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Original article

Management of Idiopathic CNS inflammatory diseases during the COVID-19 pandemic: Perspectives and strategies for continuity of care from a South East Asian Center with limited resources.

Viswanathan S.[†,*]

Department of Neurology, Kuala Lumpur Hospital, Kuala Lumpur, Malaysia

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ABSTRACT

The Covid-19 pandemic poses a grave health management challenge globally of unprecedented nature. Management of idiopathic Central Nervous system inflammatory disorders (iCNSID) such as Multiple sclerosis, Neuromyelitis optica and its spectrum disorders and related conditions during this pandemic needs to be addressed with affirmative and sustainable strategies in order to prevent disease related risks, medication related complications and possible COVID-19 disease associated effects.

Global international iCNSIDs agencies and recent publications are attempting to address this but such guidance is not available in South East Asia. Here we outline prospectively qualitatively and quantitatively novel strategies at a tertiary center in Malaysia catering for neuroimmunological disorders despite modest resources during this pandemic.

In this retrospective study with longitudinal follow-up, we describe stratification of patients for face to face versus virtual visits in the absence of formal teleneurology, stratification of patients for treatment according to disease activity, rescheduling, deferring initiation or extending treatment intervals of certain disease modifying therapies(DMT's) or immunosuppressants(IS), especially those producing lymphocyte depletion in MS and the continuation of IS in patients with NMO/NMOSD.

Furthermore, we highlight the use off-label treatments such as Intravenous immunoglobulins/rituximab,-bridging interferons/Teriflunomide temporarily replacing more potent DMT choices,supply challenges of IS/DMT's and tailoring blood watches and neuroimaging surveillance based on the current health needs to stave off the pandemic and prevent at risk patients with iCNSID/health care workers from possibly being exposed to the COVID-19.

1. Introduction and background

On March the 11th, 2020, the World Health Organization(WHO) labelled the spread of the novel corona virus, SARS-Cov-2 producing COVID-19 disease a pandemic as the virus spread to more than 114 countries (Zhu et al., 2020; World Health Organization 2020; Novel Coronavirus Pneumonia Emergency Response Epidemiology Team 2020; Worldometer 2020; Chen et al., 2020; Adhikari et al., 2020). Malaysia, since February 2020 has seen COVID −19 infections emerging as a serious health issue (Montero-Escribano et al., 2020; Ministry of Health Malaysia 2019). This necessitated heighthened re-deployment of health services centering on COVID-19 management, restricting overseas travels, employing social distancing and a movement control order(MCO) since March 18th 2020 (Worldometer 2020; Ministry of Health Malaysia 2019). As of the 13th of June 2020, the number of COVID-19 cases nationwide had increased to 8445 cases with 120 mortalities (Worldometer 2020; Ministry of Health Malaysia 2019). Patients infected were those who had contact with clusters of cases, advanced age with multiple co-morbidities and history of travel overseas similar to recent publications (Zhu et al., 2020; World Health Organization 2020; Novel Coronavirus Pneumonia Emergency Response Epidemiology Team 2020; Adhikari et al., 2020; Ministry of Health Malaysia 2019). During **pandemics, services to non COVID related diseases** such as idiopathic Central Nervous system inflammatory disorders(iCNSIDs) like Mulitiple sclerosis(MS) and Neuromyelitis optica and its spectrum disorders(NMO/NMOSD) still need to continue. Traditional Neuroimmunology models of care in South East Asian(SEA) countries like Malaysia still emphasize the need

* Corresponding author.
E-mail address: shivenda70@yahoo.com.
† Orcid ID: Shanthi Viswanathan https://orcid.org/0000–0002–0094–0540

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for **in person face to face consultations** leading to congregation of such patients at health care facilities (Vijayasingham and Viswanathan, 2019).

1.1. Managing the pandemic impact on the neuroimmunology service at Kuala lumpur hospital, Malaysia

The main service provision issues were the need to provide uninterrupted care, overcome traditional hospital based treatment stereotypes and limit patient's/Health care worker's(HCw) risk of potential exposure to COVID-19 while identifying patients with idiopathic Central Nervous System inflammatory diseases (pwiCNSID) at risk of active disease and COVID-19 infections. Recent commentaries and studies have suggested the risk from relapses and disability progression in pwiCNSIDs far outweighs the risks of acquiring COVID-19 (Baker et al., 2020; Giovannoni et al., 2020; Brownlee et al., 2020; Giovannoni, 2020). Therefore, it was imperative to ensure patient's received uninterrupted supply of disease modifying therapies(DMT's) or immunosuppressants(IS) simultaneously allaying potential fears of continuing treatment. Currently there is insufficient data on the occurrence/behaviour of Covid-19 in pwiCNSIDs and the effects of DMT's/IS on the risk of COVID-19 infection or its complications (Willis and Robertson, 2020; D'Antiga, 2020). Initial preliminary data suggests reassuringly low severity of infections in patients receiving teriflunomide,ocrelizumab, alemtuzumab and other IS/DMT's (Baker et al., 2020; Giovannoni et al., 2020; Brownlee et al., 2020; Giovannoni, 2020; Montero-Escribano et al., 2020; Sormani, 2020; Maghzi et al., 2020; Mat´ıas-Guiu et al., 2020).

Globally, international CNSID organizations, WHO and a number of publications have given important guidance on Covid-19 preventive measures and the management of immune mediated iCNSID's during this pandemic. Similar guidance is lacking within the SEA region (Baker et al., 2020; Giovannoni et al., 2020; Brownlee et al., 2020; Giovannoni, 2020; Montero-Escribano et al., 2020; Sormani, 2020). Thus this narrative study outlines some of the methods of **treatment delivery and decisions** being rendered to pwiCNSID's prospectively seen at the national tertiary referral center, Kuala Lumpur Hospital (HKL) Malaysia a hybrid COVID-19 designated hospital from 1st of March 2020 till the 31st of May 2020,despite challenges of limited resources.

2. Objectives

The objective of this narrative was to outline prospectively with longitudinal follow up:

1 The management strategies quantitatively and qualitatively done to run this service in Malaysia during the Covid-19 pandemic incorporating current WHO and global guidance.
2 Explore tentatively, how virtual visits and other novel methods of service delivery in the absence of established teleneurology services, could help the neuroimmunology service even in resource challenged settings in stratifying patients and continuing care for pwiCNSID.

