THE NEWSLETTER FOR PROFESSIONALS INTERESTED IN **ENCEPHALITIS**

CONNECT PROFESSIONAL

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ENCEPHALITIS SOCIETY
The brain inflammation charity

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IN THIS ISSUE:

Welcome

WELCOME to the eighth edition of Connect Professional, our newsletter dedicated to health professionals interested in encephalitis.

Our newsletter is designed to showcase the work that is going on in the field of encephalitis by our colleagues around the world.

We also cover important research and activities that people in academia and medicine might find interesting.

In this edition, our main focus is Encephalitis 2021 – our annual conference – which takes place on the 7th December (see pages 7 to 10).

With COVID-19 restrictions lifted in the UK, we are hoping that a great number of you will be joining us at the Royal College of Physicians for a bumper day of talks from world-leading encephalitis experts.

For those of you who are unable to join us in-person - fear not! This year's conference can also be accessed virtually and will be recorded, so you can watch the talks from the comfort of your own home and at leisure.

We also have two free events at which we would love you to join us – in-person or virtually - on Tuesday, 6th December (see page 10).

The first of these, our Research Exchange Meeting, is an opportunity to listen to selected Conference poster authors to discuss their work.

Secondly, Dr Benedict Michael and Assist Prof Omar Siddiqi, both members of our Scientific Advisory Panel, will be offering advice on how to apply for funding and develop Fellowship and grant application writing skills. This is a great opportunity to pick the brains of two very accomplished researchers and clinicians and take a leap in your own career.

As always, this is your newsletter and we very much welcome your input – whether it be articles, research, news or events. If you would like to submit something, please email comms@encephalitis.info

See you at the Conference!

Dr Ava Easton
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Encephalitis Society
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Pictured overleaf: Scientific Advisory Panel members Dr Nicholas Davies, Professor Tom Solomon, and Professor Sarosh Irani at the Encephalitis Conference

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Calls for increase in funding during Research Month...

The need for more funding into research for neurological complications, including encephalitis, was the message behind an Encephalitis Society campaign in June.

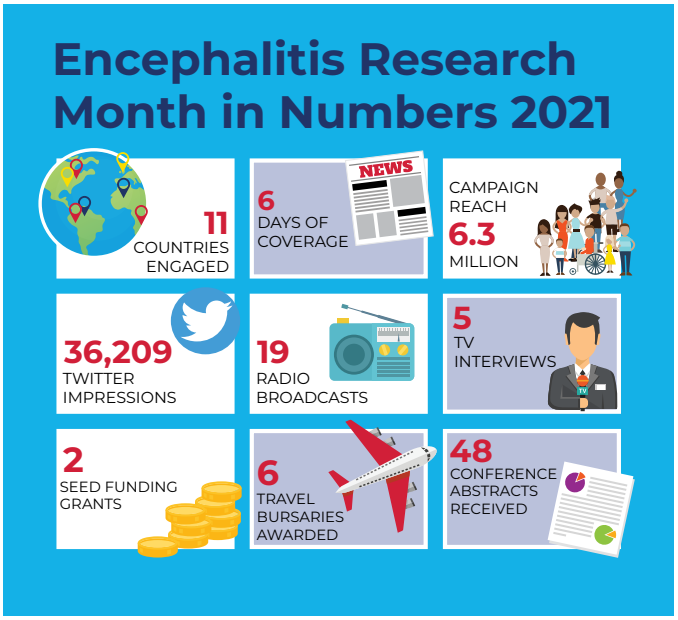
Encephalitis Research Month saw us take to the UK airwaves to highlight the drastic cuts to government funding and falling donations to medical research charities as a result of the COVID-19 pandemic.

We also invited researchers from low-to-middle income countries to apply for up to £10,000 in seed funding and awarded bursaries to six health professionals from Iran, Cameroon, Brazil, Malawi, and the Phillippines who wanted to join us at Encephalitis 2021 – our annual conference (See Pages 6-9).

Dr Ava Easton, our Chief Executive, said: "While life has been slowly returning to how it was before the COVID-19 pandemic, we have had growing concerns that research into neurological conditions such as encephalitis is getting left behind. During Encephalitis Research Month, we felt it was important to stress that more funding is needed and support of medical charities."

Since the pandemic, the country's main science funder, UK Research and Innovation (UKRI) has seen its budgets nearly halved from 245m to 125m. Such deep cuts to government research spending and our exit from Europe means the UK's position as a global science leader is under threat. Income to medical research charities, such as the Encephalitis Society which collaborates with researchers, has also taken a hit because of COVID-19.

During Encephalitis Research Month, Ava and supporters of the Encephalitis Society, spoke to UK radio and television stations to share their personal experiences of encephalitis and how research can improve outcomes and diagnosis.



"It was a successful campaign, but one that needs to continue for months, or even years, so we can ensure that research into neurological conditions does not get left behind," added Ava.

...as World Health Organization agrees to discuss new analysis

The end of Encephalitis Research Month brought welcome news about a potential partnership with the World Health Organization (WHO).

The Encephalitis Society is to begin discussions with the WHO about a new report which looks at encephalitis around the world.

The 160 page analysis - **Encephalitis: an in-depth review and gap analysis of key variables affecting global disease burden** - identifies global issues surrounding encephalitis and proposes a range of solutions, ranging from epidemiology, incidence, and economic impacts through to prevention, diagnosis and treatment, and the needs of patients and families.

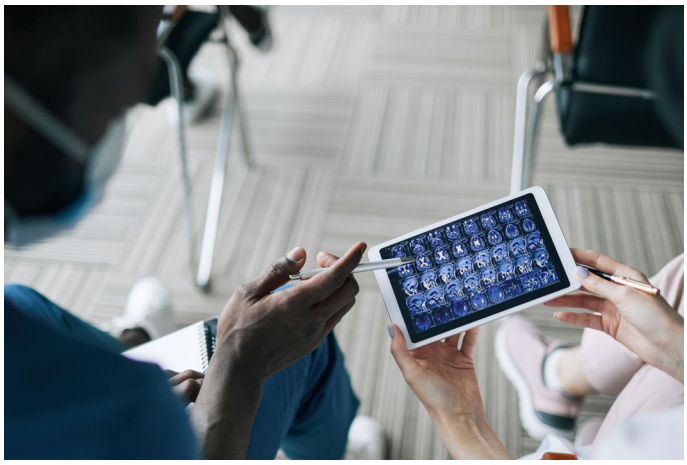
The report has been authored by Dr Julia Granerod, Alina Ellerington, our Information Manager, and members of our Scientific Advisory Panel, including Dr Nicholas Davies, Dr Benedict Michael, Professor Tom Solomon CBE, and Dr Ava Easton.

Dr Tarun Dua, Head of Brain Health at the WHO, said: "The World Health Organization is developing a new global action plan on epilepsy and other neurological disorders that will provide a comprehensive approach to addressing the burden due to neurological conditions including from encephalitis. Therefore we are delighted to receive and discuss this report with the Encephalitis Society."

