State of the Art and Future Challenges in Multiple Sclerosis Research and Medical Management: An Insight into the 5th International Porto Congress of Multiple Sclerosis

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REVIEW

State of the Art and Future Challenges in Multiple Sclerosis Research and Medical Management: An Insight into the 5th International Porto Congress of Multiple Sclerosis

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ABSTRACT

The 5th International Porto Congress of Multiple Sclerosis took place between the 14th and 16th of February 2019 in Porto, Portugal. Its intensive programme covered a wide-range of themes—including many of the hot topics, challenges, pitfalls and yet unmet needs in the field of multiple sclerosis (MS)—led by a number of well-acknowledged world experts. This meeting review summarizes the talks that took place during the congress, which focussed on issues in MS as diverse as the development and challenges of progressive MS, epidemiology, differential diagnosis, medical management, molecular research and imaging tools.

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Key Summary Points

Multiple sclerosis (MS) is an immune-driven neurological disease with a conspicuously heterogeneous distribution that affects approximately 2.3 million people worldwide.

The 5th International Porto Congress of Multiple Sclerosis took place on February 2019 in the city of Porto, Portugal, and brought together a number of world-known experts in the field who shared their latest discoveries and discussed targets in MS healthcare that have yet to be met.

This review summarizes the main talks given during the congress, including the state-of-the-art description, ground-breaking projects and promising results.

Discussed topics are as diverse as the epidemiology of MS in different continents, the development of and pitfalls in progressive MS, differential diagnosis and related diseases, medical management, cognitive impairment and its consequences, pregnancy and family planning and advances in molecular research and imaging techniques.

INTRODUCTION

Multiple sclerosis (MS) is an immune-driven neurological disease that has a profound impact on patients' quality of life (QOL). MS affects approximately 2.3 million people worldwide, and its prevalence is remarkably heterogeneous, varying from 50 to 300 patients per 100 000 inhabitants [1]. Most patients are diagnosed during early adult life, and women have a markedly higher incidence. Overall, there is evidence for MS onset being triggered by environmental factors in genetically predisposed individuals, such as low vitamin D levels, cigarette smoking and obesity in early life [1]. Approximately 85–95% of the patients present a relapsing–remitting course (RRMS),

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characterized by relapsing phases intertwined with periods of neurological stability [2, 3]. However, MS can also assume a progressive course, characterized by a steadily increasing neurological decline, either from the onset (primary progressive MS [PPMS]), or within 15–25 years of RRMS diagnosis (secondary progressive MS [SPMS]) [2, 3]. The MS diagnosis remains challenging and relies on the integration of clinical, laboratory and imaging findings, with the McDonald criteria being used by most neurologists [2].

The 5th International Porto Congress of Multiple Sclerosis, held in Porto (Portugal) in February 2019, had an ambitious programme and covered many of the hot topics, challenges and unmet needs in the MS field. In front of an audience composed of researchers, clinicians and patients, several internationally acknowledged specialists presented state-of-the-art, ground-breaking projects and promising results. The aim of this article is to provide an overview of the main issues discussed in the meeting and is based on previously conducted studies by the authors.

PROGRESSIVE MS: DEVELOPMENTS AND PITFALLS

Giancarlo Comi (San Raffaele Hospital, Italy) gave the meeting's magistral conference, in which he discussed the main advances in progressive MS and the as yet unmet needs of patients suffering from this clinical form of MS. Immunopathological studies have revealed a large overlap of lesion load between relapsing and progressive MS courses, with some qualitative differences in the distribution of lesion subtypes [4–6]. In progressive MS, most of the lesions are inactive, with only a small proportion of active lesions in the late phase and a predominance of chronically active, slowly expanding lesions, i.e. the smoldering lesions characterized by a hypocellular demyelinated core with a variable axonal degeneration and hypercellular edge of activated microglia and reactive astrocytes [4, 5]. Subpial cortical lesions, in contrast, are abundant in the progressive forms of the disease (either PPMS or SPMS), but are rarely seen among early RRMS [3–5, 7].

Moving from the disease's pathology to its clinical phenotype, Comi underscored the recent changes made to the classification of progressive MS: whereas the focus was traditionally placed on the presentation of the progressive phenotype (primary vs. secondary), the new classification now focusses on disease activity and disability evolution [8]. In fact, and while the terms PPMS and SPMS are still used, two new concepts were introduced into this classification: disease activity (based on the presence of relapses and/or active lesions, such as new T2 magnetic resonance imaging (MRI) lesions and/or gadolinium-enhancing lesions) and disability evolution (i.e. a gradual worsening of disability in a relapse-independent fashion or stable disability) [8]. For Comi, this classification provides a more accurate description of the true nature of progressive forms of MS because the presence/absence of disease activity has clear treatment implications and there is a remarkable variation in the speed of disability progression among different patients. The identification of the key factors that drive this variability will be a critical step for a better understanding of the disease and, ultimately, for improving patients' care.