3. Methods and materials

3.1. Study design, site and follow up period

This was a prospective cross sectional study with longitudinal follow up from the 1st of March 2020 till the 31st of May 2020 of all patients with iCNSIDs scheduled to attend the Neuroimmunology service at the Department of Neurology, HKL.

3.2. Patients

3.2.1. Inclusion and exclusion criteria of patient groups

Inclusion criteria included all patients with MS,NMO/NMOSD, Myelin oligodendrocyte glycoprotein disorders (MOGAD) and related disorders. Patient's actively visiting the clinics and wards during this period as new cases, follow-ups, those on maintenance oral/infusions of DMT's or IS, patients on acute rescue/maintenance treatment with Intravenous methylprednisolone(IVMP), intravenous immunoglobulin (IVIG) or therapeutic plasma exchange (TPE) were identified prospectively from the departments on-line computerized clinic/ward appointment databases(DB), hard copy clinic appointment books and iCNSIDs database.

Exclusion criteria included all other patients attending the service with non-idiopathic non CNSIDs.

3.3. Study materials

3.3.1. Study site:The neuroimmunology clinic structure

The iCNSID clinic at the Neurology Department of HKL is made up of neurologists with interests in iCNSIDs, clinic and day care nurses, study coordinators from the Clinical Research Center involved in study drug infusions,pharmacists and TPE nurses. PwiCNSID are seen at the General Neurology clinics on Mondays,Tuesdays, Thursday mornings as well as the Advanced Neuroimmunology clinic on Friday mornings. The Department of Neurology also runs an “in house” Neurology service for TPE and a day care infusion suite for various drug infusions such as IVMP, IVIG, immunosuppressants(IS) and monoclonal antibodies(mAB) (Fig. 1).

3.3.2. Investigator

An independent neurologist (SV) in charge of the iCNSIDs clinics with scheduled nurses triaged patient's appointments and identified ways to get access to care without forcing them to potentially expose themselves or HCw to COVID −19 by hospital visits as per existing Ministry of Health(MOH), Malaysia/global guidelines/publications (Ministry of Health Malaysia 2019; Giovannoni et al., 2020; Brownlee et al., 2020; Giovannoni, 2020; Multiple Sclerosis International Federation 2020; Coles et al., 2020; National MS Society 2020; Guthy Jackson Charitable Foundation 2020).

3.3.3. Procedures

Data on patient stratification, treatment decisions, modes of access and delivery of treatments, questions on presence of COVID-19 symptoms, and patient's concerns were also collected.

3.3.4. Treatment decisions

Decisions on treatments during the pandemic were done by accessing patient's preference, MOH Guidelines on Covid-19 Management 05/2020, Clinical Practice Guideline(CPG) on Management of MS Version 1,2015, (Ministry of Health Malaysia 2019) Multiple sclerosis International Federation(MSIF), National MS Society(USA),the Association of British Neurologists(ABN), the Guthy Jackson Charitable Foundation Website (GJCFW) as well as current literature published on line (Giovannoni et al., 2020; Brownlee et al., 2020; Montero-Escribano et al., 2020; Sormani, 2020; Maghzi et al., 2020; Multiple Sclerosis International Federation 2020; Coles et al., 2020;

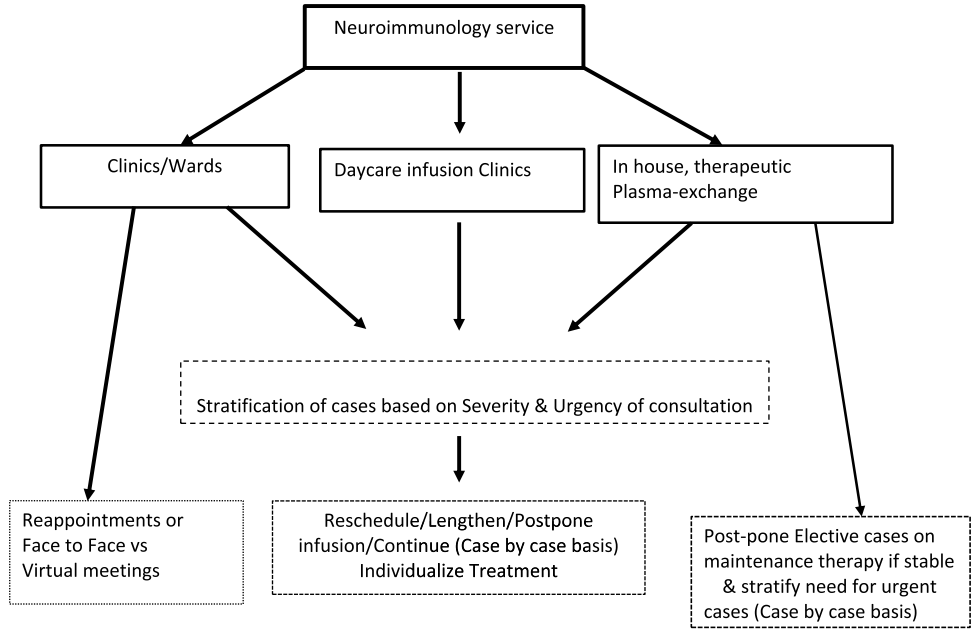


Fig. 1. Showing the scope of the Neuroimmunology Service at the Department of Neurology, Kuala Lumpur Hospital.

National MS Society 2020; Guthy Jackson Charitable Foundation 2020). Off label treatment with IVIG and rituximab was highlighted.

3.3.5. Statistical analysis

All data was compiled using SPSS version 22 (SPSS Inc,Chicago,IL, USA) looking at descriptive data,means and percentages.

3.3.6. Ethical approval, registration and patient consents

This study is part of output from the iCNSID database established at the Department of Neurology,HKL, approved by the Malaysian Medical Research Ethical committee (MREC:NMRR11–1449–10,503) that looks at non-interventional collection of data on demographics,investigations and management of pwiCNSIDs. All participants or caregivers gave informed consent either written and/ verbally.

4. Results

4.1. Sample size

A total of 317 MS,190 NMOSD, 22 MOG and 95 patients with related disorders were identified from databases. Patients on follow up with the Department of Neurology, HKL are from all 13 states within Malaysia. About 33% were actively scheduled to visit the clinics during this period from Ist of March 2020 to 31st of May 2020 for various services. Of these about 83% (230) were contacted and the remainder who were not contactable came as walk-ins.