Dr Ava Easton, Chief Executive of the Encephalitis Society, said: "We are very grateful to our colleagues at the World Health Organization for agreeing to meet with us and discuss our report which offers a comprehensive look at the impact of encephalitis around the globe. By working together, I am confident we can take a leap forward in encephalitis prevention and providing better outcomes for individuals and families affected by this often devastating neurological condition."

An executive summary of the report will be available to read in the near future.

Help needed with COVID-19 survey



How do you diagnose COVID-19 patients with neurological complications?
Researchers with the Global Covid Neurology Survey are calling on clinicians to help them better understand how neurological complications of COVID-19 are diagnosed around the world.
The project is being led by the University of Liverpool with support from World Health Organization (WHO) and World Federation of Neurology.
"We need clinicians around the world to share their experiences of how they diagnose neurological and neuropsychiatric syndromes and perceive their association with COVID-19," said Dr Arina Tamborska, NIHR Academic Clinical Fellow in Neurology at the University of Liverpool.
"Your responses will play a role in the validation of a prospective WHO clinical record form which will then be made openly available to everyone following the study's completion."
The survey will take up to 30 minutes to complete and involves questions about your clinical experience and several short case scenarios, describing patients with neurological complications as a result of COVID-19.
Participants will also be named as a collaborator in any publications arising from the survey.
Dr Benedict Michael, Senior Clinician Scientist Fellow at the University of Liverpool, added: "Whether you are a neurologist or any other healthcare professional involved in the care of COVID-19 patients, your help would be greatly appreciated with this study which we hope will lead to better treatments and outcomes for patients."

Take part in the survey by visiting:
www.redcap.link/covidneurosurvey

Study to investigate new treatment

A major global study is investigating a new treatment for anti-NMDAR encephalitis.
The ExTINGUISH NMDAR Encephalitis Trial, which launched in October, is a Phase-2b, Double-Blind, Randomized Controlled Trial which will evaluate the activity and safety of Inebilizumab in Anti-NMDAR encephalitis.
The five year study is being led by Dr Stacey Clardy (University of Utah), Dr Gregory Day (Mayo Clinic Florida) and Dr Maarten Titulaer (Erasmus University Rotterdam).
Twenty hospitals across the USA are involved in the trial, alongside two further sites in Rotterdam and Barcelona, with a target of 116 participants.
"Inebilizumab is a promising therapeutic monoclonal antibody for the treatment of NMDAR encephalitis," writes Dr Clardy in her outline of the ExTINGUISH trial.
"This humanized monoclonal antibody against the B-cell surface antigen CD19 was recently shown to be safe and efficacious in the treatment of neuromyelitis optica spectrum disorder - another antibody-mediated disorder of the central nervous system.
"Compared to other off label B-cell depleting therapies, such as rituximab, inebilizumab not only depletes CD20+ B-cells, but also CD20- plasmablasts and plasma cells, resulting in robust and sustained suppression of B-cell expression.
"The ExTINGUISH Trial will randomize 116 participants with moderate-to-severe NMDAR encephalitis to receive either inebilizumab or placebo in addition to first-line therapies.
"Patient outcomes will be ascertained at standard intervals using the modified Rankin scale and accepted safety measures (primary outcomes at 16 weeks), together with comprehensive validated neuropsychological tests, bedside cognitive screening tools, quality of life/ functional indices, and outcome prediction measures. Clinical data will be combined with quantitative measures of NMDAR autoantibody titers and cytokines implicated in B-cell activation and antibody production within the intrathecal compartment to identify treatment responders, inform the biologic contributors to outcomes, and evaluate for biomarkers that may serve as early predictors of favorable outcomes in future clinical trials in NMDAR encephalitis."
Dr Clardy added: "The ExTINGUISH Trial will prospectively study an optimized B-cell depletion therapy to promote better long-term outcomes in NMDAR encephalitis, to determine more meaningful cognitive endpoints, and to identify better biologic biomarkers to predict outcome."

THE ExTINGUISH NMDAR ENCEPHALITIS TRIAL

CBE honour for Society President

Professor Tom Solomon, the President of the Encephalitis Society, has been awarded a CBE in the Queen's Birthday Honours List for his services to Neurological and Emerging Infections Research, including during the COVID-19 response.

Professor Solomon, who joined Liverpool in 1998 from the University of Oxford, is director of the National Institute for Health Research (NIHR) Health Protection Research Unit in Emerging and Zoonotic Infections. The Unit has played a major role in the UK and international response to Ebola, Zika and most recently COVID-19.

He has had several key roles during the coronavirus pandemic, including chairing government research funding committees, advising the Medicines and Healthcare products Regulatory Agency (MHRA) on vaccine safety, and leading research on neurological complications of COVID-19.

"I am truly honoured by this award, which reflects the tremendous support I have had from family and friends, plus the enormous efforts of a very large group of colleagues over many years," said Professor Solomon. "When I first started working on emerging infections in Asia 25 years ago, many people thought this was a rather esoteric and niche subject. But over the last 18 months, we have all seen the enormous impact such infections can have, and how important an area this is."

Professor takes to the airwaves with science podcast

Professor Tom Solomon, the President of the Encephalitis Society, has added another string to his bow - podcast host.

He is the presenter of the Scouse Science Podcast, a regular discussion on Coronavirus and its impact on science and society.

Guests include leading researchers who talk about the progress being made to tackle the virus, alongside chats about the wider impact of the pandemic with some famous faces.

The podcast is available via all the usual podcast providers - simply search for "Scouse Science".

Successful launch for first ever Encephalitis Information Week

The Encephalitis Society launched its newest campaign in October – Encephalitis Information Week.

The seven-day digital campaign, which ran from the 18th to 25th October, saw us share information about encephalitis with members of the public and health professionals on our social media channels.

Volunteers also directly targeted healthcare organisations in Australia and New Zealand, asking them to share our resources with their professional members.

Topics covered included encephalitis diagnosis, guides for children, adults and health professionals, as well as mental health and wellbeing, and returning to education and work.

Julia Clark, the Encephalitis Society's Director of Engagement, said: "A dedicated annual campaign devoted to sharing information about encephalitis is something that we have been looking to introduce for some time now. "This was our first attempt and it was a success. We hope that this campaign will become a permanent and popular fixture on the calendar.

"Our volunteers wanted to approach healthcare professionals in Australia and New Zealand as it was thought that they could then share information with patients."

200 not out for study!

A project investigating the neurological and neuropsychiatric effects of COVID-19 has recruited its 200th patient.

The £2 million COVID-19 Clinical Neuroscience Study (COVID-CNS), which is being led by clinical researchers at the University of Liverpool and King's College London, is aiming to look at 800 UK patients to understand how these problems occur and develop strategies to prevent and treat them.

At the time Connect Professional went to press, 268 patients had been recruited from the nine participating sites.

