Endowed Chair and Director of the Autoimmune Neurology Program. Dr Piquet's research program seeks to advance our understanding of rare autoimmune neurologic disorders through observational studies, translational studies focused on identifying potential biomarkers associated with neurological outcomes and treatment response, and innovative clinical trials.

Leucine-Rich Glioma Inactivated-1 (LGI1) Autoimmune Encephalitis: Associated Biomarkers of Inflammation, Neuronal and Glial Injury and Associated Long-Term Outcomes

Sadie Eggmann, Tyler L. Borko, Phillip Winters, Kelli M. Money, Stefan Sillau, Sean Selva, Alanna Ritchie, Jadyn Zook, Brianna Blume, Ryan Kammeyer, Gregory Owen, Jeffrey L. Bennett, Amanda L. Piquet
Department of Neurology, University of Colorado Anschutz, Aurora, CO

Anschutz

Background

- Seizures and subacute cognitive disturbances are clinical features of LGI1 autoimmune encephalitis (LGI1-AE)
- Blood biomarkers may show promise for assessing severity and identifying disease-specific signatures.

Methods

- 21 LGI1-AE patients were enrolled between 2018-2024 and followed prospectively.
- Diagnosis confirmed by CBA on CSF and/or serum
- Biomarkers of neuronal and glial injury included NfL and GFAP and cytokine markers of inflammation including IL12p70, IL1B, IL4, IL5, IFNg, IL6, IL8, IL22, TNFα, IL1 (Simoa® SPX and SRX).
- Biomarker data was logarithmically transformed and analyzed using longitudinal regression with the ratio of means between LGI1-AE and non-inflammatory controls.
- Clinical data were collected correlated to the blood-based biomarkers to assess their relationship to disease severity and long-term outcomes.
- We profiled the plasma proteome (Olink) of LGI-AE patients aimed to identify novel biomarkers for therapeutic targeting.

Results

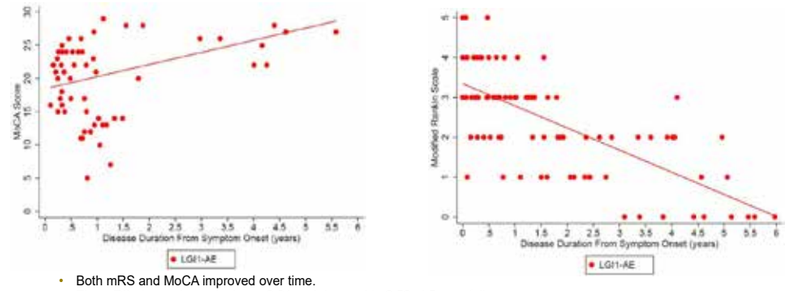
Demographics of LGI1-AE cohort

Median Age (years)	63.29
Sex distribution	76.2% M, 23.8% F
Seizures present; those with FBDS*	90.50%; 57.90%
Abnormal MRI	52.40%
Memory loss	85.70%
Received steroids	100%
Received IVIG	61.90%
Received rituximab	85.70%

*FBDS = Faciobrachial dystonic seizures

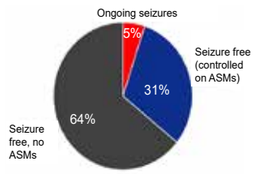
Control cohort demographics:
16 migraine headache patients
(56.3% M, 43.7% F; average age: 58 years)

Clinical Outcomes Measurements

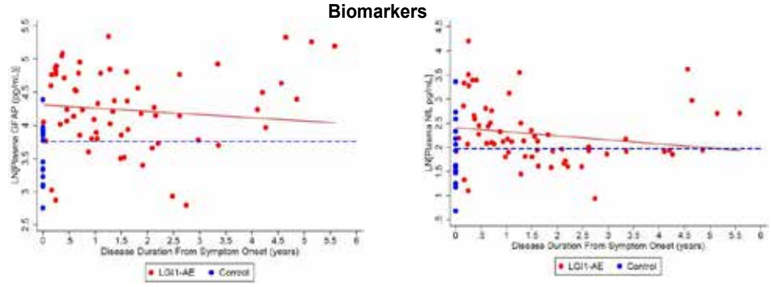


- Both mRS and MoCA improved over time.
- The mRS at symptom onset was 3.34 and dropped to 0.56 at 5-year follow up.
- Mean MoCA scores were 18.45 at the onset and increased to 29.40 at 6-year follow-up.

Seizure Freedom two years post-diagnosis



Biomarkers



- In patients presenting with lower Nfl scores at symptom onset, MoCA scores tended to recover more quickly.
- The model estimated geometric mean plasma NfL values at disease diagnosis to be 11.86 pg/mL, compared to 6.07 pg/mL in non-inflammatory controls and plasma GFAP values 77.70 pg/mL, compared to non-inflammatory controls at 36.26 pg/mL.
- Plasma levels of IL1b, IL6, and IL10 cytokines in LGI1 AE patients at the time of study enrollment showed differences compared to controls, with only IL10 being significant.
- Using proteomics (Olink platform) for biomarkers discovery, we found differences in normalized protein expression (NPX) for IL-8 ($p = 0.03$), MCP-3 ($p = 0.007$), IL6 ($p = 0.045$), CXCL11 ($p < 0.001$), IL-20RA ($p = 0.045$), CXCL9 ($p = 0.004$), CXCL1 ($p = 0.035$), FGF-21 ($p = 0.028$), TRANCE ($p = 0.004$), IL-10 ($p < 0.0001$), CXCL10 ($p = 0.034$), and CCL28 ($p = 0.005$) in LGI1 AE vs non-inflammatory controls.

Conclusions

- Clinical improvement, measured by improved MoCA and mRS scores, correlated with a decline in NfL and GFAP levels returning to levels like control populations.
- MoCA scores also improved earlier in patients with lower baseline NfL levels at symptom onset.
- In one patient with a clinical relapse, NfL and GFAP levels increased.
- NfL and GFAP may be useful measures to understand disease progression in patients with LGI1 AE, however additional studies are needed to better understand the effects of immunotherapy.
- Additionally, identifying a disease-specific inflammatory signature could identify novel biomarkers for therapeutic targeting.

References

- Borko TL, Winters P, Money KM, Sillau S, Eggmann S, Selva S, Ritchie A, Kammeyer R, Owens GP, Bennett JL, Piquet AL. Long-term outcomes in leucine-rich glioma inactivated-1 autoimmune encephalitis and associated biomarkers of inflammation and neuronal and glial injury. Front Neurol. 2025.
- Binks SNM, Klein CJ, Waters P, Pittock SJ, Irani SR. LGI1, CASPR2 and related antibodies: a molecular evolution of the phenotypes. J Neurol Neurosurg Psychiatry 2018;89:526-534.
- 2.van Sonderen A, Thijs RD, Coenders EC, et al. Anti-LGI1 encephalitis: Clinical syndrome and long-term follow-up. Neurology 2016;87:1449-1456.

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Dr Shahad Ibrahim

Cork University Hospital, Ireland.

