Encephalitis Conference 2019

Conference details: 2nd December 2019, Royal College of Physicians, London, UK. ***Report by:*** Dr Chishimba Lorraine, University of Zambia School of Medicine, Department of Internal Medicine, University Teaching Hospital, Lusaka, Zambia and edited by: Dr Ava Easton, Chief Executive, Encephalitis Society.
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2nd December 2019 saw a host of over 170 health care professionals descend on the prestigious Royal College of Physicians in London to attend the Encephalitis Society's 2019 conference. It was an event graced by delegates from various fields of medicine, science, and research. The speakers at this international event presented expert work in line with various fields that aligned with all things encephalitis. They included neurologists, neuroscientists, neuropsychologists, neuropsychiatrists, and sociologists. It was a packed house to the end of the day.

The first session was chaired by Professor Tom Solomon, a professor of neurology and Chair of the Society's Scientific Panel.

The opening presentation was given by Dr Kamran Zaman, from the ICMR-Regional Medical Research Centre, Gorakhpur in India: he discussed a study that looked into the aetiological agents of acute encephalitis syndrome (AES) in cases in Eastern Uttar Pradesh. The backdrop of the discussion was the long-standing presumption that Japanese encephalitis virus (JEV) was the cause of every encephalitis case in India, prior to a 2005 outbreak. With the development of newer serological and molecular diagnostics other infectious causes of encephalitis, including bacterial, could be identified. He reported that Orientia tsutsugamushi – the causative agent of Scrub Typhus was in fact the most common aetiological agent from the AES cases in Uttar Pradesh in the year 2018. He highlighted that despite the seasonal outbreaks over the decades which were associated with high mortality, there has been a general decline in AES in India owing to JE vaccination campaign and prophylactic use of azithromycin/ doxycycline in acute febrile illness (AFI)/ AES cases.

Dr Christopher Duncan, University of Newcastle, UK presented on the role of homozygous missense mutation in STAT2 as being responsible for the failure of regulation in interferon pathways and hence leading to unrestrained type 1 signalling in sterile encephalitis. Type I interferons (IFNs) are essential antiviral cytokines but uncontrolled activity can be harmful. Dr Duncan presented a new genetic disease associated with sterile encephalitis in two brothers carrying a homozygous missense mutation in STAT2. STAT2 is a transcription factor that functions downstream of IFN, and the pathogenic variant (STAT2-R148W) was accompanied by prolonged JAK-STAT signalling and enhanced responses to IFNα/β, due to a failure of STAT2-dependent negative regulation. These findings demonstrate a new regulatory function of STAT2, and suggest that blocking IFN signalling might offer benefit in similar neuroinflammatory diseases linked to excessive IFN activity

Dr Nicholas Davies, Professor Tom Solomon, Associate Professor Sarosh Irani.

Dr Danielle Bastiaansen from Erasmus MC University Center, Rotterdam, the Netherlands followed with a discussion on her work showing how autoimmune encephalitis could easily be misdiagnosed as dementia syndrome because about a third of AE cases presented with symptoms of dementia. Seizures were a late feature in the disease course with subtle seizures being easily missed, while dementia was of rapid progression making its suspicion more prominent than AE. Moreover, disease progression in AE can be slower over months to years. She concluded by emphasising the need for physicians to be aware of AE, especially when patients have other symptoms such as seizures in particular because AE is a treatable condition with better outcomes. She also highlighted that abnormal ancillary tests, including CSF, MRI and EEG are red flags for AE.

Dr Audrey Daisley and Dr Rachel Tams, Consultant Clinical Neuropsychologists from the Oxford Centre of Enablement, UK talked about the use of a resilience focused approach to supporting families affected by encephalitis. They acknowledged that, despite the often devastating psychological impact of this condition, there is little research into family adjustment to it and very few interventions have been developed. Dr Daisley and Dr Tams emphasised the importance of helping all members of a family, including child relatives, to understand and find ways to live as well as possible with the unique challenges that encephalitis can bring; in particular they noted the challenges for families to understand and cope with the "invisible" aspects of the illness (such as cognitive problems and fatigue), to help families discover their "new normal" and to talk through and grieve the complicated and ambiguous losses they experience. They also stressed the value in helping families connect with others in a similar situation and illustrated this in a short film of a "Family Resilience Day" (run in conjunction with the Encephalitis Society and the London Fire Service in 2018). They also presented their group work with children affected by Multiple Sclerosis in the family, and suggested that this one-day resilience group programme could be adapted for children living with encephalitis in the family whose parents are affected by encephalitis. They concluded by calling for more family focused research in this area