"We have still got a long way to go but I am confident we will reach out target of 800 recruits, thanks to the efforts of partners at hospitals across the United Kingdom." said Project co-lead, Dr Benedict Michael, Senior Clinician Scientist Fellow at the University of Liverpool and Consultant Neurologist at The Walton Centre NHS Foundation Trust.

"The better we understand how the virus causes brain complications, the better we will know how to treat patients, be it through existing or new medications. Each case is being investigated thoroughly, through examining clinical data, and laboratory and imaging markers of brain inflammation and injury."

Visit **www.covidcns.org** for more information or to take part in the study.

Centre for excellence opens in San Francisco

A new Center for Encephalitis & Meningitis has been launched at the University of California San Franscisco (UCSF).
The multi-disciplinary team which is based under one roof at UCSF's Mission Bay campus, will tackle the diverse set of infectious and autoimmune conditions that cause encephalitis and meningitis.
Under the directorship of Associate Professor Michael Wilson, it include experts in infectious, autoimmune, primary inflammatory, paraneoplastic, and other causes of encephalitis and meningitis.

The Mission Bay campus at UCSF

Novel Diagnostics

In addition to referral for existing clinical diagnostics, the Center for Encephalitis & Meningitis is focused on developing novel diagnostics to improve care for people with encephalitis and meningitis. The team also closely collaborates with the UCSF Center for Next-Gen Precision Diagnostics (NGDx), which offers a clinically approved (CLIA-certified) metagenomic deep sequencing of cerebrospinal fluid (CSF) for pathogen (infection) detection through the UCSF Clinical Laboratory

Cutting-Edge Research

The Center will conduct research to develop novel methods for autoantibody detection, including phage display technology as well as rodent brain slice assays. Research is also ongoing to understand host immune responses to infection and in autoimmune encephalitis and meningitis.

Healing, Rehabilitation & Repair

Consistent with the mission of the Center for Encephalitis & Meningitis to improve care and outcomes for people with encephalitis and meningitis, Center clinicians focus on strategies to promote and accelerate healing and rehabilitation, including collaboration with expert rehabilitation providers focused on neurorecovery. The Center also conducts basic and clinical research to understand mechanisms of injury and repair in encephalitis and meningitis.

For more information, visit
www.encephalitis.ucsf.edu

National encephalitis study goes above and beyond

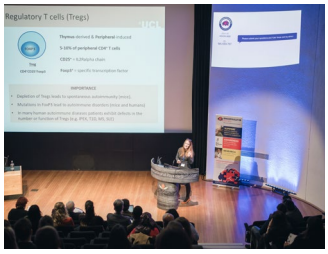
A UK-based encephalitis study is to continue recruiting patients – despite hitting its target of 90 patients.
Researchers with The DexEnceph study of dexamethasone in Herpes Simplex Encephalitis have been given the go ahead to continue patient recruitment until February 2022 by the National Institute for Health Research (NIHR).
The study is being led by the University of Liverpool with the Encephalitis Society also involved as one of the partner organisations.
Professor Tom Solomon CBE, the study's chief investigator, said the hope was to increase the chance of proving any important findings.
"We are enormously grateful to the DexEnceph team, including all the staff in hospitals across the country, plus of course patients, relatives and careers. It's a real vote of confidence that the NIHR is allowing us to continue recruitment."
Professor Solomon, of the (NIHR) Health Protection Research Unit in Emerging and Zoonotic Infections, added that he hopes to announce the results of the study at the 2022 Encephalitis Conference.

Mental health survey

Dr Thomas Pollak and colleagues at King's College London (KCL) have launched a global study looking at the mental well-being of people after encephalitis.
The online questionnaire is open to anyone aged 18 and older.
Dr Pollak, who is a Clinical Lecturer in Psychiatry at KCL. said: "Responses to this survey will help us build a clear picture of life with post-encephalitis symptoms and, as a result, steer our research into treatment options and give us a better idea of whether people are being given the support they may need.
Take part in the survey:
www.bit.ly/KCLencephalitis

Enceph-IG: help needed

Secondary and tertiary care centres in the UK are needed for an autoimmune encephalitis study.
Enceph-IG is a phase III, double blind, randomised placebo control trial which aims to establish whether or not early treatment with intravenous immunoglobulin improves recovery in adults with autoimmune encephalitis.
The trial is being led by Professor Tom Solomon, of the University of Liverpool, and run by the Centre for Trials Research at Cardiff University.
It has been funded through the National Institute for Health Research Efficacy and Mechanism Evaluation programme.
If you would like to know more about the trial or to register as a site, email
EncephIG@Cardiff.ac.uk



Excitement for 2021 Conference

Encephalitis 2021 – our annual conference – will be returning bigger and better on Monday, the 7th December.

As well as our one-day Conference, attendees are also invited to join us the day before for our Research Exchange Meeting and a workshop which will offer tips on applying for grant funding or Fellowships.

All our events will be 'hybrid' – with attendees invited to join us in-person at the Royal College of Physicians in London or virtually.

Dr Ava Easton, Chief Executive of the Encephalitis Society, said: "We are very excited about our new additions to the Conference which we hope will not only offer insight into the latest developments in encephalitis research, but also help the next generation of scientists who we hope will become leaders in their field in the future.

"Places are now available for all our Encephalitis 2021 events and we hope to see you there in London or online!"

Encephalitis 2021 is open to professionals of all levels, including medical students, junior doctors, and PhD students, through to senior clinical lecturers, consultants, and professors and experts with equivalent professional experience.

Find out more and book your place at Encephalitis 2021

www.encephalitis.info/conference

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Global line-up of speakers set for hybrid conference

Eighteen speakers from around the world will be sharing their latest research at Encephalitis 2021 on Tuesday, 7th December.
The conference, which takes place at the Royal College of Physicians in London, will cover hot topics, critical research questions, and approaches to the key clinical challenges informed by the latest research.
This year's event will truly be an international affair with speakers hailing from Senegal, India, France, Brazil, Spain, Cameroon, Germany, the USA, and UK.
Confirmed keynote speakers are Professor Jerome Honnorat, Hospices Civils de Lyon; Assistant Professor Deanna Saylor, Johns Hopkins University School of Medicine; and Winifred Mercer Pitkin Assistant Professor Kiran Thakur, of Columbia University Irving Medical Center.



KEYNOTE SPEAKERS... Prof Jerome Honnorat, Asst Prof Deanna Saylor, and Asst Prof Kiran Thakur

The programme for Encephalitis 2021 has been put together by the Encephalitis Society's Scientific Advisory Panel, members of which will be chairing the conference throughout the day.
"We are delighted at the breadth and depth of the talks planned for Encephalitis 2021," said Dr Ava Easton, Chief Executive of the Encephalitis Society.
"With the world's eyes focused on COVID-19, we were a little concerned that it may have a been a difficult 18 months for encephalitis research, but that has not been the case at all.
"We have worked hard to ensure that this year's conference will be of interest to all professionals involved in the clinical care or research of encephalitis."