When seizures signal FLAMES: a cortical relapse in adult MOGAD

Dr Shahad Ibrahim is a final-year trainee in General Internal Medicine in Ireland and a second-year Master's student in Neuroscience and Neurodegeneration at the University of Sheffield. She graduated from medical school at the University of Medical Sciences and Technology (UMST) in Sudan. She is working toward a career in neurology, with hopes of joining specialist training next year. She is especially drawn to neuroinflammatory conditions like NMOSD, MOGAD, and MS.

Unmasking FLAMES in an Adult with Relapsing MOGAD: A Case-Based Insight into a Rare Cortical Phenotype

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[1]Department of Neurology, University Hospital Waterford

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Background

- FLAMES (FLAIR-hyperintense Lesions in Anti-MOG-associated Encephalitis with Seizures) is a recently characterised phenotype of myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), defined by cortical FLAIR hyperintensities, seizures, and mild CSF pleocytosis.
- While MOGAD is already distinguished from multiple sclerosis and aquaporin-4-positive neuromyelitis optica spectrum disorder (NMOSD), FLAMES further broadens the spectrum of its clinical and radiological manifestations (Budhram et al., 2019; Juryńczyk et al., 2019).
- Often described in children with encephalopathic symptoms, adult cases can present more subtly.

Case Presentation

- This report details the clinical course of a 25-year-old male with relapsing MOGAD, who initially presented with optic neuritis and later developed longitudinally extensive transverse myelitis (LETM). He was maintained on immunosuppressive therapy.
- Seven months after initial diagnosis, he experienced a generalised tonic-clonic seizure without prodromal symptoms. MRI brain showed T2/FLAIR hyperintensities in the left frontal cortex. The episode followed a period of non-adherence to steroid-sparing treatment (Mycophenolate motefil) and increased shift-work stress.
- Persistently positive serum anti-MOG antibodies, seizure onset, and cortical imaging findings were consistent with a FLAMES-type relapse. Management included high-dose corticosteroids, levetiracetam, and escalation to rituximab.
- The patient exhibited clinical and radiological features consistent with FLAMES. Notably, the cortical hyperintensity on imaging supported the diagnosis.
- His prior visual and sensory symptoms partially improved, and seizure did not recur following treatment escalation. Clinical stability was achieved, and he returned to normal function.

Discussion

- This case contributes to the understanding of FLAMES as a distinct MOGAD phenotype in adults, differing from the more encephalopathic paediatric presentation.
- The presence of isolated seizures, minimal systemic symptoms, and clearly localised cortical abnormalities may delay recognition. Radiological confirmation in this case strengthens the diagnosis, especially in contrast to previously reported radiologically silent episodes (Budhram et al., 2019; Juryńczyk et al., 2019).
- Sustained immunosuppression remains vital to reduce relapse risk.

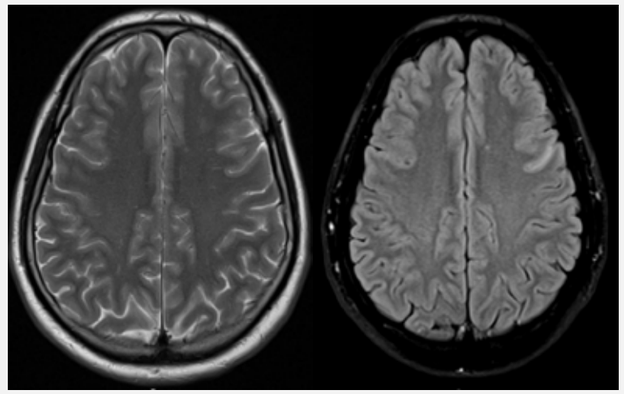


Figure 1: T2 (Left), T2 FLAIR (Right) imaging showing cortical hyperintensity

Conclusion

FLAMES should be considered in adult MOGAD patients with new-onset seizures, particularly during treatment lapses. The presence of cortical FLAIR lesions reinforces its diagnosis, even in the absence of classic encephalitic symptoms. Long-term immunotherapy and adherence are essential to prevent relapse and long-term neurological complications.

References

Budhram, A., Mirian, A., Le, C., Hosseini-Moghaddam, S.M., Sharma, M., & Nicolle, M.W. (2019). Unilateral cortical FLAIR-hyperintense lesions in anti-MOG-associated encephalitis with seizures (FLAMES): Characterization of a distinct clinico-radiographic syndrome. *Journal of Neurology*, 266(10), 2481–2487. https://doi.org/10.1007/s00415-019-09415-3

Juryńczyk, M., Jacob, A., Fujihara, K., et al. (2019). Myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease: practical considerations. *Practical Neurology*, 19(3), 187–195. https://doi.org/10.1136/practneurol-2018-002060

Ms Simona Serra

Karolinska Institutet, Sweden

Broad-spectrum antimicrobial activity of AnnexinA1 and Ac2-26 peptide: a new antimicrobial drug with neuroprotective properties

Simona Serra received her B.Sc. with honors in Biotechnology from the University of Salento (Lecce, Italy) in 2021, followed by an M.Sc. with honors in Molecular and Cellular Biology from the University of Bologna (Bologna, Italy) in 2023. Her undergraduate studies was supported by several scholarships, including an Erasmus grant from the University of Bologna and a Stifelsen Dementia Association scholarship. Simona is now a doctoral student in F. Iovino's laboratory at the Department of Neuroscience, Karolinska Institutet (Stockholm, Sweden), where she investigates 1) the molecular mechanisms of neuronal damage during the pathogenesis of meningoencephalitis, primarily caused by Streptococcus pneumoniae (pneumococcus), and 2) the antimicrobial properties of specific human peptides that can be used as new neuroprotective treatments against bacterial meningoencephalitis Her latest study, published in iScience, demonstrates how a single amino acid substitution significantly enhances the cytotoxicity of pneumolysin (the main pneumococcal toxin) towards neuronal cells (DOI: 10.1016/j.isci.2024.109583).

Broad-spectrum Antimicrobial Activity of AnnexinA1 and Ac2-26 Peptide: A New Antimicrobial Drug With Neuroprotective Properties

Simona Serra, Salem Tesfay, Marina Anastasov, Federico Iovino

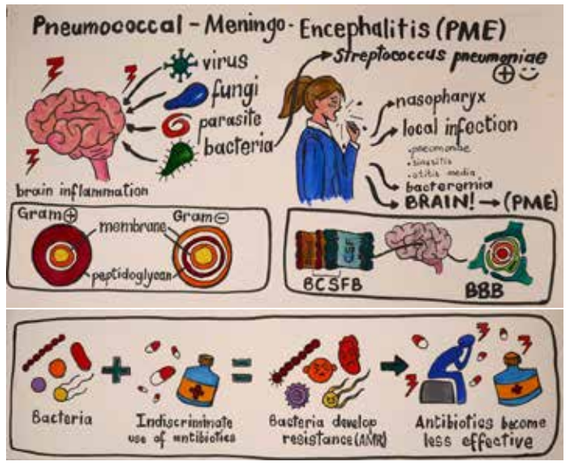
Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden

Conclusions

AnnexinA1 and its active peptide Ac2-26 show antimicrobial effect against both Gram-positive and Gram-negative bacteria. This breakthrough discovery has the potential to pave the way for a novel antibiotic therapy.

