TGHN Workshop Report Guide – COVID-19 Hub

Neurological disorders associated with COVID-19: Guillain-Barré Syndrome Cases and Patients on Immunomodulators

Introduction

On 9th June, The Global Health Network (TGHN) supported the virtual open workshop, '*Neurological disorders associated with COVID-19: Guillain-Barré Syndrome Cases and Patients on Immunomodulators*'. This workshop contributed to the workshop series on the COVID-19 response from various regions across the globe that are being organized by TGHN at the University of Oxford, UK in partnership with the Brain Infections Group.

Brain Infections Global is a NIHR Global Health Research Group which aims to improve the management of acute brain infections. This GHRG links Liverpool, with its outstanding reputation in brain infections research, to the internationally renowned Warwick Centre for Applied Health Research and Delivery, and to leading research institutes in Malawi, India and Brazil. To aid research into the neurological effects of COVID-19 they have set up the COVID-Neuro Network, an international collaboration part of Brain Infections Global, led by the Liverpool Brain Infections Group from the University of Liverpool.

This webinar was run on the basis that although the predominant clinical presentation is with respiratory disease, neurological manifestations are being increasingly recognised and observed. After a successful first webinar (which can also be found on here) the aim of this webinar was to examine further the neurological disorders associated with COVID-19 infection with particular focus on cases of Guillain-Barré Syndrome (GBS) and discussion around the management of those patients on immunomodulators.

The identification of potential research gaps in the neurological disorders associated with COVID-19, as well as tools and methods to go about addressing these research gaps, was also an aim of the webinar.

The workshop was chaired by Professor Tom Solomon and featured a panel of 2 experts – Dr M Netravathi and Professor Bart C Jacobs – representing India and the Netherlands respectively. A total of 305 persons registered for the webinar. On the day of the webinar more than 130 participants joined through zoom and others viewed the session through live streaming via the Facebook page of TGHN, spanning 15 countries in North America, Europe, Africa and South Asia.

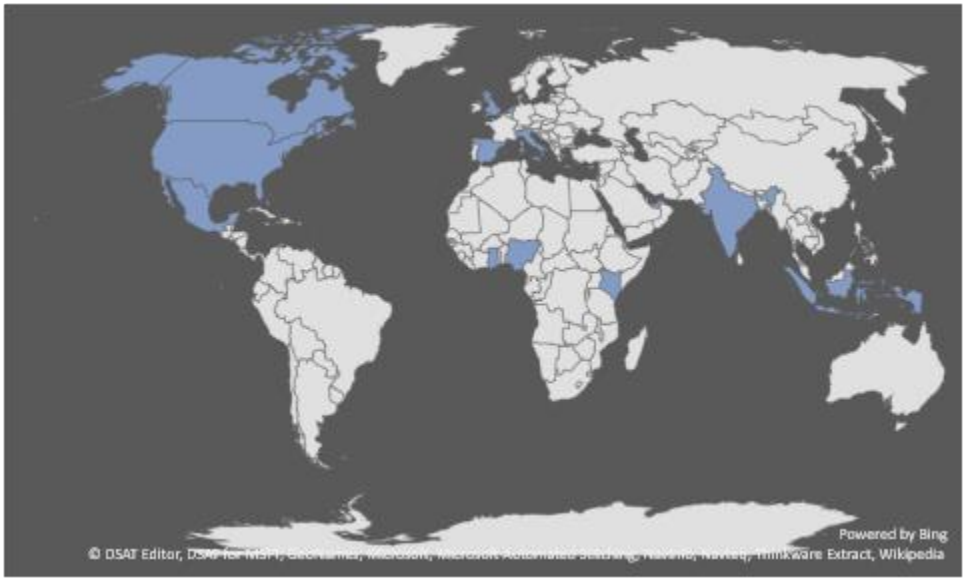


Figure 1 Location of attendees. Participants attended the workshop from the 15 countries shaded in dark blue.

Summary of Panellist Presentations:

Guillain-Barre Syndrome (GBS) following SARS-CoV-2 infection

Professor Bart C. Jacobs MD, PhD

Professor in Neurology and Immunology, Consultant in Neurology, Chair Steering Committee of International Guillain-Barré syndrome (GBS) Outcome Study (IGOS).
Based at the Departments of Neurology and Immunology at the Erasmus MC, University Medical Center Rotterdam, The Netherlands.