SESSION ONE

Chair: Prof. Angela Vincent, University of Oxford, Oxford, UK
Moderator: Dr Benedict Michael, Institute of Infection and Global Health, University of Liverpool; UK

9.35am - Analysing clinical text from electronic health records to diagnose anti-NMDAR encephalitis, a feasibility study
Dr Helena Ariño, Institute of Psychiatry, Psychology & Neuroscience, King's College London, UK

9.50am - Defining the neuroinvasive potential of SARSCoV-2 in brain autopsies of COVID-19 patients
Dr Emily Happy Miller, Columbia University Irving Medical Center, and New York Presbyterian Hospital, New York, USA

10.05am - Immune and genetic signature of breast carcinomas triggering Yo paraneoplastic cerebellar degeneration
Prof Virginie Desestret, Hospices Civils de Lyon, Université Claude Bernard Lyon, France

10.20am - KEYNOTE LECTURE - Paraneoplastic Encephalitis
Prof. Jerome Honnorat, Hospices Civils de Lyon, France

Encephalitis 2021 is kindly sponsored by:

Brain Infections Global
NIHR Health Protection Research Unit in Emerging and Zoonotic Infections at University of Liverpool
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THE LANCET Neurology

Session Two

Chair: Prof. Tom Solomon CBE, University of Liverpool; Brain Infections Group, UK
Moderator: Dr Thomas Pollack, King's College London, UK

11.15am - Dissecting CASPR2-antibody encephalitis with patient derived CASPR2-specific monoclonal antibodies
Dr Bo Sun, University of Oxford/John Radcliffe Hospital, Oxford, UK

11.30am - Clinical and laboratory findings of acute encephalitis syndrome (AES) associated with scrub typhus infection in children admitted to tertiary care hospitals in South India
Dr Tina Damodar, Department of Neurovirology, NIMHANS, Bangalore, India

11.45am - Infectious encephalitis during the second wave of COVID-19: an observational study among hospitalised patients in Dakar, Senegal
Dr Jamil Kahwagi, Centre Hospitalier National Universitaire de Fann, Dakar, Senegal

12pm - Direct evaluation of cervical lymph node and ovarianteratoma as sites of autoimmunisation in NMDAR- antibody encephalitis
Dr Adam Al-Diwani, Department of Psychiatry, University of Oxford, Oxford

12.15pm - INVITED GUEST LECTURE - Developing Neurological Care and Training in Resource-Limited Settings
Assist Prof Deanna Saylor, Johns Hopkins University School of Medicine, USA

Session Three

Chair: Assoc. Prof Sarosh Irani, John Radcliffe Hospital, Oxford, UK
Moderator: Dr Jess Fish Institute of Health & Wellbeing, University of Glasgow; UK

2pm - Inborn errors of TLR3- or MDA5-dependent type I IFN immunity in children with enterovirus rhombencephalitis
Dr Jie Chen, The Rockefeller University, New York, USA

2.15pm - Spatial and temporal brain atrophy in anti-IgLON5 disease
Ms Selina Yogeshwar, Charité- Universitätsmedizin Berlin, Germany

2.30pm - Encephalitis and autoimmune encephalitis in pediatric patients from Brazil
Dr Renata Barbosa Paolilo, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP), São Paulo, Brazil

2.45pm - Novel treatment of an NMDAR-Ab mediated seizure model
Dr Sukhvir Wright, Institute of Health and Neurodevelopment, Aston University, Birmingham, UK

ENCEPHALITIS CONFERENCE

Find out more and book your place for Encephalitis 2021
www.encephalitis.info/conference

Session Four

Chair: Assoc. Prof Sarosh Irani, John Radcliffe Hospital, Oxford, UK
Moderator: Dr Jess Fish Institute of Health & Wellbeing, University of Glasgow; UK

3.30pm - Etiological diagnosis in central nervous system infections: multiplex PCR
Dr Álvaro Bonelli, Rey Juan Carlos University Hospital, Móstoles, Madrid, Spain

3.45pm - Encephalitis Society Funded Research

SARS-CoV-2 infection causes dopaminergic neuron senescence
Dr Oliver Harschnitz, Sloan-Kettering Institute for Cancer Research, New York, USA

Etiologies of encephalitis in non-HIV infected patients in Cameroon
Dr Adawa Manuela, COVID 19 ORCA Patient Management Center; Yaoundé, Cameroon

Investigating long-term neuropsychological outcomes in paediatric autoimmune encephalitis using magnetoencephalography
Charly Billaud, School of Health and Life Sciences, Aston University, Birmingham, UK

4.15pm - KEYNOTE LECTURE - Arthropod-borne Encephalitides
Winifred Mercer Pitkin Assistant Professor Kiran Thakur, Columbia University Irving Medical Center, USA

4.45pm - Our Year - the Encephalitis Society
Dr Ava Easton, the Encephalitis Society

4.50pm - Awards and Prizes for Best Oral and Poster Presentations
Dr Ava Easton and Dr Nicholas Davies

Fly in for one of our satellite meetings

New additions to this year's Encephalitis Conference are a pair of satellite events involving members of the Encephalitis Society's Scientific Advisory Panel. Both events are free, take place on Monday, 6th December, and can be attended in-person at the Royal College of Physicians in London or virtually. Email conferences@encephalitis.info to book your place by 1st December.

How to Get Your Fellowship or Grant

Monday, 6th December – 1.30pm to 2.30pm GMT
Hybrid session: face-to-face (Royal College of Physicians, London) and virtual

This workshop is for researchers from junior to intermediate level who are beginning their research careers and will share advice on how to apply for funding as well as develop Fellowship and grant application writing skills.

By attending this workshop, attendees will:

- Know how to find grant funding opportunities.
- Gain advice on important tips on writing, along with guidance on what reviewers will be looking for.
- Explore the most common mistakes made by the applicants.
- Hear from Clinical Academics about obtaining funding to support research in both high and medium-low income countries.

This workshop will be delivered by:

Dr Benedict Michael
NIHR HPRU for Emerging and Zoonotic Infection, and Clinical Infection Microbiology and Immunology, IVES, University of Liverpool; UK

Assist Prof Omar Siddiqi
Harvard Medical School, USA; University of Zambia School of Medicine, Zambia.

Research Exchange Meeting

Monday, 6th December - 2.30pm to 4.30pm GMT
Hybrid session: face-to-face (Royal College of Physicians, London) and virtual.

This meeting is a free two hour session where selected Conference Poster authors or researchers with preliminary data will be invited to present and discuss their research.

To reserve a place, please email conferences@encephalitis.info with your name, title, institution and how you would like to attend - face-to-face or virtual.