The late morning session was chaired Dr Bonnie-Kate Dewar and the first presenter was Professor Ajit Rayamajhi from the Kanti Children's Hospital, Kathmandu, Nepal. He presented on the role of fluid management in the outcome of children with Acute Encephalitis Syndrome (a group of symptoms and signs used by World Health Organization to help diagnose acute viral encephalitis). Data on optimum fluid management for patients with non-traumatic brain injury, in particular AE is limited. Low admission weights which could be malnutrition or dehydration related

in children with encephalitis has been associated with poor outcomes. He reported low admission weight-for-age and loss of weight after admission as correlates for poor outcomes. The children with bad outcome tended to have low admission weight for age and more fluid deficit with a trend for higher admission serum lactate levels which meant that they could have been dehydrated. He indicated that high serum lactate could also be harmful to the brain and thus contribute to poor outcome, hence the need for optimum and appropriate fluid management to mitigate poor outcomes.

Dr Ana Arenivas from The Institute for Rehabilitation and Research Memorial Hermann and Baylor College of Medicine Houston, USA presented that age is associated with long term adaptive behaviour after anti-NMDAR encephalitis (anti-NMDAR). She showed that in comparison to adolescent and adults, children with anti-NMDAR may experience deficits in adaptive function, despite no differences in mRS score between groups. Further, males may experience more adaptive behaviour challenges than females. Results suggest distinct consequences of the disease on the early developing brain. Findings underscore the importance of ongoing monitoring of functional outcomes to inform appropriate treatment planning and advocacy. Future longitudinal and prospective research should examine children with anti-NMDAR longitudinally to better understand the impact of other variables (e.g., pharmacological, rehabilitative, behavioural intervention) on additional cognitive and behavioural outcomes.

Dr Fabian Docagne's presentation (French Institute for Health Research, France) followed on how B-cell response mediates experimental NMDA receptor autoimmune encephalitis. He presented findings of a recent animal model which suggested that B-cell response could lead to autoimmune reaction against NMDAR that would then drive the encephalitis-like symptoms despite overt T-cell recruitment. This is unlike other autoimmune neurological diseases such as multiple sclerosis that is mediated by T cells. The autoimmune response was associated with B cell infiltration and no T cell, toward the ventricles, and depletion of B cell reduced the severity of the symptoms in the mice. These findings call for further work in encephalitogenic mechanisms in animal models and testing immune system therapeutic strategies.

Dr Ava Easton, Chief Executive of the Encephalitis Society presented on vaccine-preventable encephalitides using case studies to illustrate often-devastating patient outcomes in Rabies, Japanese encephalitis, and tick-borne encephalitis.

A keynote lecture entitled *Diagnosing infectious encephalitis including PCR multiplex panels and meta-genomics* was presented by Associate Professor Matthijs Brouwer, Academic Medical Centre, Amsterdam. His talk focused on diagnosing infectious encephalitis which can be caused by many different organisms including viruses, bacteria, parasites, and fungi. Identification of the causative aetiology is important as it improves the outcome if the correct treatment is started early during infectious encephalitis. The clinical history, physical exam and cranial imaging all help in arriving at the possible aetiology of encephalitis. Useful clues to exotic micro-organisms include a history of travel and animal contact. Cranial imaging is useful and may give a clue especially in Herpes Simplex Virus encephalitis with characteristic changes involving the temporal lobe due to swelling. CSF studies however are the gold standard to identification of the various aetiologies. Microscopic examination and culture can be done on CSF to identify various organisms. The drawback with culture is that it may take weeks to get to the offending organism, about 3-6 weeks for tuberculosis (TB) and up to 8 weeks for fungi. When checking for viruses in cerebral spinal fluid CSF there is always the chance that the virus may not be detected as it may be only in the brain parenchyma and not in the CSF. This then becomes the basis for a repeat lumbar puncture (LP) usually within a few days. Polymerase Chain Reaction (PCR) is a valuable tool to identify many viruses and several bacteria, but is less sensitive in cases such as TB and Borellia (50% and 18% respectively). PCR may be especially helpful in patients treated with antibiotics in whom bacteria no longer grow in cultures. PCR multiplex panels are relatively new modality able to identify 14 targets including 6 bacteria, 7 viruses and Cryptococci, but does not include TB. So far the additional value above culture, PCR and serology is not obvious. Next generation sequencing is an important research technique for finding new viruses but so far is not very sensitive. He explained that there appears to be clinical relevance for this mode of diagnosis in a selected population but does not replace currently used microbiological diagnostics. Other novel methods such as patterns of metabolism, proteins and lipids in the CSF may also show what the cause of encephalitis is, and are currently still subject to scientific research.