In the narrative review below we present data on:

1. The Neuroimmunology service provision during the height of COVID-19 at HKL:
a) Patient Triaging: Stratification of visits into
- Virtual visits (in the absence of teleneurology services) or
- Face to face consultations

This was based on:

i) patient's factors/preference and
ii) disease specific reasons
b) Infusion clinics and TPE Services
c) Management of relapses in iCNSIDs
d) Management of new iCNSIDs cases on DMTs/IS and on maintenance treatments
e) Laboratory and Neuroimaging surveillance
f) Modes of Delivery of DMT's/IS and Supply of DMT's/IS

1. Neuroimmunology service provision

a). Patient triaging:

Patient's were contacted prior to visits and triaged after obtaining consent by the Neurologist(SV). Methods of contacting patients is highlighted below. A total of 230 patients were contacted with 15% actually calling in themselves. Patient visits were divided into those that could be converted and supported by **virtual visits not fulfilling the definition of telemedicine** and those **needing a face to face** (Abboud et al., 2020; Lee et al., 2020; Malaysia's Telemedicine 1997) (Fig. 1,2,3).

i). Patients specific factors/preference:

There were 5 categories of patients. Those who were willing to postpone their interactions by 3 to 4 months till the epidemiology of the cases nationwide reduced (carry forward medications provided) (25%), those willing for virtual consults (30%), 30% insisting on face to face visits, 5% who were uncontactable but walked in as scheduled cases and 10% who walked in as unscheduled cases.

ii). Disease specific factors:

Patients were stratified clinically according to severity of complaints, disease activity and by neuroimaging into active or not, highly active or aggressive disease types, stable or not in terms of symptoms, necessitating urgent investigations or review of adverse reactions to treatments. Stratification was based on evidence from the Clinical Practice Guideline(CPG) on Management of MS Version 1, 2015 (Malaysian Clinical Practice 2015). Treatment was further **individualized as** per current recommendations by the local MOH authorities on COVID-19 management (Ministry of Health Malaysia 2019), international professional and patient bodies and recent commentaries in Neurology periodicals on management of pwiCNSIDs (Baker et al., 2020; Giovannoni et al., 2020; Brownlee et al., 2020; Giovannoni, 2020; Multiple Sclerosis International Federation 2020; Coles et al., 2020; National MS Society 2020; Guthy Jackson Charitable Foundation 2020; Abboud et al., 2020) (Fig. 1,2,3).

New referrals seen were urgent/semi-urgent and where non-urgent

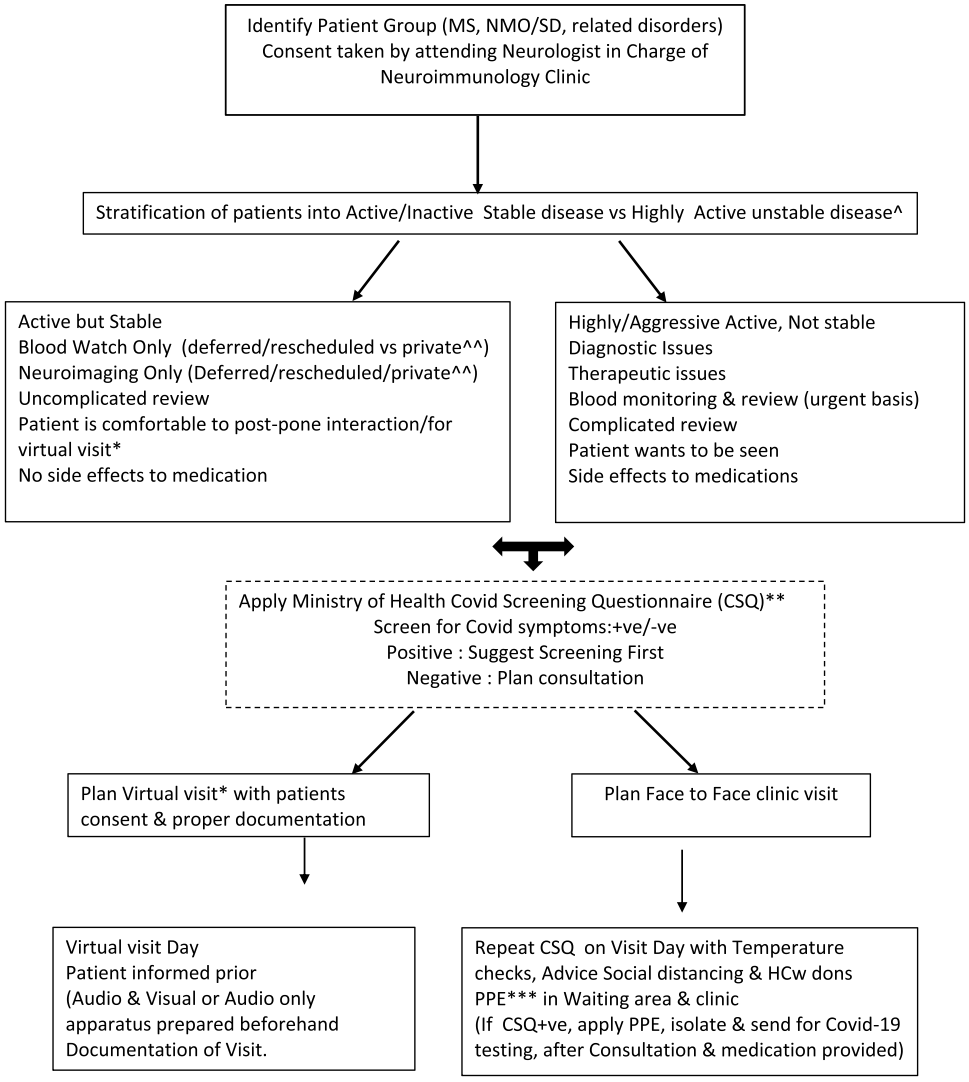


Fig. 2. Virtual and Face to face visit Triaging and Stratification in the absence of Telemedicine facilities at the HKL Neuroimmunology Clinic.

with patient's consent were post-poned to 2 to 4 months later or referred to another non COVID-19 designated hospital. (See Fig. 1,2,3).