Bursaries awarded

Six bursaries have been awarded to attendees of this year's Encephalitis Conference.
Sadly, due to COVID-19 travel restrictions in their respective countries, five winners have had to defer their attendance until next year's event.
The winners come from Cameroon, Malawi, Iran, Brazil and the Philippines.
Dr Ava Easton, our Chief Executive, said: "We wanted to lend a helping hand to researchers in low-to-middle income countries who may otherwise been unable to join us because of their institutions financial restrictions.
"Sadly, COVID-19 means many of them will only be able to join us virtually this year. However, we are very happy to say that the bursaries will be extended for next year's conference."

The travel bursaries were kindly sponsored by:

The de Laszlo Foundation

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Aston University | iHN Institute of Health & Neurodevelopment

WE NEED YOU!

Do you have any new research, appeals, events, or news that you want to share with other healthcare professionals and researchers who have an interest in encephalitis?

We want to hear from anyone who wants to feature articles in Connect Professional - our biannual newsletter - or our new monthly e-shot which we hope to launch in early 2022.

Email comms@encephalitis.info with any news that you want us to share or tag us in on Twitter - @encephalitis

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Projects chosen for £10k seed funding

Researchers from India and Senegal are latest to receive seed funding from Encephalitis Society research scheme

Researchers in Senegal and India have both received grants of up to £10,000 from the Encephalitis Society's **Encephalitis Futures - International Research Seed Funding** project.

This is the third year that we have awarded seed funding to innovative research projects into encephalitis with, this year, a specific focus on projects in low-to-middle income countries.

Dr Ava Easton, Chief Executive of the Encephalitis Society, said: "We decided to concentrate our efforts on low-to-middle income countries this year as there is a real need for our support and we hope our funding will go much further.

"We are sadly not in a position to fund large-scale research projects so we have to be creative by supporting smaller or pilot projects whose researchers can then look to secure funding for larger scale projects."

She added: "We received 13 applications for seed funding this year which was very gratifying and tells us that there is a need for us to support projects. The decision to award grants to these two projects was very difficult, but ultimately, we believe that they have the potential to make a difference to the lives of many people."

Validation of the Paediatric Autoimmune Encephalitis Severity Score (PASS) in children with autoimmune encephalitis

Dr. Priyanka Madaan • Pediatric Neurology Unit, Department of Pediatrics, Post graduate Institute of Medical Education and Research (PGIMER) • Chandigarh, India

Autoimmune encephalitis is a common cause of encephalitis in children. It is a condition in which the child's own immune system acts against the brain cells, leading to dysfunction of the brain. Affected children can lose awareness of self and surroundings, and be unable to sleep or communicate. They can also have seizures or other violent involuntary movements. The condition can be very disabling and lead to a state where the child is bed-bound and dependent. Fortunately, there are drugs that when used appropriately can result in complete recovery in a significant number of children.

The measurement of severity of autoimmune encephalitis using a standard score is important to better understand the severity of the disease, to aid in decision-making regarding treatments, and to compare the experiences of various canters across the world. Although the Clinical Assessment Scale in Autoimmune Encephalitis (CASE) has been validated for rating the severity of autoimmune encephalitis in adults, it does not consider the differences between childhood and adult presentations, or the developmental context of age-appropriate skills in childhood. Hence, the development of an objective autoimmune encephalitis severity assessment tool for children is required. The Paediatric Autoimmune Encephalitis Severity Score (PASS) is a score recently developed by a consensus of experts across the world. In this study we aim to validate this scoring tool to document the severity of autoimmune encephalitis in children. This score is anticipated to guide documentation of clinical severity during the active phase of the disease. It will serve as a numerical measure of severity for systematically evaluating treatments and comparing severity and outcomes across centers. Better and uniform evaluation of disease severity will ultimately lead to improvement in the care and outcomes in children with autoimmune encephalitis.

Implementing a hospital-based encephalitis surveillance in Senegal to decipher main causes of viral encephalitis in a West-African Low-Income Country

Dr Jamil Kahwagi • Clinique de Neurosciences Ibrahima Pierre Ndiaye Chnu Fann • Dakar, Senegal

Background

Acute meningoencephalitis is a serious disease associated with high mortality. They can be caused by pathogens (bacteria, fungi, viruses, parasites) or be of autoimmune origin. Viruses play an important role in encephalitis, but little is known about their mode of action. A viral aetiology would be suspected in most cases, but current diagnostic tools only allow to search for a limited number of viral agents already known. To date, in Senegal, very little data is available on the main etiological causes of infectious meningoencephalitis. This lack of knowledge impacts the management of patient, and it is essentially based on a probabilistic approach. This study aims to increase our knowledge of the viral aetiologies of meningoencephalitis in Senegal.

Methods

The protocol will be part of the routine hospital management for patients with infectious meningoencephalitis. Various biological samples will be taken, such as cerebrospinal fluids (CSF), whole blood, oropharyngeal and nasopharyngeal swabs, and urine. In addition to the samples, socio-demographic, clinical and exposure data will be collected in a questionnaire to describe the epidemiology of encephalitis cases and identify potential risk factors. We will make the use of a multiplexes detection system (RT-PCR) enabling the detection of the major encephalitis-associated viruses.

Expected results

The project will identify the main viral aetiologies associated with encephalitis, clinical description of cases, identification of risk factors and better management of infectious encephalitis

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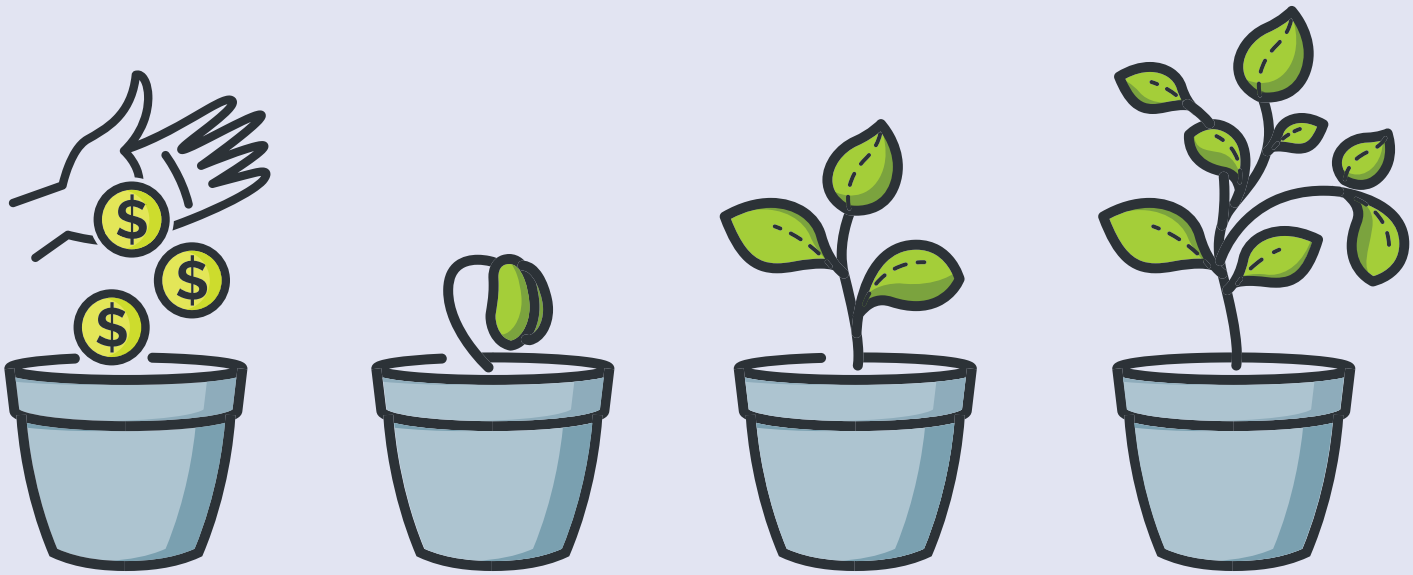