Audience shot.

Following lunch the third session was chaired by Dr Nicholas Davies, Chelsea and Westminster Hospital and the first presentation was given by Dr Aline de Moura Brasil Matos a neurologist from the Tropical Medicine Institute at University of São Paulo in Brazil. Her talk focused on a study on the triple arboviral epidemics in the Brazilian northeast between 2015 and 2017. Dengue virus (DENV), Zika virus (ZIKV) and Chikungunya virus (CHIKV) are endemic to Brazil and a look at the epidemics revealed an increase in Chikungunya cases over time, along with a rise in incidence of a variety of neurological syndromes observed following these epidemics. In previous reports, few describe Chikungunya neutropism and patients often manifested with non-neurological symptoms such as rash and arthralgia. The study demonstrated CHIKV as the commonest viral aetiology for encephalitis during the epidemics, and other neurological presentations such as myelitis or acute polyneuropathy could occur along with the encephalitis. The greater neutropism seen with CHIKV not seen with the other arboviral agents of the epidemics might probably be attributed to likely infection of astrocytes

Dr Luisa Diaz-Arias, from Johns Hopkins, Baltimore, USA presented research findings regarding fatigue in encephalitis survivors. Recognition and treatment of fatigue in these individual would improve quality of life. Using the modified Fatigue impact scale, they demonstrated that fatigue, in physical (86% of participants), cognitive (83%) and psychological domains was commonly reported by encephalitis survivors, with women tending to report more fatigue than their male counterparts. Sleep quality and depression were also reported with modest association to fatigue but they could not completely account for it, hence a call to further explore biological underpinnings of fatigue in survivors of encephalitis.

The second keynote address of the day was provided by Professor Emma Morris, Institute of Clinical Cell and Gene Therapy, University College London, UK. Professor Morris focused on the role of T cell immunity in autoimmune encephalitis. Professor Morris was able to

take the audience through the workings of the immune system including the selection, maturation and development of a sub-population of T cells, in the thymus, into a regulatory T cells (Treg) that is important in suppressing the immune system and maintaining immune tolerance. The regulatory T cell contain a transcription factor FoxP3 gene that determines the function of the Treg cells. Mutation to this gene can lead to deleterious effects via severe autoimmunity and immune dysregulation. Regulatory T cells have been used in cancer immunotherapy as genetically engineered T cells. The CAR T cells are Tregs engineered to have genes that encode chimeric antigen receptors (CAR) in order for them to have specific antigen targets. In haematological cancer immunotherapy the CAR T cells are designed with CD19 antigen as their target. CD19 is a surface marker expressed by all B cells including the neoplastic lineages. With the use of CAR T cell immunotherapy Professor Morris indicated observation of organ specific autoimmunity. There is an observed association between CAR T cells and autoimmune encephalitis through neurotoxicity. She indicated that patients present with seizures and slow waves on EEG and that one of the initial signs that point to autoimmune encephalitis from CAR T cell therapy is a change in handwriting. The takeaway message was that T cell immunity plays a role in autoimmune encephalitis.