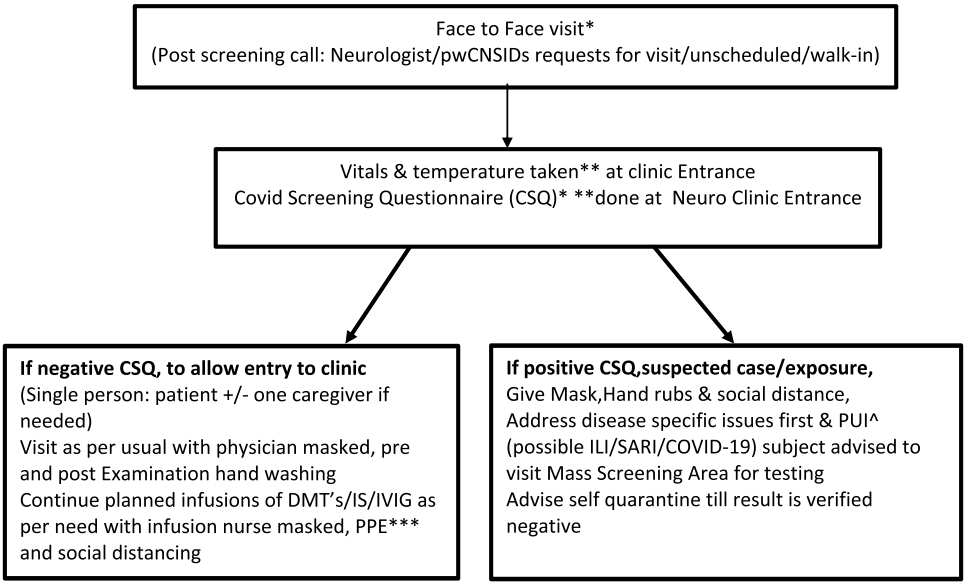
Based on this stratification: a total of 66 patients were seen as scheduled face to face clinic visits, 40 as unscheduled walk-in patients solely to the clinics and 64 as virtual visits from 1st of March to 31st of May 2020. The remainder opted for reappointments in 3–4 months with medication only pick-ups (60) (Table 1).

iii). Virtual Visits:.

1 Methods of contacting patients virtually in the absence of Teleneurology:

Audio visual or audio consultations were planned. These virtual visits did not fulfil the current conventional definition of teleneurology (Lee et al., 2020; Malaysia's Telemedicine 1997; Mehrotra et al., 2020) as this service is not available at HKL. This included utilization of land line telephone/handphones, Whatsapp with or without video, Face time, SMS(Short messaging system), Emails, Video conferencing through computer based programmes and webcams or Skype. All virtual visits were documented within case notes. Patient's were informed that a follow-up call/clinic visit would be done within 4 to 8 weeks time. From our survey, the majority of the consultations were telephone consultations (40%) with or without follow-up video calls (20%), whatsapp with or without video(25%), face time (20%), SMS (10%),emails(5%) and video calls via webcams alone (10%) (Fig. 2)

2 Preparation for Virtual Consultations:



- ***Health care worker –nurse /clinic assistant will administer questionnaire, temperature check, vitals**
- ****HCw will be attired in personal protective equipment (PPE) (level of PPE as required by MOH) and wear a mask while doing the tasks Ref MOH[7]**
- *****Level of PPE as determined by local Ministry of Health Ref MOH[7]**
- **^PUI: Person under investigation**
- **ILI: Influenza like illness**
- **SARI: Severe acute respiratory illness**
- **DMT: Disease modifying therapies**
- **IS: immunosuppressants**

Fig. 3. Protocols for Health care workers (HCw) dealing with Face to Face visits.

Table 1
Types of consultations based on disease specific factors from March 2020 till May 2020 at the height of the COVID-19 pandemic.

Type of consultation	Number/n	Percentage/%
Scheduled Face to face	66	38.8%
Unscheduled Walk in (Face to face)	40	23.5%
Virtual Visits (non telemedicine type)	64	37.6%
Total consultations	170	100%

*Reappointments (60 patients) not included in the table.

Patient triaging was paramount with review of patient's source documents, investigation results including blood watches and neuroimaging. Patient's consent, preparation for virtual consultation and best modality to contact patients' was decided in advance. The treating neurologist (SV) decided beforehand what information to provide to the patients' prior to contacts and ensured patients' were prepared with their audio/audio-visual aids. A brief explanation for the reason for the contact and the need to continue care without a face to face visit was made. From a medico-legal aspect the Insurance provider to the Neurologist was informed via email about these virtual visits (Fig. 2).

A preplanned set of questions was administered. This involved asking about new symptoms, side effects to existing medications, blood and urine examination results, discussing recent neuroimaging reports, checking on adequacy of medication supplied (DMT's/IS) and methods of collection, symptoms and signs of any infections including COVID-19, mood issues and follow-up appointments in the future depending on the local COVID-19 epidemiology. Patient's were also given the opportunity to ventilate their concerns; with the main questions being; "Were they at risk of COVID-19/a relapse, should they continue or stop treatments and preventive steps to take. Information on the hospitals to access if having contact or symptoms suggestive of COVID-19 and preventive strategies was given too (World Health Organization 2020; Ministry of Health Malaysia 2019; Brownlee et al., 2020; Montero-Escribano et al., 2020; Malaysian Clinical Practice 2015) (**See below##)** (Fig. 2).

3 Covid-19 specific questions to assess risk and exposure either via virtual or face to face visits and results. (See Covid Screening Questionnaire(CSQ): Appendix 1**)**

Are you experiencing any fever, cough, sore throat, diarrhea or shortness of breath?
Have you had any recent contacts with Covid-19 positive patients?
Have you visited any large religious gatherings of late?
Have you or your relatives gone overseas or just returned from overseas?

The CSQ was administered to all 170 patients (87 MS, 74 NMO/NMOSD,5 MOGAD,4 other CNSIDs) of which 152 were negative. Ten patients had influenza like illness(ILI) (Ministry of Health Malaysia 2019; Fitzner et al., 2018) (all COVID-19 negative), 1 with MS and 1 with NMO/NMOSD had Severe Acute Respiratory Illness (SARI) (2) (Ministry of Health Malaysia 2019; Fitzner et al., 2018) and were COVID-19 negative too, the latter developing Herpes Zoster ophthalmicus. Only 19 of this group though asymptomatic had independently tested for COVID-19 due to concerns being on DMT's/IS. All were negative (Table 2).

4 Neurological examinations during virtual visits

Table 2
Results of Covid Screening Questionnaires(CSQ) applied to 170 pwCNSIDs.