With an aim to highlight the ongoing research into the possible association between COVID-19 and the research areas requiring greater focus, key points covered in the presentation were:

- GBS is a rapidly progressive, immune-mediated polyradiculoneuropathy which is heavily associated with preceding infection, commonly of Campylobacter Jejuni but also other viruses such as Zika

- There are currently 33 cases found associating COVID-19 with GBS, of which 7 have been confirmed to have had COVID-19. While the majority of normal GBS symptoms are of typical prevalence, respiratory failure has been observed in 40% of these patients whereas it is usually only seen in 20% - the reason for this is yet to be discovered. The following table shows the symptoms, disease characteristics and outcomes of all possible COVID-19/GBS patients identified so far:

Infectious symptoms	70% fever, 70% cough/dyspnea, 27% anosmia/ageusia, 27% diarrhea
Time infectious symptoms and onset GBS	3-24 days
Clinical phenotype	52% sensorimotor, 27% pure motor, 15% MFS, 6% pharyngeal variant
EMG subtype	60% demyelinating and 40% axonal subtype
Respiratory failure	42%
Outcome	6% died, 12% still ventilated at publication

- International GBS Outcome Study (IGOS) is a multicenter observational cohort study aiming to identify clinical and biological determinants and predictors of disease course in Guillain-Barré syndrome using extensive serological testing. It so far has recruited 1902 patients from across the globe of patients within 2 weeks of onset of symptoms, whether mild/severe, treated/untreated, common/rare GBS variants
- Prof Jacobs described the aims. methods and results of a sub-study of IGOS which he is currently working on. Studying 42 patients with GBS from Jan 30th to May 30th, the sub-study is aiming to describe the clinical presentation and course in relation to SARS-CoV-2 infection and determine a possible association between GBS and SARS-CoV-2:
    - While the data collection and analysis are ongoing, preliminary results were shown by case studies
    - 3 case studies are discussed in the webinar with a variety of GBS severity and outcomes
    - The usual treatments for GBS (IVIg and plasmapheresis) are looking to be effective so far

During his presentation, Prof Jacobs call for any interested attendees to submit case data to be used in their upcoming meta-analysis.

- Finally, Prof Jacobs highlighted future studies needed, including:
    - Testing biosamples for serology of SARS-CoV-2 and other infectious agents
    - A case-control study to determine association between SARS-CoV-2 infection and GBS
    - Immunological studies to look for the presence of antibodies to peripheral nerves and a possible mechanism.

Managing Patients on Immunomodulators during the COVID-19 period

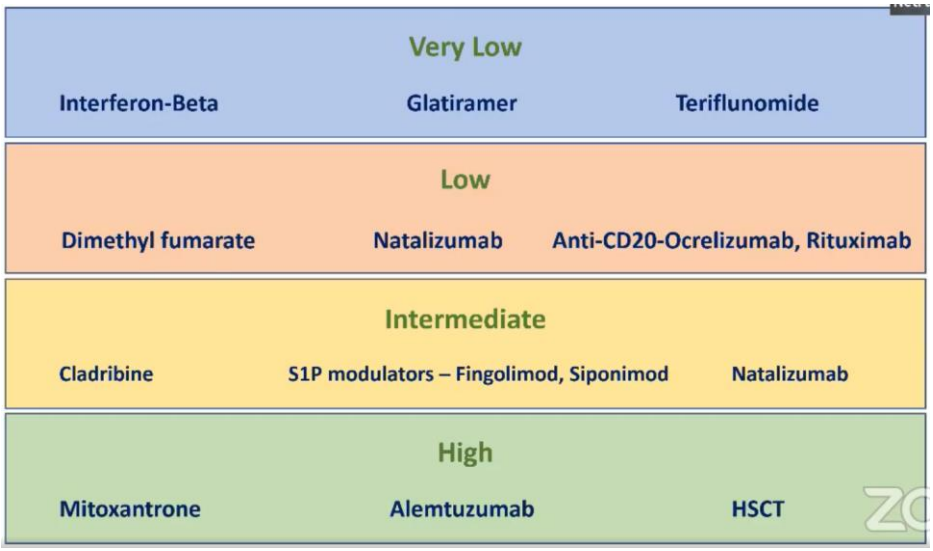
Dr M Netravathi

An additional professor in Neurology at the National Institute of Mental Health and Neuro-Sciences (NIMHANS) India: Areas of specialist interest include central nervous system demyelinating disorders, neuro-infections, and paediatric movement disorders.