CFU count, OD measurement, Immuno-Electron Microscopy and LDH assay display a notably significant bactericidal effect of AnnexinA1 and Ac2-26 peptide on bacteria, coupled with no cytotoxicity towards neuronal cells.

Introduction



Aim of the study

AnnexinA1 and Ac2-26 peptide show a great **antimicrobial effect**, overcoming the current AMR burden. This research has the potential to introduce a **new antibiotic drug** into clinical use, thereby improving health outcomes related to infections and reducing the ease with which the bacteria can spread.

Methods

The bacteria involved in this study are:

- Gram-positive → *Streptococcus pneumoniae*
- Gram-negative→ *Escherichia coli* and *Pseudomonas aeruginosa*

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More details:

Results

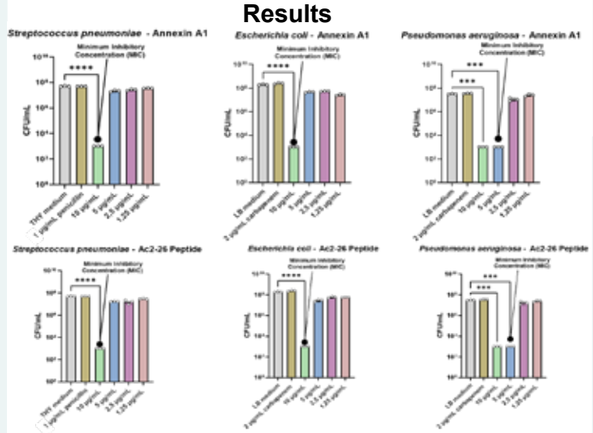

Fig 1. Determination of the **Minimum Inhibitory Concentration (MIC)** of AnnexinA1 and Ac2-26. Bacterial strains tested: penicillin resistant *Streptococcus pneumoniae* SP6, carbapenem-resistant *Escherichia coli* ST131 and carbapenem-resistant *Pseudomonas aeruginosa* P476.

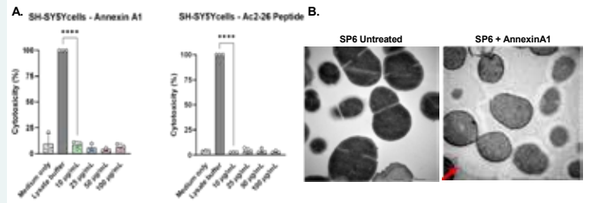

Fig.2 A) Cytotoxicity assessment of AnnexinA1 and Ac2-26 peptide on SH- SY5Y-derived human neuronal cells. **B) Cryo-electron microscopy** analysis of *Streptococcus pneumoniae* SP6: untreated and after treatment with AnnexinA1.

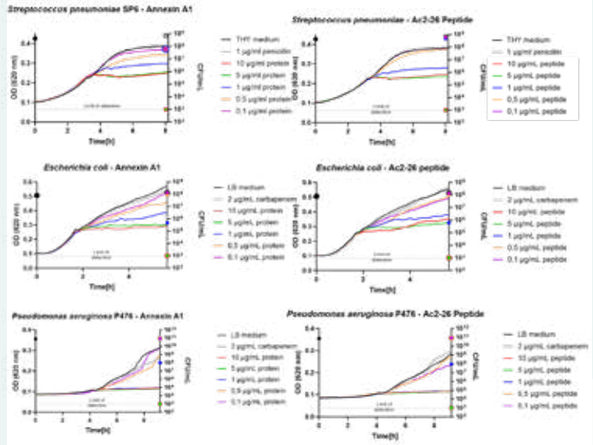

Fig 3. Assessment of bacterial growth and bacterial viability through CFU count and OD measurement. Bacteria were challenged with a titration of AnnexinA1 and Ac2-26 peptide, penicillin and carbapenem.

Ongoing work:

- STED microscopy, *in vivo* experiments, mechanism of action.

THERAKIND ÅHLÉN-STIFTELSEN Swedish Research Council CINCATE StratNeuro Karolinska Institutet

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Dr Sobia Muhammad Asad Khan

The Aga Khan University, Pakistan

Assessing the impact of Biofire® FilmArray® Meningitis/ Encephalitis Panel result on antimicrobial stewardship in hospitalized paediatric patients with suspicion of infectious meningoencephalitis

Dr Sobia Muhammad Asad Khan has completed her Bachelors of Medicine, Bachelors of Surgery (MBBS) from Ziauddin University (Karachi, Pakistan) in 2018, currently working as a post graduate trainee in the Clinical Microbiology residency program at the Aga Khan University since 2021. Throughout her residency, she has been involved in various research projects mainly focusing on infectious meningoencephalitis and vector borne diseases and has received prizes for research paper presentations by the Pakistan Association of Pathologists and Medical Microbiology and Infectious Disease Society Pakistan (MMIDSP) Conference. Moreover, she has represented her institute at multiple international forums. Her on-going research projects include: 1. Predictors of expedited hospital discharge in pediatric patients with acute meningoencephalitis admitted to a tertiary care hospital in Karachi, Pakistan 2. Arboviral encephalitis in Pakistan 2017- 2020 – Clinical and laboratory features and neurological outcomes 3. Epidemiology and clinical characteristics of Varicella Zoster Virus reactivation encephalitis among patients with acute encephalitis syndrome in southern Pakistan 4. Pyrethroid resistance in Culex species in Karachi, Pakistan among many others.

Predictors of expedited hospital discharge in pediatric patients with acute meningoencephalitis at a tertiary care hospital in Karachi, Pakistan

Sobia Muhammad Asad Khan, Syeda Rija Zehra, Sadia Shakoor, Joveria Farooqi, Muhammad Naeem, Erum Khan

Introduction

- Overall deaths due to meningitis have decreased, yet hospitalization stay and costs remain a significant concern.
- In Pakistan, the overall annual rate of hospitalization from meningoencephalitis (ME) is reported to be 5.7/100,000 population, highest among children <5 years.
- Rapid molecular tests and various predictive models have been studied to distinguish viral from bacterial meningitis, enabling early discharge of patients needing only supportive care.
- No such study has been conducted in resource-limited settings like Pakistan, where efficient resource allocation is essential.
- Thus, we evaluated predictors of early discharge (ED) in pediatric patients admitted to a tertiary care hospital with suspected infectious ME.

Methods

Retrospective cross-sectional study, conducted at a tertiary care hospital in Karachi, Pakistan.

Patients <18y with acute infectious ME defined as per Justin et al.; who underwent CSF Multiplex PCR testing (May 2017–Jan 2023) were included.

Medical records were reviewed for clinical and laboratory data. Variables associated with ED were identified by multivariate logistic regression in STATA 13.1

Results

- Of the 631 included patients, 30.1% (n=190) had an early discharge (ED).
- 20.8% (n=131) patients tested positive for any pathogen on CSF multiplex PCR panel.
- 15.4% and 5.4% (n=97 and n=34) were found to have viral and bacterial etiology respectively whereas majority i.e. 79.2% (n=500) had unspecified etiology.
- Male to female ratio was 1.3:1. Median age of the patients was 4.73± 5.2 years.
- Median length of hospital stay was 6.9 ± 5.5 days.
- Results of univariate and multivariate analysis are shown in Table 1.
- On multivariate logistic regression; presence of viral etiology was significantly associated with ED. Age <1 month, altered consciousness, positive blood culture and high CSF protein were negatively associated with it.