International Consensus Recommendations for the Treatment of Pediatric NMDAR Antibody Encephalitis

OBJECTIVE

To create an international consensus treatment recommendation for pediatric NMDA receptor antibody encephalitis (NMDARE).

METHODS

After selection of a panel of 27 experts with representation from all continents, a 2-step Delphi method was adopted to develop consensus on relevant treatment regimens and statements, along with key definitions in pediatric NMDARE (disease severity, failure to improve, and relapse). Finally, an online face-to-face meeting was held to reach consensus (defined as ≥75% agreement).

RESULTS

Corticosteroids are recommended in all children with NMDARE (pulsed IV preferred), with additional IV immunoglobulin or plasma exchange in severe patients. Prolonged first-line immunotherapy can be offered for up to 3–12 months (oral corticosteroids or monthly IV corticosteroids/immunoglobulin), dependent on disease severity. Second-line treatments are recommended for cases refractory to first-line therapies (rituximab preferred over cyclophosphamide) and should be considered about 2 weeks after first-line initiation. Further immunotherapies for refractory disease 1-3 months after second-line initiation include another second-line treatment (such as cyclophosphamide) and escalation to tocilizumab. Maintenance immune suppression beyond 6 months (such as rituximab redosing or mycophenolate mofetil) is generally not required, except for patients with a more severe course or prolonged impairments and hospitalization.
For patients with relapsing disease, second-line and prolonged maintenance therapy should be considered. The treatment of NMDARE following herpes simplex encephalitis should be similar to idiopathic NMDARE. Broad guidance is provided for the total treatment duration (first line, second line, and maintenance), which is dictated by the severity and clinical course (i.e., median 3, 9 and 18 months in the best, average, and worst responders, respectively). Recommendations on the timing of oncologic searches are provided.

CONCLUSION

These international consensus recommendations for the management of pediatric NMDARE aim to standardize the treatment and provide practical guidance for clinicians, rather than absolute rules. A similar recommendation could be applicable to adult patients.

Nosadini M, Thomas T, Eyre M, et al.
International Consensus Recommendations for the Treatment of Pediatric NMDAR Antibody Encephalitis
Neurol Neuroimmunol Neuroinflamm. 2021 Jul 22;8(5):e1052. doi: 10.1212/NXI.0000000000001052. PMID: 34301820; PMCID: PMC8299516.
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Updated Diagnostic Criteria for Paraneoplastic Neurologic Syndromes

OBJECTIVE

The contemporary diagnosis of paraneoplastic neurologic syndromes (PNSs) requires an increasing understanding of their clinical, immunologic, and oncologic heterogeneity. The 2004 PNS criteria are partially outdated due to advances in PNS research in the last 16 years leading to the identification of new phenotypes and antibodies that have transformed the diagnostic approach to PNS. Here, we propose updated diagnostic criteria for PNS.

METHODS

A panel of experts developed by consensus a modified set of diagnostic PNS criteria for clinical decision making and research purposes. The panel reappraised the 2004 criteria alongside new knowledge on PNS obtained from published and unpublished data generated by the different laboratories involved in the project.

RESULTS

The panel proposed to substitute "classical syndromes" with the term "high-risk phenotypes" for cancer and introduce the concept of "intermediate-risk phenotypes." The term "onconeural antibody" was replaced by "high risk" (>70% associated with cancer) and "intermediate risk" (30%–70%

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Rituximab Treatment and Long-term Outcome of Patients With Autoimmune Encephalitis. Real-world Evidence From the GENERATE Registry

Background and Objectives

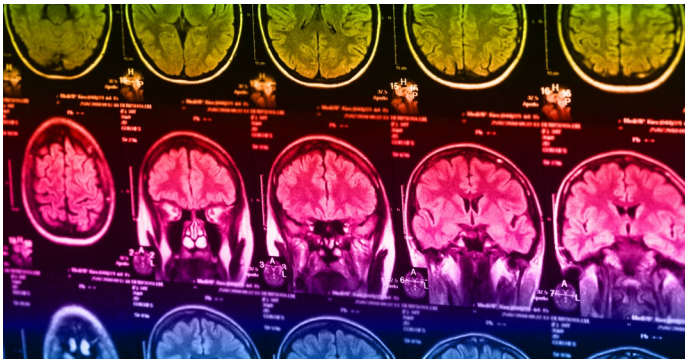
To determine the real-world use of rituximab in autoimmune encephalitis (AE) and to correlate rituximab treatment with the long-term outcome.

Methods

Patients with NMDA receptor (NMDAR)-AE, leucine-rich glioma-inactivated-1 (LGI1)- AE, contactin-associated protein-like-2 (CASPR2)-AE, or glutamic acid decarboxylase 65 (GAD65) disease from the GErman Network for Research on Autoimmune Encephalitis who had received at least 1 rituximab dose and a control cohort of non–rituximab-treated patients were analyzed retrospectively.

Results

Of the 358 patients, 163 (46%) received rituximab (NMDAR-AE: 57%, CASPR2-AE: 44%, LGI1-AE: 43%, and GAD65 disease: 37%). Rituximab treatment was initiated significantly earlier in NMDAR- and LGI1-AE (median: 54 and 155 days from disease onset) compared with CASPR2-AE or GAD65 disease (median: 632 and 1,209 days). Modified Rankin Scale (mRS) scores improved significantly in patients with NMDAR-AE, both with and without rituximab treatment. Although being more severely affected at baseline, rituximab-treated patients with NMDAR-AE more frequently reached independent living (mRS score ≤2) (94% vs 88%). In LGI1-AE, rituximab-treated and nontreated patients improved, whereas in CASPR2-AE, only rituximab-treated patients improved significantly. No improvement was observed in patients with GAD65 disease. A significant reduction of the relapse rate was observed in rituximab-treated patients (5% vs 13%). Detection of NMDAR antibodies was significantly associated with mRS score improvement. A favorable outcome was also observed with early treatment initiation.