Diagnosis/Number:n	CSQ negative/n	CSQ positive/n		ILI*/n	SARI**/n	COVID-19 positive in 19 pts with CSQ –ve /n
		Covid-19 +ve	Covid-19 -ve			
MS	77	Nil	10	5	1	Nil
NMO/NMOSD	71	Nil	3	3	1	Nil
MOGAD	2	Nil	3	1	0	Nil
Others	2	Nil	2	1	1	Nil

Abbreviations: pwCNSIDs: patient's with Central nervous system inflammatory diseases; n: number of patients; CSQ: Covid screening questionnaire, +ve: positive;, -ve: negative; ILI: Influenza like illness *;SARI**: severe acute respiratory illness; NMO/NMOSD: Neuromyelitis optica/neuromyelitis optica spectrum disorder;MS: Multiple sclerosis;MOGAD: Myelin oligodendrocyte glycoprotein; pts: patients.
CSQ: available in Appendix 1.
*/**: Look at WHO definition for ILI or SARI and risk for COVID-19 (Fitzner et al., 2018).

This was done on a case by case basis only for a small number of follow-up patients. It was done for cases on follow-up during routine calls or where new symptoms were found. Tools for virtual neurological examinations were accessed from websites like the Telemedicine and Covid-19 website from the American Academy of Neurology 2020 (Dorsey and Topol, 2020 ; Evans et al., 2020).

iv). Out patient Face to face consultations:

Face to Face consultations were done with certain precautions. All pwiCNSIDs/their caregivers coming in were advised to wear a mask especially patient's on DMT's/IS, practice social distancing by lining up outside the clinic with a gap of one meter in between, seated in the waiting areas with 2 seats in between, practice good cough and hand hygiene as well as minimize social interactions with other patients during the clinic visits if possible as advocated by WHO, MOH and MSIF (World Health Organization 2020; Ministry of Health Malaysia 2019; Multiple Sclerosis International Federation 2020). Only 30 patients were allowed to enter the clinic at any given time per session (Fig. 3).

b). DMT and is clinics:

i). Infusions of DMT/IS/high efficacy Oral DMT/IS:

As cases of COVID-19 peaked in March and April 2020 locally, decisions on whether to continue or defer infusions of DMT's/IS were individualized based on disease severity whether active but stable versus highly active/aggressive but unstable with risks for further deterioration/disabilities including patient's preference after weighing the risks versus benefits and urgency of treatment (Fig. 2). This stratification was adapted based on the CPG for Management of MS Version 1,2015 (with subsection on NMO/NMOSD), recent publications,GJCF, ABN and MOH suited to the local pandemic (Ministry of Health Malaysia 2019; Baker et al., 2020; Giovannoni et al., 2020; Brownlee et al., 2020; Giovannoni, 2020; Multiple Sclerosis International Federation 2020; Coles et al., 2020; National MS Society 2020; Guthy Jackson Charitable Foundation 2020; Abboud et al., 2020).

Those who were stable clinically over the last 3 to 6 months in terms of number of relapses, with absence of worsening of Expanded disability status scale (EDSS)/Timed 25 foot walk and had not had any recent hospitalizations for IVMP/TPE, with/without last known neuroimaging within the last 6 months either showing stable disease (ie no strategic or new enhancing/enlarging lesions within the brain or spinal cord) had their planned infusions deferred for 3 to 6 months till local cases settled (Table 3). Some patients were still awaiting approval for treatment funding. In others, CD 19/20 and white cell enumeration studies (30%) where available were also looked at to help guide decisions on continuing rituximab (4 patients). This was not available in all cases due to limited local testing abilities.

At our center, rituximab is given as induction therapy as a single short course 1 g 2 weeks apart or as 6 monthly courses up to 2 years followed by de-escalation to modest potency IS/DMT's or longer as maintenance treatment in NMO/NMOSD/MS (Malaysian Clinical Practice 2015; Ong et al., 2020). Alternatively, we use IVIG as acute treatment for relapses and maintenance treatment in NMO/NMOSD, MOGAD, ADEM and MS patients (Malaysian Clinical Practice 2015; Ong et al., 2020; Salzer et al., 2016; Viswanathan et al., 2015; Olyaeemanesh et al., 2016; Sutton and Visintini, 2018; Lünemann et al., 2016; Young et al., 2020; Tsantes et al., 2019). Based on modest local data and guidelines,it is given as induction monthly infusions for 3 months followed by 3 monthly infusions (Malaysian Clinical Practice 2015; Ong et al., 2020; Viswanathan et al., 2015). During this pandemic IVIG was given as bridging to pwMS unable to obtain supply/funding for first line injectables/orals, as add-on to existing IS (Azathioprine/Mycophenolate mofetil/cyclophosphamide) (Young et al., 2020; Tsantes et al., 2019) in NMO/NMOSD/MOGAD (Young et al., 2020) or for those deferring more aggressive DMT/IS 's such as rituximab (Malaysian Clinical Practice 2015; Viswanathan et al., 2015; Olyaeemanesh et al., 2016; Sutton and Visintini, 2018; Young et al., 2020; Tsantes et al., 2019) (See Table 3).

During this period a total of 33 patients were scheduled for infusions either in day care or the ward. Amongst the MS group, 7 patients with highly active relapsing disease were planned for alemtuzumab (5 new cases and 2 on maintenance treatment) of which 4 new cases deferred their infusions based on personal preference and stable disease activity. They were given bridging interferons or cyclical IVIG as alternatives. Two maintenance Alemtuzumab patients continued their 2nd year infusions as did a new case due to ongoing highly active disease (initially deferred). Majority of the pwiCNSID's on rituximab continued infusions except one who deferred it for 3 months due to stable disease and fear of COVID-19 infections. Patient's on Eculizumab, Toclizumab and cyclophosphamide continued infusions without any untoward adverse events.

ii). TPE: (Table 4):

9 patients were scheduled for urgent (4) and elective (5) TPE of

Table 3
Results of stratification of infusion DMT's/IS's according to disease activity.