	Unadjusted			Adjusted		
	OR	95% CI	P-value	OR	95% CI	P-value
Age Categories						
< 1 month	0.23	(0.08,0.68)	0.007	0.29	(0.09,0.90)	*0.033
>= 1 months to < 5 Years	0.88	(0.62,1.26)	0.486	0.84	(0.57,1.23)	0.381
5 >= Years <=18	1.00			1.00		
Sex						
Female	1.00	(0.71,1.41)	0.986			
Clinical Features						
Fever	1.08	(0.70,1.66)	0.721			
Fits	1.03	(0.73,1.45)	0.874			
Altered Consciousness	0.33	(0.17,0.67)	0.002	0.36	(0.76,0.74)	*0.006
Headache	2.76	(0.17,0.67)	0.002			
EEG						
Abnormal	0.26	(0.13,0.54)	<0.001			
Blood Culture						
Pathogen Isolated	0.16	(0.05,0.53)	0.003	0.23	(0.06,0.77)	*0.017
Etiology						
Viral	2.99	(1.92,4.66)	<0.001	2.79	(1.74,4.46)	*<0.001
Bacterial	0.35	(0.12,1.00)	0.051	0.93	(0.29,2.95)	0.897
CSF Multiplex PCR Panel						
Positive	1.96	(1.31,2.92)	0.001			
Negative	1.00					
Biochemical Parameters						
CSF Glucose (mg/dl)	1.00	(0.99,1.00)	0.184			
CSF Protein (g/dl)	0.99	(0.98,0.99)	<0.001	0.99	(0.98,0.99)	*<0.001
CSF Total Leucocyte Count	1.00	(1.00,1.00)	0.091			
CRP (mg/L)	1.00	(0.99,1.00)	0.345			

Table 1 Predictors of early/expedited discharge in hospitalized pediatric patients (N=631) with acute infectious ME.

Discussion

Hospitalization due to acute infectious ME in children is a significant concern. Previous studies link poor outcomes to comorbidities, high CSF leukocytes, impaired consciousness, and positive blood culture, while viral etiology correlates with better outcomes. Our findings align, showing shorter hospital stays with viral causes. Limitations of the study include: (i) Long-term neurological sequelae were not assessed (ii) Time to antimicrobial therapy and adjunct treatments like steroids was not examined, which may have an impact on primary outcome.

Conclusion

Viral etiology is a significant cause of pediatric meningoencephalitis and timely detection in older children facilitates early discharge, yielding substantial economic and public health benefits. Majority i.e., 80% (n=77) of the cases with viral etiology were attributed to enterovirus in this study. Thus, in resource limited settings, age- specific diagnostic protocols may be formulated with incorporation of targeted enterovirus PCR.

References

1. Choi JJ, Westblade LF, Gottesdiener LS, Liang K, Li HA, Wehmeyer GT, et al. Impact of a Multiplex Polymerase Chain Reaction Panel on Duration of Empiric Antibiotic Therapy in Suspected Bacterial Meningitis. Open Forum Infect Dis. 2021;8(10):ofab467
2. Hueth KD, Thompson-Leduc P, Totev TI, Milbers K, Timbrook TT, Kirson N, et al. Assessment of the Impact of a Meningitis/Encephalitis Panel on Hospital Length of Stay: A Systematic Review and Meta-Analysis. Antibiotics (Basel). 2022;11(8)
3. McDonald D, Gagliardo C, Chiu S, Di Pentima MC. Impact of a Rapid Diagnostic Meningitis/Encephalitis Panel on Antimicrobial Use and Clinical Outcomes in Children. Antibiotics (Basel). 2020;9(11).
4. Hasbun R, Wootton SH, Rosenthal N, Balada-Llasat JM, Chung J, Duff S, et al. Epidemiology of Meningitis and Encephalitis in Infants and Children in the United States, 2011-2014. Pediatr Infect Dis J. 2019;38(1):37-41.

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Predictors of expedited hospital discharge in pediatric patients with acute meningoencephalitis admitted to a tertiary care hospital in Karachi, Pakistan

Dr Sobia Muhammad Asad Khan has completed her Bachelors of Medicine, Bachelors of Surgery (MBBS) from Ziauddin University (Karachi, Pakistan) in 2018, currently working as a post graduate trainee in the Clinical Microbiology residency program at the Aga Khan University since 2021. Throughout her residency, she has been involved in various research projects mainly focusing on infectious meningoencephalitis and vector borne diseases and has received prizes for research paper presentations by the Pakistan Association of Pathologists and Medical Microbiology and Infectious Disease Society Pakistan (MMIDSP) Conference. Moreover, she has represented her institute at multiple international forums. Her on-going research projects include: 1. Predictors of expedited hospital discharge in pediatric patients with acute meningoencephalitis admitted to a tertiary care hospital in Karachi, Pakistan 2. Arboviral encephalitis in Pakistan 2017- 2020 – Clinical and laboratory features and neurological outcomes 3. Epidemiology and clinical characteristics of Varicella Zoster Virus reactivation encephalitis among patients with acute encephalitis syndrome in southern Pakistan 4. Pyrethroid resistance in Culex species in Karachi, Pakistan among many others.

Assessing the impact of Biofire® FilmArray® Meningitis/Encephalitis Panel result on antimicrobial stewardship in hospitalized paediatric patients with suspicion of infectious meningoencephalitis

Sobia Muhammad Asad Khan, Syeda Rija Zehra, Joveria Farooqi, Farah Mansuri, Ayesha Sadiqa, Farah Naz, Nasheet Sagri, Erum Khan, Sadia Shakoor

INTRODUCTION

Rapid diagnosis is crucial for timely administration of targeted therapy and improved clinical outcomes in patients with acute infectious meningo-encephalitis (ME). Although most cases are attributed to viral etiology, broad spectrum antimicrobials are used indiscriminately owing to severity of the disease, specially in paediatric patients. In Pakistan, multiplex PCR panels are implemented at limited centres and its utility as antimicrobial stewardship tool has not been evaluated.

OBJECTIVES

- The primary objective was de-escalation of antimicrobial therapy within 48 hours in children with suspected meningoencephalitis, who tested negative for treatable pathogens by CSF multiplex PCR panel (MEP).
- Secondary objectives were total duration of antibiotic therapy during hospitalization (in days), hospital length of stay (LOS), and in-hospital mortality.

MATERIALS AND METHODS

We performed retrospective analysis of paediatric patients (≤18 years) admitted to a tertiary care hospital with suspicion of infectious ME (defined as per Justin et al.); who underwent CSF MEP testing between May 2017- Jan 2023.

Appropriate antimicrobial therapy was defined as tailoring or discontinuing the empiric antimicrobial regimen based on the identification of a specific pathogen or the absence of a detectable viral or bacterial etiology, respectively.

Electronic records were screened for demographic data, etiology, clinical features, comorbid conditions, laboratory and CSF findings, imaging, EEG, concomitant infections, outcomes (LOS, mortality), and antimicrobial use before and after CSF MEP test.