Dr Frederik Bartels, University of Berlin, Germany discussed the findings of their study on failure of brain growth in children with myelin oligodendrocytes glycoprotein (MOG) antibody-associated encephalitis. The backdrop to their study was acute disseminated encephalomyelitis (ADEM) an acquired demyelinating syndrome that commonly affects children and affects brain growth over time. ADEM is characterised by encephalopathy, polyfocal neurological symptoms and predominant white matter changes on MRI scans. Over the years it has been shown that many children with ADEM are also seropositive for autoantibodies against myelin oligodendrocyte glycoprotein MOG, so that potentially this could be a separate disease entity (MOG spectrum disorder). ADEM though typically monophasic can also have a relapsing course with ADEM-Optic neuritis phenotype and studies have shown negative influence on brain growth over time. Dr Bartels research, based on MRI scans illustrated that though no differences were found in whole brain volume between MOG antibody-positive and MOG antibody-negative ADEM patients, there was significant brain volume reduction with a corresponding CSF fluid volume expansion in patients with ADEM (MOG anti-body negative and positive) compared with healthy controls. He also demonstrated that there was failure of age-expected brain growth in patients with ADEM compared to controls.

Dr Georgios PD Argyropoulos, University of Oxford, UK described a novel disorder of emotional dysregulation following auto-immune limbic encephalitis characterised by pathological tearfulness. The acute phase of autoimmune limbic encephalitis may be characterised by psychiatric and behavioural symptoms with high T2 signal in the limbic system on MRI. Following immunosuppressive therapy many patients recover satisfactorily, though a substantial proportion develop atrophy in the limbic system and residual cognitive impairment with deficits centering on episodic memory. The study by Dr Argyropoulos and team demonstrated that half the patients in the chronic post-acute phase of autoimmune limbic encephalitis reported tearfulness that was unrelated to depression, impulsiveness, executive dysfunction, memory impairment or acute phase amygdala abnormalities. Instead the study demonstrated a correlation between pathological tearfulness with specific emotional brain networks. Abnormal resting-state functional connectivity between the hippocampus and the posteromedial cortex and right middle frontal gyrus, abnormal hemodynamic activity in the left fusiform gyrus, right inferior parietal lobule and ventral pons, and volume reduction in the right anterior hippocampus, left fusiform gyrus and cerebellum correlated with this novel phenomenon. He indicated potential of these findings to inform future pharmacological therapies.

Delegates from Malawi, Zambia and Harvard, USA.

The conference sessions concluded with a debate chaired by Professor Tom Solomon entitled "This house believes ALL patients with suspected Autoimmune Encephalitis should receive IVIG as an adjunct to corticosteroids". For and against the motion were Associate Professor Sarosh Irani, and Dr Nicholas Davies respectively. An in-house pre and post-debate poll was carried out with members of the audience participating in the voting process through an online portal. The background for the debate was the lack of consensus on IVIG as an adjunct in the first-line treatment for suspected autoimmune encephalitis, with different groups using it as such and other groups preferring plasmapharesis over IVIG, with no evidence for superiority of either approach. The audience favoured use of IVIG as an adjunct to corticosteroids in both the pre and post-debate poll. Professor Sarosh Irani was convincing in his arguments for the motion so that more votes went to the motion after the debate.

Phillipa Chapman, Director of Services, Encephalitis Society presented a video highlighting a range of events and activities that took place in the year 2019 to mark and celebrate the 25th anniversary of the Society.

The day drew to a conclusion with awards: best oral presentation was awarded to Dr Frederik Bartels, Department of Neurology, University of Berlin for his presentation on "Failure of brain growth in children with MOG antibody-associated encephalitis". Best poster presentation was awarded to Giuliano Tomei of Oxford Health NHS Trust; Department of Psychiatry, University of Oxford (other authors: Ksenija Yeeles, Iona Cairns, Jessica Venkaya, Isobel Harrison, Alasdair Coles, Michael Zandi, Peter Jones, Belinda Lennox) for his work on "Anti-neuronal membrane antibody associated psychosis: clinical and demographic characteristics from a screening cohort ". A long-standing volunteer award was presented to Rachel Tarlton for her work over the last 10 years with the Encephalitis Society.

Closing remarks were delivered by Dr Ava Easton after which there was a networking opportunity over wine and snacks.

Many thanks go to the sponsors of the event: ACNR, Aston Neuroscience Institute, Brain Infections Global, Cambridge University Press, Euroimmun, Liverpool Brain Infections Group, NIHR, Oxford University Press, Routledge, The Lancet Neurology, University of Liverpool, Valneva

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Prizes will be awarded again for best Oral and Poster presentations.