Name of Infusion DMT/IS or Oral DMT/IS	Planned number of CNSID's patients/ Disease stratification(#)	Number of patients who received infusions	Number of patients who deferred by (3–6 months) infusions/oral/injectable DMT/IS	Number of patients who got alternative DMT's/IS out of those who deferred
Alemtuzumab ("A")	7 (6 relapsing MS, 1 Highly active relapsing secondary progressive MS)	3 (2 maintenance & 1 new highly active case)	4	3 given bridging interferon beta- 1a and 1 given cyclical IVIG (deferred "A" for 3–6 months)
Rituximab	8 (4 MS Highly active, 4 NMO/NMOSD	6 {Decision to treat based on relapses, MRI brain & spine,	1 deferred initially, then given as highly	Nil
4 new cases, 4 maintenance cases	(1 as induction)	EDSS and CD19,20/white cell enumeration studies (3)}	active, another 1 deferred for 3 months	
Cyclophosphamide	2 (1 MS Highly active, 1 NMOSD)	1(NMOSD)	1 (MS)	Nil
1 new, 1 maintenance case				
Eculizumab	5	4	Nil	1 (changed to rituximab d/t cost)
5 maintenance cases				
Tocilizumab	1	1	Nil	Nil
1 maintenance case				
Intravenous Immunoglobulins	10 (4 active/Highly active MS)	10	Nil	Nil
	(4 NMO/NMOSD (active/Highly active)			
	2 MOGAD			
Fingolimod	2 Highly active MS	1	1	Interferon Beta
Cladiribine	2 Highly active MS	1	1	Teriflunomide

Abbreviations:MS: Multiple sclerosis; NMO/NMOSD:Neuromyelitis optica, neuromyelitis optica spectrum disorders; DMT/IS: Disease modifying therapies/Immunosuppressants; d/t: due to;IVIG: Intravenous Immunoglobulins, EDSS: Expanded disease status scale; MRI: Magnetic resonance imaging.
Disease activity stratification #: Active/Highly active or inactive stable: Based on definition in Clinical practice guidelines on Management of Multiple Sclerosis, Version 1, 2015 (Malaysian Clinical Practice 2015).

which only 5 cases were done and the remainder 4 cases were re-scheduled in view of redeployment of TPE staff nurses to COVID-19/ SARI wards.

c. Injectables or oral DMT's/IS:

Existing pwiCNSIDs on injectables such as interferon beta 1a/1b (65) Teriflunomide(15) and Fingolimod (31, except 2)were continued on their medications as per current recommendations. We also initiated one on cladiribine and fingolimod(2 patients) towards the end of April-May due to aggressive disease without any short-term adverse events. As for patients on Azathioprine, mycophenolate mofetil and methotrexate for NMO/NMOSD, none stopped. All patients were updated during virtual and face to face visits on the need for adherence and the safety of continuing DMT's/IS with the usual preventive measures (World Health Organization 2020; Ministry of Health Malaysia 2019). Only 1 patient with spinal MS requested to stop her Fingolimod via virtual consultation as she had been relapse free for 4 years. Thus far she is relapse free. Another patient deferred Fingolimod initiation upon his own request. None of the NMO/NMOSD or MOGAD patients requested to stop their oral steroids or IS (Table 3).

d. Management of existing/new patients on DMT's/IS needing blood watches during the Covid pandemic

Blood and urine test monitoring intervals for injectable or oral DMT's/IS and infusion drugs especially those on modest or potent lymphocyte depletors used in pwiCNSIDs were lengthened or frequencies were reduced to 2 monthly (for modest to high risk rituximab, alemtuzumab,cyclophosphamide and cladiribine), 3–4 monthly (for interferons, teriflunomide, fingolimod,azathioprine,mycophenolate mofetil,methotrexate) (Coles et al., 2020; Azathioprine, 2020; Sormani, 2020; Sutton and Visintini, 2018). Where possible, patient's did testing at the nearest public or private laboratories if affordable. Results were then sent in virtually (55%)/face to face(45%) to the Neurologist/s concerned. Neuroimaging unless urgent (determined by disease activity) was deferred 6 monthly to annually.

2. Supply of disease modifying treatments

i). Continuation of medications in neuroimmunology through value added service system(VASS) provided by the pharmacy

Patients needing maintenance therapy of DMT's/IS were provided the option of collecting the medications via the **Value Added service (VAS)** provided by MOH at the pharmacy at KLGH or supply via:

1 Postal services-Fast Post
2 Drive through Pharmacies (At Public hospitals)
3 Locker 4 U (medications delivered to designated lockers)
4 Pharmacy Appointment and collection system through telephone or SMS
5 Pre-written prescriptions with pick-ups by caregivers face to face.

ii). Supply of DMT's/IS to patients at HKL. DMT's or IS supplied to patients at our center are subsidized by a number of sources ie MOH hospitals, governmental or non-governmental organizations(NGO), insurance or self pay. During this period, continued supply was paramount. 65% of patient's (MS/NMO/NMOSD:287 patients) on treatment were on maintenance therapies with oral, injectable and intravenous DMT's/IS and 35% on pulse therapies. In 80% of cases there were no shortfalls. Shortfalls were noted amongst interstate patients and NGO sources due to travel restrictions. These patients were helped with temporary supply from the nearest public hospitals. In rare cases with MS (10%), patient's had drug intervals reduced in frequency ie subcutaneous Interferon beta injected twice a week or teriflunomide 14 mg/Fingolimod 0.5 mg taken every other day till supply resumed. Similarly, in the NMO/NMOSD or MOGAD groups drugs such as azathioprine, MMF and methotrexate were more readily

Table 4
Number of patient's with relapses treated with Intravenous steroids/Intravenous Immunoglobulins/Therapeutic Plasma Exchange from 1st March 2020 till 1st May 2020 (at the height of the COVID-19 pandemic in Malaysia) and adverse effects experienced.

Disease/Drug Treatment	IV MP	IVIG	TPE (March & May 2020, April no cases)	Adverse events/Covid-19 (after IVMP/IVIG or PE)
MS	8	2	1	Nil/Nil
NMO/NMOSD	7	2	3	Herpes Zoster after IVMP/Nil
MOGAD	2	2	1	Tooth infection after IVMP/Nil
RECURRENT ADEM	2	1	1	Hepatic Encephalopathy/Nil

Abbreviations:MS: Multiple sclerosis; NMO/NMOSD:Neuromyelitis optica, neuromyelitis optica spectrum disorders; MOGAD: Myelin oligodendrocyte glycoprotein disorder; ON: ADEM:Acute disseminated encephalomyelitis; IV MP: Intravenous methyl prednisolone; IVIG: Intravenous Immunoglobulins; TPE:Therapeutic plasma exchange.

available(100%) without shortfalls and IS infusions with rituximab were continued or replaced with IVIG (Table 3).