Discussion

We provide real-world data on immunosuppressive treatments with a focus on rituximab treatment for patients with AE in Germany. We suggest that early and short-term rituximab therapy might be an effective and safe treatment option in most patients with NMDAR-, LGI1-, and CASPR2-AE.

Class of Evidence

This study provides Class IV evidence that rituximab is an effective treatment for some types of AE.

Thaler F.S., Zimmermann L., Kammermeier S., et al
Rituximab Treatment and Long-term Outcome of Patients With Autoimmune Encephalitis. Real-world Evidence From the GENERATE Registry
Neurol Neuroimmunol Neuroinflamm Nov 2021, 8 (6) e1088; DOI: 10.1212/NXI.0000000000001088

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Continued from Page 14

associated with cancer) antibodies. The panel classified 3 levels of evidence for PNS: definite, probable, and possible. Each level can be reached by using the PNS-Care Score, which combines clinical phenotype, antibody type, the presence or absence of cancer, and time of follow-up. With the exception of opsoclonus-myoclonus, the diagnosis of definite PNS requires the presence of high- or intermediate-risk antibodies. Specific recommendations for similar syndromes triggered by immune checkpoint inhibitors are also provided.

Conclusions

The proposed criteria and recommendations should be used to enhance the clinical care of patients with PNS and to encourage standardization of research initiatives addressing PNS.

Graus F., Vogrig A., Muñiz-Castrillo S., et al
Updated Diagnostic Criteria for Paraneoplastic Neurologic Syndromes
Neurol Neuroimmunol Neuroinflamm Jul 2021, 8 (4) e1014; DOI: 10.1212/NXI.0000000000001014
(Article Open Access under the Creative Commons Attribution License CC BY)

Use and Safety of Immunotherapeutic Management of N-Methyl-D-Aspartate Receptor Antibody Encephalitis. A Meta-analysis.

IMPORTANCE
Overall, immunotherapy has been shown to improve outcomes and reduce relapses in individuals with N-methyl-D-aspartate receptor (NMDAR) antibody encephalitis (NMDARE); however, the superiority of specific treatments and combinations remains unclear.

OBJECTIVE
To map the use and safety of immunotherapies in individuals with NMDARE, identify early predictors of poor functional outcome and relapse, evaluate changes in immunotherapy use and disease outcome over the 14 years since first reports of NMDARE, and assess the Anti-NMDAR Encephalitis One-Year Functional Status (NEOS) score.

DATA SOURCES
Systematic search in PubMed from inception to January 1, 2019.

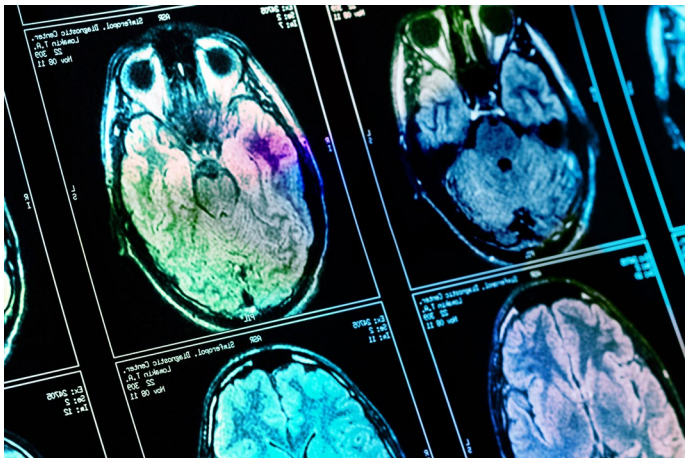
STUDY SELECTION
Published articles including patients with NMDARE with positive NMDAR antibodies and available individual immunotherapy data.

DATA EXTRACTION AND SYNTHESIS
Individual patient data on immunotherapies, clinical characteristics at presentation, disease course, and final functional outcome (modified Rankin Scale [mRS] score) were entered into multivariable logistic regression models.

MAIN OUTCOMES AND MEASURES
The planned study outcomes were functional outcome at 12 months from disease onset (good, mRS score of 0 to 2; poor, mRS score greater than 2) and monophasic course (absence of relapse at 24 months or later from onset).

RESULTS
Data from 1550 patients from 652 articles were evaluated. Of these, 1105 of 1508 (73.3%) were female and 707 of 1526 (46.3%) were 18 years or younger at disease onset. Factors at first event that were significantly associated with good functional outcome included adolescent age and first-line treatment with therapeutic apheresis, corticosteroids plus intravenous immunoglobulin (IVIG), or corticosteroids plus IVIG plus therapeutic apheresis. Factors significantly associated with poor functional outcome were age younger than 2 years or age of 65 years or older at onset, intensive care unit admission, extreme delta brush pattern on electroencephalography, lack of immunotherapy within the first 30 days of onset, and maintenance IVIG use for 6 months or more. Factors significantly associated with non relapsing disease were rituximab use or maintenance IVIG use for 6 months or more. Adolescent age at onset was significantly associated with relapsing disease. Rituximab use increased from 13.5% (52 of 384; 2007 to 2013) to 28.3% (311 of 1100; 2013 to 2019) (P < .001), concurrent with a falling relapse rate over the same period (22% [12 of 55] in 2008
and earlier; 10.9% [35 of 322] in 2017 and later; P = .006). Modified NEOS score (including 4 of 5 original NEOS items) was associated with probability of poor functional status at 1 year (20.1% [40 of 199] for a score of 0 to 1 points; 43.8% [77 of 176] for a score of 3 to 4 points; P = .05).

CONCLUSIONS AND RELEVANCE
Factors influencing functional outcomes and relapse are different and need to be considered independently in development of evidence-based optimal management guidelines of patients with NMDARE.



Nosadini M, Eyre M, Molteni E, et al.
Use and Safety of Immunotherapeutic Management of N-Methyl-d-Aspartate Receptor Antibody Encephalitis: A Meta-analysis.
JAMA Neurol. 2021 Sep 20:e213188. doi: 10.1001/jamaneurol.2021.3188. Epub ahead of print. PMID: 34542573; PMCID: PMC8453367
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Oxford Autoimmune Neurology Group

Professor Sarosh Irani talks about his role as head of the Oxford Autoimmune Neurology Group and the team's work in treating patients and researching autoantibody-mediated diseases

I am a clinician scientist, more specifically a neurologist who sees patients with autoimmune brain diseases and tries to better understand their underlying condition. The overall aim is to improve treatment options for our patients, and others with similar problems around the world. To do this, my team relies heavily on the amazing altruism of our patients who donate clinical information, time and their samples (including blood, spinal fluid and lymph node tissue) to our research efforts. These samples are key to understanding the causes and factors which propagate these diseases, and over 95% of our patients very generously help with these studies.