Descriptive statistics of all measured variables and parameters were tabulated. The Chi-squared test was applied. All tests were two-tailed, and a *P*-value ≤ 0.05 was considered statistically significant. Data were analyzed using SPSS Software (version 28).

RESULTS

- Of the 640 admitted patients ≤18y with acute infectious ME who underwent CSF MEP testing, 21.5% (N=138) had a positive result.
- Male: female ratio was 1.3:1.
- Most of the patients i.e. 39.2% were between 3 months- 3 years of age.
- Overall, 73.5% (N=471/640) patients had an appropriate change of antimicrobial therapy.
- The rate was significantly higher among patients with positive MEP as compared to those with negative MEP results i.e. 83.3% vs 70.7% respectively [OR=2.18 (95% CI=1.27, 3.37 p=0.003).
- The mean duration of antimicrobial treatment was 5.6±4.4 days and we found no statistically significant difference between the two groups [(95% CI 5.2, 5.9); p=0.405].

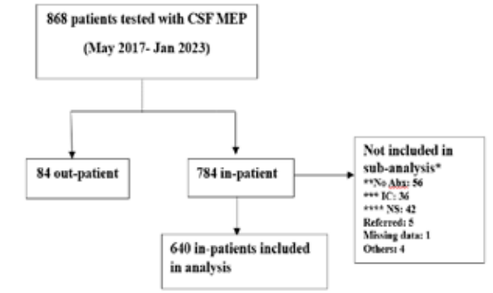

Figure 1: Flow diagram of pediatric patients with acute ME with CSF sent for MEP between May 2017 to Jan 2023.
** Abx: antibiotics (patients who did not receive empirical antibiotics at all, or received after sending MEP or antibiotics stopped before MEP was reported)
*** IC: immunocompromised
**** NS: patients with neurosurgical interventions

Discussion

- We report the impact of a positive MEP result on change in antimicrobial therapy practice in paediatric population studied over an extensive period of 5 years through vigorous data review of patients admitted to a tertiary care centre in southern Pakistan.
- Several studies conducted in Western countries have established that molecular testing panels can decrease unnecessary antibiotic therapy, length of hospitalization, and hospital costs.
- In Pakistan, inappropriate antibiotic use remains widespread due to limited awareness, highlighting the need to assess the impact of costly rapid diagnostics on antimicrobial stewardship.
- Although total antimicrobial duration was not significantly different, appropriate therapy modifications were more frequent in MEP-positive patients, likely reflecting strong clinical microbiology support at the study site.

Conclusion

The likelihood of change to appropriate antimicrobial therapy was doubled in patients with a positive CSF MEP finding. Thus, underscoring the value of incorporating syndromic panels into routine diagnostic workup to promote targeted antimicrobial use and support stewardship efforts in acute pediatric meningoencephalitis.

References

1. Justin J Choi, Lars F Westblade, Lee S Gottesdiener, Kyle Liang, Han A Li, Graham T Wehmeyer, Marshall J Glesby, Matthew S Simon, Impact of a Multiplex Polymerase Chain Reaction Panel on Duration of Empiric Antibiotic Therapy in Suspected Bacterial Meningitis, *Open Forum Infectious Diseases*, Volume 8, Issue 10, October 2021.
2. Aronson PL, Lyons TW, Cruz AT, et al. Impact of Enteroviral Polymerase Chain Reaction Testing on Length of Stay for Infants 60 Days Old or Younger. *J Pediatr*. 2017;189:169-174.e2. doi:10.1016/j.jpeds.2017.06.021.
3. Markovich K, Wingler MJB, Stover KR, Barber KE, Wagner JL, Cretella DA. Analysis of the Clinical Impact of the BioFire FilmArray Meningitis Encephalitis Panel on Antimicrobial Use and Duration of Therapy at an Academic Medical Center. *Diseases*. 2022;10(4):110. Published 2022 Nov 20. doi:10.3390/diseases10040110.

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Ms Sophia Rekers

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Spatial Navigation Impairments in Post-Acute Autoimmune Encephalitis

Sophia Rekers is a researcher in cognitive neuroscience and neuropsychology with a focus on the mechanisms and clinical relevance of human spatial navigation. She holds an M.Sc. in Clinical and Health Psychology from Freie Universität Berlin. She is currently based at the Cognitive Neurology Lab at Charité - Universitätsmedizin Berlin and is pursuing her PhD through the Berlin School of Mind and Brain. Her work aims to advance the understanding of spatial navigation beyond episodic memory by clarifying how distinct navigational processes are affected across neurological disorders, with a specialization in neurological autoimmune diseases. She is also committed to integrating the perspectives of people with lived experience to identify real world needs and co-design assistance and rehabilitation tools for spatial navigation and memory. She develops, validates, and creates normative data for open-access, virtual reality-assisted paradigms that capture naturalistic navigation behavior. Combined with structural neuroimaging and patient-reported outcomes, she uses these assessments to better understand human spatial navigation, characterize disease mechanisms, and quantify meaningful impairments. Her broader goal is to embed psychometrically sound and ecologically valid assessments into research and clinical practice by developing accessible, interpretable, and scalable methods that offer robust translational insight into cognitive impairments and the everyday challenges they create.

Spatial Navigation Impairments in Post-Acute Autoimmune Encephalitis — Distinct from Memory Impairments?

Sophia Rekers, Antoine Coutrot, Guido Cammà, Katharina Wurdack, Maron Mantwill, Harald Prüss, Michael Hornberger, Hugo Spiers, Carsten Finke

BACKGROUND – AIE & NAVIGATION vs. MEMORY

NMDAR and LGI1 encephalitis are associated with long-term cognitive impairments & structural damage of key brain regions for **memory** and **spatial navigation** (e.g. hippocampus, cingulum, temporal, and parietal regions).

Reduced episodic **memory** performance is well documented in both AIE variants.

However, **spatial navigation** abilities are rarely assessed, despite reports of spatial orientation problems in about 50% of patients, largely due to the lack of ecologically valid normed tools.

Do post-acute NMDAR and LGI1 encephalitis patients exhibit navigation impairments?

Are these impairments dissociable from episodic memory dysfunction?

Are navigation impairments associated with distinct structural brain alterations?

PARTICIPANTS

	NMDAR Encephalitis	LGI1 Encephalitis
n (patients)	46	28
Mean age (range)	34.2 y (19–71)	62.9 y (33–84)
Sex	91 % female	64 % male
Median time since symptom onset	6.4 y (0.3–18.9)	2.8 y (0.3–10.9)
Median residual disability (CASE)	0 [0–6]	2 [0–6]

Controls: age- and sex-matched healthy participants

NAVIGATION ASSESSMENT & EVALUATION

VIENNA Young: Virtual Environments Navigation Assessment for young and middle-aged adults [1]

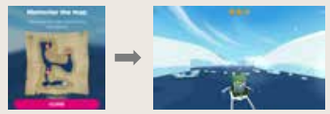
Passive, map-assisted navigation test, 12 increasingly complex virtual hallway environments

spatial information continuously visible: emphasizes spatial–executive processing > episodic memory

regression-based norm data from n = 422, open access

Sea Hero Quest [2]:

Active wayfinding task, requiring navigation of a boat through virtual water environments



requires memorization & recall: initially presented map no longer visible while navigating

average norm samples: NMDARE = 1756, LGI1E = 1051

Verbal episodic memory: Rey Auditory Verbal Learning Test-RAVLT (learning, delayed recall, recognition)

Normative reference: Percentiles (PR) derived from age- and sex-adjusted normative data

performance categories: below average: PR < 9, low average: PR = 9–24, normal: PR > 24

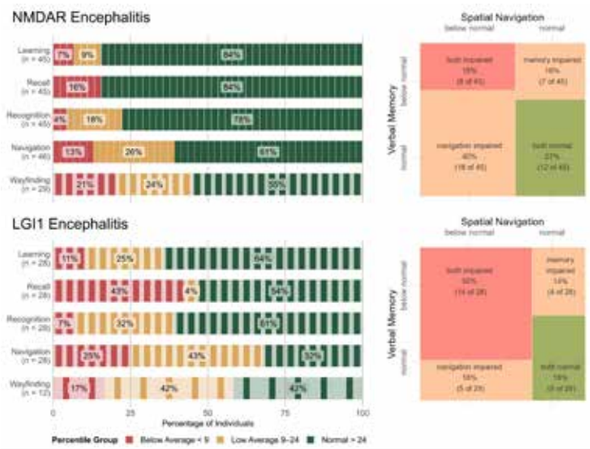
domain-level classification: “below normal” if any test in a domain was PR ≤ 24,

“within normal expectations” only if all tests were PR > 24

RESULTS

Memory and spatial navigation impairments

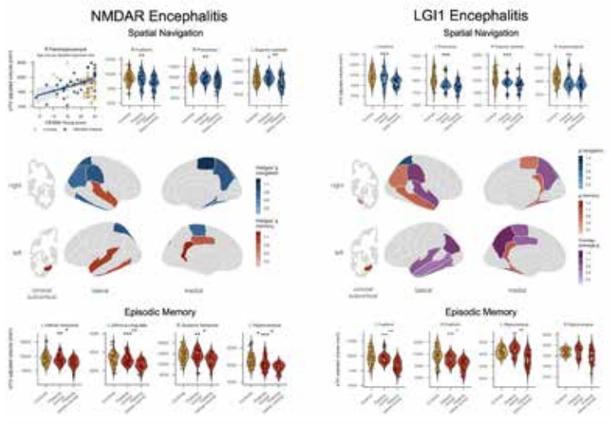
Significantly more navigation than memory impairment in NMDARE but not LGI1E



MRI findings

Hippocampal atrophy associated with memory, but not navigation impairments

Spatial navigation impairment in both variants associated with volume reductions in: precuneus, fusiform, superior parietal, supramarginal, paracentral



DISCUSSION

Both passive-executive and active-memory-focused navigation tests uncovered spatial-navigation impairments in **58% of NMDARE patients** (> than memory), and **68% LGI1E patients**. This is consistent with patient reports and highlights a gap in current diagnostic and rehabilitation practice.

MRI findings highlight a selective vulnerability of the posterior-medial and parietal navigation network beyond classical memory structures.

NMDARE showed **navigation**-impairment-specific volume reductions **distinct from memory**-impairments-specific and included right **parietal cortex and parahippocampal place area**, regions strongly connected to frontal navigation hubs.

LGI1E showed **widespread**, bilateral volume loss with **strongly overlapping navigation- and memory**-related effects, consistent with more global network disruption. Yet, domain specificity persisted, with **hippocampal** volume loss linked to **memory** and **superior parietal** volume loss to **navigation** impairment.

CONCLUSION

Spatial navigation is as impaired as, or more impaired than, memory in NMDAR and LGI1 encephalitis and shows distinct neuropathological correlates.

Ecologically valid, normed tools like VIENNA Young and Sea Hero Quest provide biologically grounded measures to advance monitoring of cognitive profiles and associated needs of patients with autoimmune encephalitis.

OUTLOOK

Ongoing work investigates whether navigation impairments are linked to altered microstructural integrity using diffusion tensor imaging (DTI).

[1] Rekers S, Meyer TC, Finke C. Psychometric data and regression-based norms for the virtual environments navigation assessment for young and middle-aged adults (VIENNA Young). *Computers in Human Behavior Reports*. 2025;19:100730. doi:10.1016/j.chbr.2025.100730

[2] Coutrot A, Silva R, Manley E, et al. Global Determinants of Navigation Ability. *Current Biology*. 2018;28(17):2861-2866.e4. doi:10.1016/j.cub.2018.06.009

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VIENNA Young

ENCEPHALITIS CONFERENCE 2025

Associate Professor Stéphane Kouadio Koffi

Université Félix Houphouët-Boigny, Côte d'Ivoire.

Place of herpesviridae (CMV, VZV, EBV, HHV6, HSV 1/2) in the viral etiology of encephalitis in Côte d'Ivoire

Dr Stéphane Koffi is an Ivorian medical microbiologist and Associate Professor of Bacteriology and Virology at the Félix HOUPHOUËT-BOIGNY University of Abidjan. His research focuses on antimicrobial resistance, and emerging zoonotic infections using a One Health approach.

For more than 10 years, he has led multidisciplinary research in Côte d'Ivoire and has established collaborations with national institutions responsible for biomedical research, epidemiological surveillance, and microbiological monitoring. He has authored more than 40 peer-reviewed scientific publications and contributes to national efforts to translate research findings into public health and policy-relevant outcomes.

His current work addresses neglected infectious diseases such as leptospirosis and viral encephalitis, by characterising pathogens and transmission dynamics.

Dr Koffi is actively engaged in strengthening Côte d'Ivoire's scientific and research capacity and has supervised numerous Master's and PhD candidates in both medical and biological sciences.

PLACE OF THE *HERPESVIRIDAE* (HSV 1&2, VZV, EBV, CMV, HHV6,) IN THE VIRAL ETIOLOGY OF ENCEPHALITIS IN CÔTE D'IVOIRE

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INTRODUCTION

Encephalitis is a serious neurological syndrome characterized by inflammation of the brain parenchyma, which can lead to serious neurological complications and even death. Viruses of the *Herpesviridae* family, namely *Herpes Simplex* Virus 1 and 2 (HSV), *Varicella-Zoster* Virus (VZV), *Epstein-Barr* virus (EBV), *Cytomegalovirus* (CMV), and human herpesvirus 6 (HHV6) are major pathogens responsible for viral encephalitis, particularly in immunocompromised individuals. In West Africa, and particularly in Côte d'Ivoire, the involvement of these viruses in encephalitis remains under-documented, despite a high prevalence of HIV-related immunodeficiency in this region.

Keyword: Viral Encephalitis, *Herpesviridae*, HIV Infection, Côte d'Ivoire, PCR

Study objective:
This study aims to evaluate the prevalence of different Herpesviruses in cases of encephalitis in Côte d'Ivoire and to determine their association with HIV infection.