With an aim to highlight the difficulties of and guidelines on making decisions relating to the initiation/continuation of immunomodulatory drugs in patients with demyelinating diseases, the key points covered in the presentation were the need to determine

- whether the many patients on immunosuppressants and immunomodulators are at an increased risk of severe COVID-19 infection
- discussed when to pause, discontinue or amend treatment plans for patients with autoimmune disorders on individual basis, using several case studies (a summary for each drug mentioned can be found in the table below). These include, for example, the possibility of using alternative techniques such as Extended Interval Dosing for Natalizumab in the treatment of Highly Active Multiple Sclerosis (HAMS)

Dr Netravathi also described how various drugs used in the treatment of Multiple Sclerosis (MS) and other autoimmune disorders should be used in the current context of COVID-19. First, she stratified the risk into VERY LOW/LOW/INTERMEDIATE/HIGH risk categories: according to the treatments in place:



Then according to the risk categorization, she suggested which drugs should be initiated, continued according to the stages of the infection as follows:

Table 1: Disease Modifying Agents

Risk Category	Drug	Start Treatment?	Continue Treatment?	COVID infection
VERY LOW	Interferon-Beta	YES	YES	YES
	Glatiramer	YES	YES	YES
	Teriflunomide	YES	YES	YES
LOW	Natalizumab (EID)	YES	YES	YES
	Dimethyl fumarate	Probably	Continue/Switch	Continue
	Anti CD20: (Rituximab/Ocrelizumab)	Probably	Risk Assessment/ Continue/ Suspend	Temporary Suspension
INTERMEDIATE	Cladribine	Probably	Risk Assessment/ Continue/ Suspend	Temporary Suspension
	S1P moderators – Fingolimod, Siponimod	Probably	Continue	Temporary Suspension
	Natalizumab (SID)	YES	Continue/consider EID	Continue/consider EID
HIGH	Mitoxantrone	NO	Suspend Dosing	Suspend Dosing
	Alemtuzumab	NO	Suspend Dosing	Suspend Dosing