My clinical work is focused on caring for patients with brain diseases which are either associated with or caused by autoantibodies. As many of these diseases are treatable with interventions which modulate the immune system, this puts me in the very privileged position of being able to offer potentially life-changing therapies to many patients. Despite this, many of our patients do not have optimal outcomes. This can be for a variety of reasons including: one, the patients are identified and treated too late; two, there are limited effective medications for their condition; and thirdly, despite some recovery they have residual impairments which are can significantly impair their life. We try to address these issues. Firstly, we have demonstrated that autoantibody specificities can have a remarkably close relationship with the patient phenotypes. For example, the psychopathological features and movement disorder in patients with NMDAR-antibodies,(1, 2) and the seizure semiologies in patients with LGI1-antibodies, notably Faciobrachial dystonic seizures.(3, 4) These observations improve the recognition of patients with encephalitis. Also, we disseminate knowledge about these diseases to other health care professionals, by speaking at clinical meetings around the world and writing reviews to describe the core features of these illnesses,(5, 6) and to the public by holding annual events at which the public (and patients) can gain a better understanding of these conditions.

Next, to address the paucity of treatment options, we work with pharmaceutical companies to establish clinical trials (we are the UK's major centre in a trial to treat patients with LGI1-antibodies) and investigate the immune system

Continued on Page 18

Professor **Sarosh Irani** is a Clinician-Scientist, Associate Professor and Consultant Neurologist and head of the Oxford Autoimmune Neurology Group. They work to improve treatments and outcomes for patients with autoantibody-mediated diseases of the nervous system, and understand the biology behind these conditions. In his clinical work, he runs the UK's major clinic which has cared for over 200 patients with autoantibody-associated neurological disorders of the central nervous system, in particular forms of autoimmune encephalitis.

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Journal of Neurology, Neurosurgery & Psychiatry (2018), doi:10.1136/jnnp-2018-318584.

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Brain. 141, 348–356 (2018).

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The autoantibody-mediated encephalitides: from clinical observations to molecular pathogenesis
Journal of Neurology, 1–19 (2019)

The Oxford Autoimmune Neurology Group

Continued from Page 17

abnormalities which lead to these conditions (more to come on that). Finally, we have identified that patients commonly suffer from mood problems, marked fatigue and residual cognitive problems despite making some improvements.(7)

With a team of talented scientists, we aim to bring patient-focused and more basic observations to understand multiple aspects of these diseases. To date our laboratory findings have included:

One: Discovery of new autoantibodies such as those which target LGI1 and CASPR2.(8) Hence, our work has defined immunotherapy-responsive conditions. It has also identified autoantibodies which are of limited diagnostic value: by reducing their use in diagnostics laboratories we have saved several patients unnecessary immunosuppressant medications (9, 10).

Two: Studies of the cellular and humoral human immunology to understand the basis of these diseases – a key request from our patients. We have described some of medicine's strongest genetic (HLA) associations in patients with these autoantibodies(11) and the potential of patient B cells in circulation to produce the autoantibodies in these conditions.(12, 13) In addition, we have used the immune cells within patient ovarian tumours to better understand the aetiology of these diseases.

Currently, we are using these foundations to understand the breaks in immune tolerance and developing methods to rapidly generate patient-derived monoclonal antibodies to precisely explore the neuroscience mechanisms by which the antibodies cause disease.(14) We anticipate ongoing work towards determining the mechanisms underlying aetiology and propagation of these conditions will allow the rational selection of future immunotherapies.

MRC Fellowship

Professor Sarosh Irani was awarded a prestigious Medical Research Council Senior Clinical Fellowship at the end of last year.

The head of the Oxford Autoimmune Neurology Group and his team will track autoantigen-specific B cells from their entry into circulation through to their site of pathology in the central nervous system.

They will aim to characterise which cells are potential therapeutic targets, identify stages at which they acquire pathogenicity and generate monoclonal antibodies which are valuable tools for the scientific community.

These proof-of-concept findings can readily generalise to understanding the immune contributions in a variety of common neuropsychiatric conditions.

The grant, which runs over five years, has already employed five scientists to help deliver the study.

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Latest in Oxford research

Two summaries of recent research carried out by the Oxford Autoimmune Neurology Group:

Leucine-Rich Glioma-Inactivated 1 versus Contactin-Associated Protein-like 2 Antibody Neuropathic Pain: Clinical and Biological Comparisons

Pain is a under-recognized association of leucine-rich glioma-inactivated 1 (LGI1) and contactin-associated protein like 2 (CASPR2) antibodies. Of 147 patients with these autoantibodies, pain was experienced by 17 of 33 (52%) with CASPR2- versus 20 of 108 (19%) with LGI1 antibodies ($p = 0.0005$), and identified as neuropathic in 89% versus 58% of these, respectively. Typically, in both cohorts, normal nerve conduction studies and reduced intraepidermal nerve fiber densities were observed in the sampled patient subsets.

In LGI1 antibody patients, pain responded to immunotherapy ($p = 0.008$), often rapidly, with greater residual patient-rated impairment observed in CASPR2 antibody patients ($p = 0.019$). Serum CASPR2 antibodies, but not LGI1 antibodies, bound in vitro to unmyelinated human sensory neurons and rodent dorsal root ganglia, suggesting pathophysiological differences that may underlie our clinical observations.

Ramanathan, S., Tseng, M., Davies, A.J., et al.
Leucine-Rich Glioma-Inactivated 1 versus Contactin-Associated Protein-like 2 Antibody Neuropathic Pain: Clinical and Biological Comparisons.
Ann Neurol, 90: 683-690. https://doi.org/10.1002/ana.26189
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Diagnosis - a podcast

Professor Sarosh Irani and the work of the Oxford Autoimmune Neurology Group will be featured on a new BBC podcast in the new year.
The Diagnosis, from BBC Radio 4 and BBC Sounds, will tell the story of one person's search for a diagnosis through an interview with a patient and the doctor who treated them.
The episode featuring Professor Irani is due to be broadcast in January, 2022.

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Autoimmune encephalitis: clinical spectrum and management

Autoimmune encephalitis defines brain inflammation caused by a misdirected immune response against self-antigens expressed in the central nervous system. It comprises a heterogeneous group of disorders that are at least as common as infectious causes of encephalitis. The rapid and ongoing expansion of this field has been driven by the identification of several pathogenic autoantibodies that cause polysymptomatic neurological and neuropsychiatric diseases. These conditions often show highly distinctive cognitive, seizure and movement disorder phenotypes, making them clinically recognisable. Their early identification and treatment improve patient outcomes, and may aid rapid diagnosis of an underlying associated tumour. Here we summarise the well-known autoantibody-mediated encephalitis syndromes with neuronal cell-surface antigens. We focus on practical aspects of their diagnosis and treatment, offer our clinical experiences of managing such cases and highlight more basic neuroimmunological advances that will inform their future diagnosis and treatments.

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Practical Neurology 2021;21:412-423.
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Distinctive binding properties of human monoclonal LGI1 autoantibodies determine pathogenic mechanisms
Brain. 143, 1731–1745 (2020)

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