MATERIALS AND METHODS

Study type and setting

Cross-sectional and multicenter study

Conducted in multiple university hospitals in Côte d'Ivoire

Map legend

In construction

Operational

Study population

Inclusion criteria:

✓ Patients aged 15 years and older

✓ Presenting with clinical signs of encephalitis

✓ Informed consent obtained

Exclusion criteria:

✓ Patients with contraindications for lumbar puncture

Biological sample

✓ Lumbar puncture for CSF collection

Laboratory analyses

Identification Of Herpesviruses

1 Hospitalized patient — 2 Lumbar puncture (CSF) — 3 DNA extraction

4 Amplification — 5 Result

Statistical analysis

Descriptive analyses for qualitative and quantitative variables

Correlation tests for HIV-*Herpesviridae* association

Statistical significance set at $p < 0.05$

RESULTS AND DISCUSSION

RESULTS

Population characteristics

Total participants: **388 patients**

222 females (57.22%)

166 males (42.78%)

Sex ratio : 0.75

Age distribution

Minimum age: **15 years**

Maximum age: **79 years**

Average age: **45.36 years**

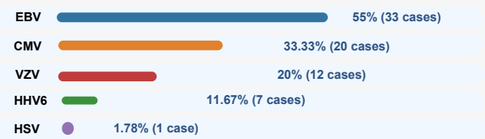
***Herpesviridae* Positivity**

15.46% (60/388)

HIV Co-infection

72.68% (282/388)

Prevalence by virus (n=60 positive cases)



HIV-Herpesviridae statistical association

72.68% of patients with *Herpesviridae* are HIV+

91.67% of PCR+ patients are HIV seropositive

OR = 3.9 (95%CI: 1.4–9.3)

p < 0.0015 (significant)

DISCUSSION

Prevalence of Herpesviridae

Our study (EBV)	55%
Zhang et al. (2025)[1]	23.6%
Neuberg et al. (2024)[2]	28%

The prevalence of EBV observed in our study (55%) is significantly higher than that reported by Zhang et al. (23.6%)[1] and Neuberg et al. (28%)[2]. This difference may be explained by the high proportion of immunocompromised patients in our Ivorian cohort.

The low prevalence of HSV (1.78%) contrasts with Western data where HSV-1 represents 50-75% of identified viral encephalitis cases[3]. This regional disparity highlights the importance of local epidemiological studies to guide therapeutic strategies

CONCLUSION

Main conclusions

(15.46%) in the etiology of encephalitis in Côte d'Ivoire, with a clear predominance of EBV (55%) and CMV (33.33%).

The significant association with HIV infection (OR = 3.9 (95%CI: 1.4–9.3)) underlines the importance of systematic screening for Herpesviridae in immunocompromised patients presenting with neurological symptoms.

The distribution of viruses differs from Western data, especially for HSV, demonstrating the importance of local epidemiological studies in sub-Saharan Africa.

REFERENCES

[1] Zhang L, Chen X, Li W, et al. Clinical features and risk factors for Epstein-Barr virus-associated encephalitis: a retrospective study. Virology Journal. 2025;22(5):128-136.

[2] Neuberg R, Pastorino B, Piorkowski G, et al. Viral etiologies of encephalitis in immunocompromised patients: a multi-center study. Journal of Clinical Virology. 2024;158:104-112.

[3] Smith JB, Thompson KM, Martins P, et al. Herpesviridae in the changing landscape of viral encephalitis diagnosis and management. The Lancet Infectious Diseases. 2023;23(8):954-965.

ACKNOWLEDGEMENTS

Encephalitis International — The brain inflammation non-profit

ENCEPHALITIS CONFERENCE 2025

Dr Sukhvir Wright

Aston University, UK, & Birmingham Women's and Children's Hospital NHS Foundation Trust, UK

MRI cortical thickness in paediatric auto-immune encephalitis

Dr Sukhvir Wright is a consultant paediatric neurologist and Wellcome Clinical Research Career Development Fellow. Dr Wright's primary research and clinical interests are in neuro-immunological diseases of childhood, including autoimmune encephalitis and immune-mediated epilepsy. In the laboratory, Dr Wright uses electrophysiological techniques to investigate the pathophysiological and epileptogenic actions of human-derived neuronal autoantibodies in laboratory models, and the effects of novel treatments. She also uses novel non-invasive imaging techniques (e.g. OPM-MEG) for assessing long-term outcomes in children with neuro-immunological disorders.

MRI cortical thickness in paediatric auto-immune encephalitis

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Charly Billaud was funded by a Silver Jubilee PhD studentship from Encephalitis International

Background: Autoimmune encephalitis (AE) is an inflammatory brain disease marked by seizures, movement disorders, psychiatric symptoms, and cognitive deficits. It arises from various autoimmune mechanisms, including antibody-mediated neural inflammation and demyelination. While MRI abnormalities such as T2/FLAIR hyperintensities and regional atrophy are common in some AE cases like acute disseminated encephalomyelitis (ADEM), antibody-positive subtypes (e.g., NMDAR, DPPX, GlyR) often show normal scans during the acute phase. Recent analyses suggest brain volume reductions occur months to years after disease onset. The measurement of cortical thickness, which has received relatively little attention in research on AE, serves as another relevant indicator of brain atrophy. Here, we tested the hypothesis that whole brain cortical thickness of children with AE is different compared to age-matched healthy children.

Methods: This study used secondary data from children with autoimmune encephalitis and healthy controls. Participants were recruited from Birmingham Children's Hospital and the local community between 2018–2023. Informed consent was obtained for all participants. MRI scans were acquired at Aston University and Birmingham Children's Hospital, with clinical status assessed using the modified Rankin Scale. Structural MRI scans were preprocessed using FreeSurfer v6.0, including skull stripping, tissue segmentation, and cortical surface reconstruction. Cortical thickness was calculated as the average distance between white and pial surfaces. Manual edits and Qoala-T quality checks ensured scan reliability. Whole-brain cortical thickness was analysed using general linear models, controlling for age, sex, and contrast-to-noise ratio (CNR). Regional analysis focused on bilateral orbitofrontal and temporal poles using MANCOVA. Assumptions for statistical validity were tested, and sample sizes were determined based on power analyses to detect moderate-to-large effect sizes.

Results

MRI scans of 60 children were acquired. Demographic information is presented in **Table 1**. The AE group comprised 1 anti-NMDAR, 1 antibody negative AE, and 10 ADEM cases. Three children had relapsing disease (>1 clinical attack) all of which presented with MOG-positive ADEM. Comorbid neurodevelopmental diagnoses, only made after the initial AE/ADEM insult, were present in three participants from the AE group: one had diagnoses of autism spectrum disorder (ASD), attention deficit hyper-activity disorder, dyspraxia and focal epilepsy; one had a diagnosis of epilepsy, and one had a diagnosis of ASD. All patients were treated with 1st line therapy (e.g. steroids / IVIG), within 4 weeks of presentation – other than one patient with MOG positive ADEM who improved before treatment could be given. Four patients also received 2nd line therapy, specifically those with relapsing disease, and the case of NMDAR AE.