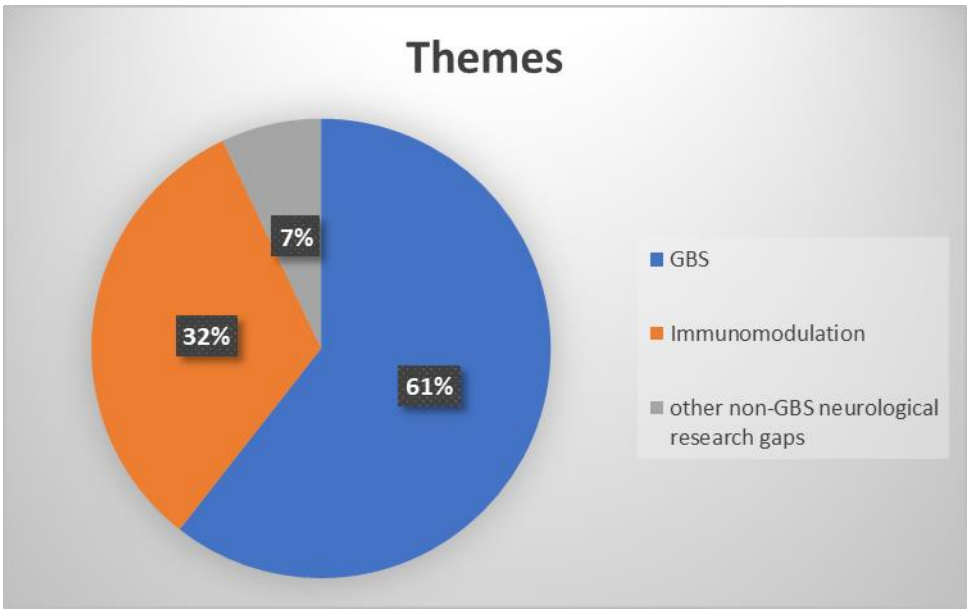
	HSCT	NO	Suspend Dosing	Suspend Dosing

Table 2: Other Immunosuppressants

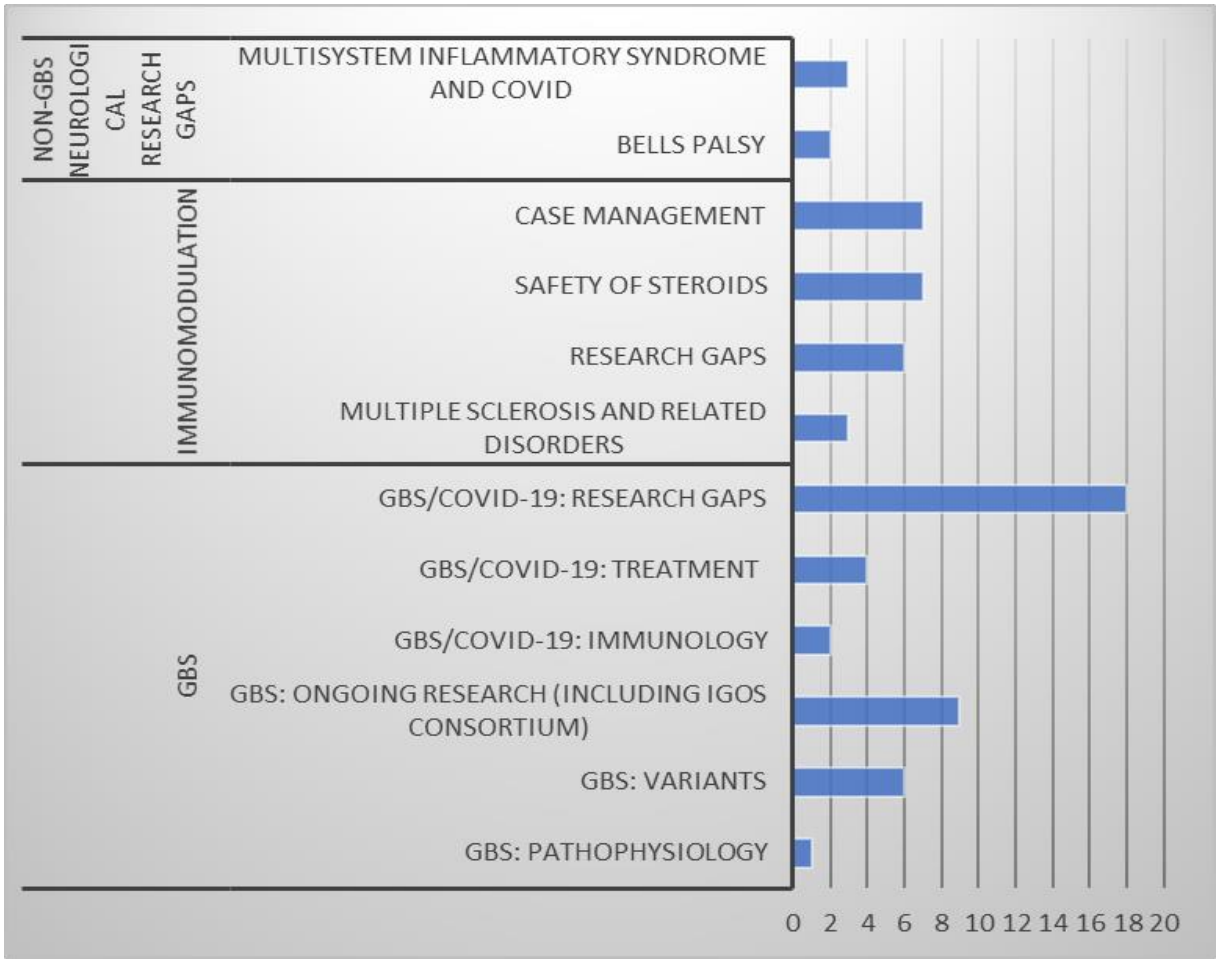
Drug	Start Treatment?	Continue Treatment?	COVID infection
Azathioprine	Probably/No	YES	Risk assessment/No
Mycophenolate mofetil	Probably/No	YES	Risk assessment/No
Cyclophosphamide	No	No	No

Summary of Q&A, open discussion and comments

In the following Q&A session, the following 'themes' and sub-themes emerged during the talks and from the attendees' questions:



These 3 themes could then be grouped into the following sub-themes:



Immediate research priorities identified

Consolidating feedback from the panellists and the questions and comments made by the workshop participants has produced the following consensus on the immediate research priorities for '***Neurological disorders associated with COVID-19'***:

- Conduct serological testing to identify preceding SARS-CoV-2 infection in GBS patients
- Explore the relationship between COVID-19 and onset of GBS, including whether GBS variants are more prevalent after COVID infection than others
- Immunological studies of COVID patients to look for antibodies against peripheral nerves
- Determine whether the increased incidence of Bell's Palsy is GBS/COVID related
- Development of a technique to culture of the virus from CSF
- Examine risks and benefits of starting/continuing patients on different steroids and other immunomodulatory drugs

Resources:

Brain Infections Global website – an opportunity to contribute patient data to the meta-analysis on the association between COVID-19 and GBS can be found here

Diagnosis and management of Guillain–Barré syndrome in ten steps: a paper authored by Professor Jacobs detailing the diagnosis and management of patients with GBS

Call to action and next steps

If you are involved in COVID-19 research surveillance, diagnostics, research ethics and regulatory review, new interventions, prevention, public health measures and the allocation of scarce resources for managing this outbreak, please contact us to share any relevant protocols, associated tools and your experiences.

Please send in your comments and feedback on the COVID-19 webinar '**Neurological disorders associated with COVID-19: Guillain-Barré Syndrome Cases and Patients on Immunomodulators'**. Further virtual workshops are planned, which will be topic-specific and in response to demand. If you would like us to conduct a workshop related to a specific theme of COVID-19 research, please let us know what topics would be most helpful. You can get in touch here info@theglobalhealthnetwork.org