3. Managing relapses in neuroimmunological diseases during Covid-19 pandemic

A total of 19 CNSID's patients had relapses during this period (8 NMOSD,2 MOGAD,1 recurrent ADEM and 8 MS relapses). All were treated with intravenous methyl prednisolone(IVMP) between 500 mg to 1000 mg (at day care/ward) for durations of 3 to 5 days. None of these patients within the last 3 months developed any COVID-19 infections. However other infections were noted ie Herpes Zoster ophthalmicus etc. (Table 4). Relapses of iCNSID's were stratified according to severity having ruled out pseudorelapses (Malaysian Clinical Practice 2015; Bhatia et al., 2020). Only significant relapses (19 patients) were treated namely those causing significant disability as a result of motoric, eye, brainstem or cerebellar involvement or debilitating sensory relapses disturbing activities of daily living. Most were treated as day care with rare admissions for complicated cases. Part of the work up prior to giving IV MP/IVIG/PE included blood works, cRP, urine screens and chest xrays in addition to asking for symptoms of COVID-19,ILI or SARI. On discharge, the patient gets a follow-up telephone call at two weeks and is reviewed back in the clinic at 2 months or via virtual contact with blood works (Fig. 2), Table 4.

5. Discussion

5.1. Restrategizing treatments for patients with CNS inflammatory disorders

This narrative, highlights important issues with regard to continuity of care for pwiCNSIDs during the time of COVID-19 in regions with limited resources. Here we stratified visits with proper documentation, individualized MS and NMO/NMOSD treatments based on disease activity/severity, utilized virtual visits with existing means in the absence of teleneurology services, advised on COVID prevention measures and utilized the CSQ to screen patient's for risk of Sars CoV-2 infection. Stratification of use of high risk DMT's/IS or IV steroids with post treatment social distancing/masking and alternative agents namely IVIG for relapses/maintenance treatment was achievable without severe adverse events or COVID-19 infections in the short term (Baker et al., 2020; Giovannoni et al., 2020; Brownlee et al., 2020; Sutton and Visintini, 2018).

Globally, National professional bodies (MSIF,ABN etc.) and experts on CNSIDs have issued guidelines or general comments primarily focusing on MS disease-modifying therapies (DMTs) and NMO/NMOSD/MOGAD care during the time of COVID-19 (Baker et al., 2020; Buonomo and Brescia Morra, 2020; Giovannoni et al., 2020; Brownlee et al., 2020; Giovannoni, 2020; Multiple Sclerosis International Federation 2020; Coles et al., 2020; National MS Society 2020; Guthy Jackson Charitable Foundation 2020; Abboud et al., 2020; Malaysian Clinical Practice 2015). In Asia or South East Asia no such recommendations exists as yet and our center utilized the former documents in addition to WHO, local MOH directives and local expertise for guidance with local adaptation (World Health Organization 2020; Ministry of Health Malaysia 2019). Furthermore, pathways for access to iCNSIDs centers such as the COVID-19 Safe pathway from Italy are unavailable regionally.

Giovannani G et al., Baker D et al. (for MS), Brownlee W et al., (MS and related disorders) and ABN in recent publications have stratified MS treatments into low risk (interferons, glatiramer acetate,teriflunomide,dimethyl-fumarate),modest risk (fingolimod,ocrelizumab and rituximab) and high risk therapies (cladiribine and alemtuzumab) based on the biology and effect on the immune system. The authors suggested general principles in continuing treatments in pwiCNSIDs with or without mild symptoms of COVID-19 and deferring /discontinuation in those with severe disease temporarily. Caution was advised in initiation of modest or high risk DMT's at risk of lymphopenia such as B cell depletors; cladiribine or alemtuzumab for new patients. Proper stratification of risk versus benefits was advised or to defer treatment by 3 to 6 months with use of bridging therapies (Baker et al., 2020; Giovannoni et al., 2020; Brownlee et al., 2020; Giovannoni, 2020; Montero-Escribano et al., 2020; Multiple Sclerosis International Federation 2020; Coles et al., 2020).

Careful consideration was also advised on the use of acute relapse treatment with steroids for pwiCNSIDs deferring for mild/insignificant relapses though IVIG and TPE was thought to be safer (Baker et al., 2020; Giovannoni et al., 2020; Brownlee et al., 2020; Guthy Jackson Charitable Foundation 2020). Brownlee W et al. and Abboud H et al. highlighted the importance of cautious IS continuation in patients with NMOSD prone for devastating relapses and further suggested consideration should be given to stopping DMTs/IS in pwCNSIDs who are hospitalized with severe or complicated COVID-19 infections temporarily (Baker et al., 2020; Giovannoni et al., 2020; Brownlee et al., 2020; Guthy Jackson Charitable Foundation 2020). In all cases, proper pre-screening for symptoms of COVID-19 was advised. Recent studies from our center showed benefit of alternatives like short course induction rituximab followed by IS and IVIg in patient's with NMO/NMOSd as maintenance therapies as well as modest quality

evidence showing the benefits of IVIG maintenance in pwiCNSIDs (MS, MOGAD) as bridging therapies (Malaysian Clinical Practice 2015; Ong et al., 2020; Viswanathan et al., 2015). In the majority of the pwiCNSIDs we continued DMT's or IS without interruptions or lengthened/deferred for the short term potent DMT's/IS(oral/infusions) and blood/neuroimaging surveillances with a plan for revision once the local epidemiology of COVID-19 cases reduced. Others were given bridging therapies with Interferons or IVIG or reduced intervals of interferons/teriflunomide/fingolimod in clinically stable patients temporarily as a necessity where supply issues were present though not for long-term. This was based on modest efficacy evidence from low dose interferons, Teriflunomide (7 mg) and alternate day Fingolimod studies (Malaysian Clinical Practice 2015; Longbrake et al., 2018; He et al., 2016).