Child characteristics	Controls (N=48)	AE (N=12)	Statistics	
			Test	*p* value
Sex (female:male)	23:25	8:4	χ^2 = 1.352	.245
Age in years (mean±sd) at scan IQR	10.5 ± 2.5 3.8	10.7 ± 3.5 7.3	*t* = -0.128	.899
Age of onset IQR	NA	3.91 ± 2.2 3.5	NA	NA
mRS at scan IQR	NA	0.92 ± 0.9 1	NA	NA

Table 1. Demographic and clinical characteristic of children with autoimmune encephalitis and typically developing children*; AE = Autoimmune Encephalitis. mRS = modified Rankin Scale.*

The whole-brain general linear model analyses revealed a single significant cluster in the posterior left hemisphere, showing differences in cortical thickness while accounting for age, sex, and CNR, which can be seen in the cluster depicted in Figure 1. The cortical thickness of the cluster was lower in the AE group (peak tailarach coordinates (X,Y,Z) = −17.9, −80.2, 39.4; cluster size = 681.55 mm^2; N vertices= 1182; corrected cluster-wise *p* = 0.00459; cluster-wise Cohen's *d*= -8.3773).

Accounting for the Destrieux atlas parcellation, the cluster covered the top part of the superior occipital gyrus, the bottom part of the superior parietal lobule as well as a small part of the intraparietal, transverse parietal and parietooccipital sulci (Figure 1), all in the left hemisphere.

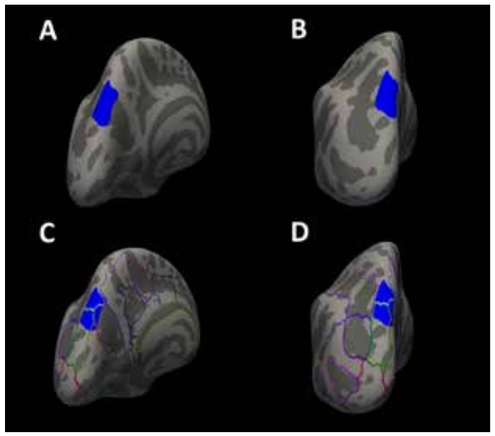

Figure 1. Comparison of cortical thickness between children with autoimmune encephalitis and typically developing children. A & B) Cluster showing lower cortical thickness in the AE group, from different angles; C & D) Same cluster superposed over the Destrieux Atlas parcellation. The cluster covers the superior occipital gyrus (bottom of the cluster); the superior parietal lobule (top); a slight part of the intraparietal sulcus and transverse parietal sulcus (left); and the parietooccipital sulcus (right).

No multivariate effect on the cortical thickness of the regions-of-interest was found (Roy's Largest Root = .095, F(df) = 1.207(4); p = .319; partial η2 = .087). A small univariate effect was observed, with autoimmune encephalitis predicting lower left orbitofrontal thickness (F = 4.407, p = .040, Partial η2 = .075).

This suggests the encephalitis group may have a lower average cortical thickness in the left orbitofrontal cortex compared to controls, independently of age and sex. Age also had a negative effect on the right orbitofrontal thickness.

Discussion: Children with AE may have long-term alterations in their brain's cortical thickness, which has received limited attention to date. This study supports the clinical relevance of advanced neuroimaging analyses for paediatric AE, by revealing findings that are not visible nor detectable in conventional MRI assessments. The present cohort had a relatively thinner grey matter thickness in left posterior and orbitofrontal areas compared to their typically developing peers. Thickness in such areas has been linked to emotional difficulties and general intellectual functioning. This highlights a need for further investigations regarding the link between thinning with the long-term emotional difficulties observed in AE. We will now concentrate on longitudinal imaging focused on cortical thickness to see how these structures evolve across the development of children with AE. This will better identify those most at risk of poorer long-term outcomes once the acute medical episode has resolved.

References: 1. Cellucci T, Van Mater H, Graus F, et al. Clinical approach to the diagnosis of autoimmune encephalitis in the pediatric patient. Neurology-Neuroimmunology Neuroinflammation. 2020;7(2) 2. Nillo RM, Broce IJ, Uzgil B, et al. Longitudinal analysis of regional brainchanges in anti-NMDAR encephalitis: a case report. BMC Neurol. 2021;21:1-6.

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Immunocompromised but survivable: miild to critical care cases of meningoencephalitis.

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Immunocompromised but survivable: Mild to critical care cases of meningoencephalitis.

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Background: In immunocompromised patients it can be difficult to appreciate the impact of CNS infection and role of treatment on patient outcomes in ICU, especially when presentations are atypical or fall out the diagnostic range.[1] The aim of this case series is to describe the clinical course, treatment considerations and outcomes of meningoencephalitis in this population.[1]

Methodology: We performed a retrospective evaluation of all immunocompromised patients above the age of 18 who had positive CSF finding (detection of pathogen by microscopy, culture or Ag testing), presenting to King's College Hospital, London, from January 2023 to May 2025, using electronic patient record (EPIC). Immunosuppression was defined as pharmacological immunosuppression (Immunomodulatory therapy, steroids, chemotherapy), haematological malignancy, and HIV. Their semiology of presentation, comorbidities, degree of immunosuppression, level of organ support needed, length of stay and outcomes (survival, modified Rankin Score at ICU discharge and hospital discharge) were evaluated.

Results: 141 positive CSF samples which belonged to 97 patients were identified, and each patient's notes were reviewed for immunocompromised status. Age <18y, contaminant and nosocomial CSF infection were excluded. 5 patients were recognized who fulfilled the criteria.

Pt	Immunosuppression	CSF Culture/Ag testing	Definitive antimicrobial treatment	modified Rankin Score at discharge
1	HIV (CD4 count 14 cells/mm^3)	Cryptococcus neoformans	Amphotericin B, Flucytosine, Fluconazole	1
2	HIV (CD4 count 19 cells/mm^3)	Cryptococcus neoformans	Amphotericin B, Flucytosine, Fluconazole	4
3	HIV+ pregnancy (CD4 count 556 cells/mm^3) Recurrent cryptococcus meningitis	CrAg positive, No growth	High dose fluconazole	0
4	HIV (CD4 count 406 cells/mm^3)	Streptococcus Pneumoniae	Ceftriaxone, Dexamethasone	2
5	KT (MMF, Tacrolimus, Prednisolone)	Cryptococcus neoformans	Amphotericin B, Flucytosine, Fluconazole	0

Headache was a consistent feature in all patients. Other features of presentation included focal neurology, seizures, and neurological obtundation. Two patients required admission to ICU with varying need for organ support. Discharge destination ranged from home to neurorehabilitation.

Conclusion: This case series underscores the varied presentation and severity of meningoencephalitis in immunocompromised patients. It highlights the need for a low threshold of suspicion and broad differential diagnoses, particularly for opportunistic infections. Clinical complexity and prognosis were influenced by the degree of immunosuppression. With timely recognition and appropriate critical care, patients were discharged, suggesting meningoencephalitis should not always be viewed as a poor prognostic indicator, even with multi-organ involvement. In our study, viral PCR was not assessed. Further studies are needed to better characterise this condition in ICU patients and inform treatment decisions.

Reference:

1. Karen C. Bloch, Carol Glaser, David Gaston, Arun Venkatesan, State of Art: Acute Encephalitis, Clinical Infectious Disease, 2023;77(5):e14-33
2. Sonneville R, et al. Clinical features, etiologies, and outcomes in adult patients with meningoencephalitis requiring intensive care (EURECA): an international prospective multicenter cohort study. Intensive Care Med. 2023;49(5):517-529. doi:10.1007/ s00134-023-07032-9

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