However, with the unfolding COVID −19 pandemic, Guidelines for clinicians managing and treating iCNSIDs may change in the future especially with highly potent DMT's/IS. As such either vaccination when available or revised risk mitigation protocols incorporating prior testing for COVID-19 in addition to other opportunistic infections may be needed before initiation of treatment. Studies are also needed to identify the true prevalence and incidence of Covid-19 in neuroimmunological disorders as is currently underway by several groups globally including MSIF which will hopefully answer these issues. **It is important for countries within South East Asia to participate in these initiatives to identify any differences in risks, presentation and management of COVID-19.**

5.2. Covid-19/SARI and ILI cases

From our preliminary survey, we have identified IFI and SARI in our patients with NMO/NMOSD and MS but not COVID-19 as yet. Though this is reassuring we postulate this may be due to the success of social distancing, the MCO and adherence by our pwiCNSIDs or reflects the lack of testing of everyone except high risk groups. Therefore, if we do antibody screening tests for all pwiCNSIDs (including asymptomatic patients) in the future, will we know the true asymptomatic exposure rates (Gandhi et al., 2020; Ciampi et al., 2020). However, it is not feasible/cost effective to screen all pwiCNSIDs for COVID-19 yet as a pre-screening requirement or before initiating new treatments of iCNSID due to resource limitations but this may evolve in the future with better tests (Gandhi et al., 2020). Alternatively, for now we found it helpful to do the CSQ, chest imaging and stratification of patients as ILI or SARI with high risk or low risk for COVID-19 and to do COVID-19 testing in these groups alone (Gandhi et al., 2020; Ciampi et al., 2020).

Globally, intial data from an Italian MS cohort has shown the majority of patients with MS (pwMS) developing mild Covid-19 disease (96%) with severe disease/fatalities seen only in those with advanced age, advanced/progressive MS with multiple comorbidities (Sormani, 2020). So too, majority of patients on Teriflunomide, Fingolimod, ocrelizumab and recently alemtuzumab who developed COVID-19 reassurringly recovered needing only temporary stoppage of medications in severe infections or none at all (Sormani, 2020; Maghzi et al., 2020; Mat´ıas-Guiu et al., 2020; Lünemann et al., 2016; Young et al., 2020; Bhatia et al., 2020).

5.3. Virtual visits in the absence of teleneurology services

A recent article in NEJM catalyst outlined the fast pace of expansion of teleneurology in physician based outpatient specialities in the US as well as the potential benefits in terms of enabling patients to obtain care, coordinate testing and triage clinical needs without the risk of exposure to COVID-19 (Mehrotra et al., 2020). Current global guidelines/publications recommend the use of these portals to limit pwiCNSIDs exposure to Sars CoV-2 (Ciampi et al., 2020; Bonavita et al., 2020; Burke et al., 2020; Robb et al., 2019). Though such teleneurology portals are unavailable in Malaysia, with multi-modality methods of contact and delivery we were able to make use of existing portals of multimedia communication with proper documentation and legal support to sustain access for pwiCNSIDs to health care, blood watch monitorings and medications while reducing the risk of hospital visits.

6. Conclusion

This narrative quantitatively and qualitatively describes our attempt at dealing with the neuroimmunology service during this pandemic. PwiCNSIDs **are not going to take a hiatus during this pandemic** and we as physicians operating in modest to low resource countries need to be ready to deal with this pre and post Covid-19. Though uncertainties exist about the longevity of these adjustments nevertheless these methods have managed in sustaining the service to pwiCNIDS in resource challenged settings such as Malaysia in the interim period with plans needed for an exit strategy in the future.

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Data statement

All data is part of the idiopathic Central Nervous system inflammatory disorders database divided into Multiple Sclerosis, Neuromyelitis optica and its spectrum disorders and related disorders. It is annually renewed. It is a database approved by the Malaysian Medical Research Ethical committee (MREC:NMRR11–1449–10,503)

Declaration of competing interests

The author declares no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Appendix 1: Covid Screening Questionnaire: used with permission from MOH

NAMA :		UMUR :	
NO I/D :		JANTINA :	

TANDAKAN √ DI RUANG YANG BERKENAAN

BAHAGIAN A : SIMPTOM

GEJALA	YA	TIDAK	TARIKH SIMPTOM
DEMAM :			
BATUK :			
SAKIT TEKAK :			
SESAK NAFAS :			

BAHAGIAN B : SEJARAH PENDEDAHAN (14 HARI SEBELUM MEMPUNYAI SIMPTOM)

NEGARA YANG DILAWATI :	CHINA	HONG KONG	MACAU	TAIWAN	KOREA SELATAN	JEPUN
	ITALI	IRAN	JERMAN	SEPANYOL	PERANCIS	DENMARK

KONTAK RAPAT KEPADA KES POSITIF COVID-19	YA	JIKA YA ; TARIKH BERJUMPA KONTAK RAPAT :
	TIDAK	

JIKA PESAKIT MENANDA **√ 'DI KEDUA-DUA BAHAGIAN A DAN B'**, ARAHKAN PESAKIT UNTUK MENJALANI SARINGAN DI CMSA

NAMA :		UMUR :	
NO I/D :		JANTINA :	

TANDAKAN √ DI RUANG YANG BERKENAAN

BAHAGIAN A : SIMPTOM

GEJALA	YA	TIDAK	TARIKH SIMPTOM
DEMAM :			
BATUK :			
SAKIT TEKAK :			
SESAK NAFAS :			

BAHAGIAN B : SEJARAH PENDEDAHAN (14 HARI SEBELUM MEMPUNYAI SIMPTOM)

NEGARA YANG DILAWATI :	CHINA	HONG KONG	MACAU	TAIWAN	KOREA SELATAN	JEPUN
	ITALI	IRAN	JERMAN	SEPANYOL	PERANCIS	DENMARK

KONTAK RAPAT KEPADA KES POSITIF COVID-19	YA	JIKA YA ; TARIKH BERJUMPA KONTAK RAPAT :
	TIDAK	

JIKA PESAKIT MENANDA **√ 'DI KEDUA-DUA BAHAGIAN A DAN B'**, ARAHKAN PESAKIT UNTUK MENJALANI SARINGAN DI CMSA

Appendix 2

Disease Activity Stratification based on Clinical Practice Guidelines on the Management of Multiple Sclerosis, Version I, 2015.

Active MS refers to patients who have had two or more attacks in the last two years.

Highly active MS /non-responders are individuals who have failed to respond to full and adequate course (one year of treatment) of DMT and have these features

≥1relapse in the previous year while on treatment or
unchanged increased ongoing severe relapses compared with the previous year and
≥T2 lesions on brain MRI or
≥1Gd-enhancing lesions on brain MRI

Rapidly evolving aggressive MS are those with:

- ≥2 disabling relapses in the last one year and ≥1Gd-enhancing lesions on brain MRI or a significant increase in T2 lesion load compared to previous recent MRI scan or increase in two points in the EDSS in the past 12 months. This can occur prior to or after initiation of first-line therapy.

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