Another aspect addressed by Comi was the need for better diagnostic and monitoring tools. In this context, he highlighted the recent advances in MRI technology, as well as the importance of measuring brain and spinal cord atrophy and of complementing the traditional assessments with functional measures, such as evoked potentials and optical coherence tomography (OCT) (some of these aspects were discussed in more detail by other speakers and are described in following sections of this article). He also underscored the role of body fluid biomarkers, highlighting the particularly attractive findings made in the context of neurofilaments [9].

Finally, Comi mentioned the lack of therapeutic alternatives for progressive MS: in fact, despite the notable growth of the RRMS therapeutic armamentarium, few disease-modifying drugs (DMDs) have shown positive results in patients with progressive MS. Those which

did—siponimod and ocrelizumab—mostly target inflammatory elements of the disease cascade [10, 11]. Nonetheless, Comi considered that an improvement of care in progressive MS will require looking beyond the inflammatory pathway, extending research towards neuroprotective and repair-promoting strategies.

EPIDEMIOLOGY AND RECENT ADVANCES

The geographical distribution of MS is one of the most striking aspects of this disease's epidemiology: with a number of exceptions, its prevalence seems to increase with increasing distance from the equator [1]. However, there are also some remarkable geographical disparities in the availability of neurologists and diagnostic tools, as well as in MS severity and progression. To achieve an integrated insight into these issues, specialists from all over the world were invited to discuss the main aspects of MS epidemiology in their respective regions and the main concerns of neurologists, as well as some of the latest developments in research.

Ayşe Altintaş (Koç University, Turkey) gave a general overview of MS prevalence and state of care in Turkey. Interestingly, although Turkey has long been considered to be a low-incidence country—the 2013 MS International Foundation report estimates its prevalence to be in the range 20.01–60 cases per 100,000 inhabitants [12]—recently published articles have suggested otherwise. For example, Börü et al. have assessed the prevalence of MS among the inhabitants of three Turkish cities, two of which are located in the Black Sea region (Artvin and Ordu) and one located in the Mediterranean region (Gazipaşa) [13]. These cities, which were chosen due to their location and low immigration rate, were reported to have an MS prevalence of 18.6, 55.5 and 52.0 cases per 100,000 inhabitants, respectively [13]. Another study, which focussed on the prevalence of MS in the Middle Black Sea Region of Turkey, reported 43.2 cases per 100,000 inhabitants [14]. Other studies have described an MS prevalence of 41.1 cases per 100,000 inhabitants of Geyve (a rural area in the Black Sea Region) and of 101.4 cases per 100,000 inhabitants of the district of Maltepe (Istanbul) [15, 16]. Consequently, it is now believed that the true prevalence of MS in Turkey should be within these latter limits. On the other hand, with respect to specialist care and resources, Turkey seems to be in a fairly good position. According to Altintaş, there are over 2000 neurologists in the country, of whom 118 are currently dedicated to studying and managing MS and other demyelinating diseases. The McDonald criteria are usually applied for diagnosis, and the number of available MRI scanners exceeds 800. Most therapies and DMDs are available and easily accessible to patients (through the public health system and/or private health insurances), and treatment strategies follow the international guidelines with minor local adjustments.

Najib Kissani (University Hospital Mohamed VI, Morocco) addressed the prevalence and the progression of MS in Africa. African countries can be divided into three different zones according to their MS prevalence: the north, comprising countries such as Morocco, Tunisia, Egypt and Algeria, which is described as a mild to high prevalence area (30–80 cases per 100,000 inhabitants); the south, namely South Africa, which is a mild prevalence area (10–30 cases per 100,000 inhabitants); and the rest of sub-Saharan Africa, which is a very low prevalence area (< 5 cases per 100,000 inhabitnts). This scenario, however, is likely driven by a high rate of underdiagnosis, stemming from the worrisome lack of resources and specialists in many sub-Saharan countries. Interestingly, and despite the low prevalence, MS cases in Africa seem to be characterized by a higher severity and a faster progression rate (when compared to the rest of the world). Indeed, in one Moroccan cohort including 380 patients with MS (372 of whom were Caucasian), the time to progression to an Expanded Disability Status Score (EDSS) of 6 was only 10 years. Importantly, this higher severity seems to be independent of the delay in diagnosis (which was 2.5 years in the Moroccan series). Other studies have reported similar trends in severity [17, 18], and Sidhom et al. highlighted that the higher severity in North Africans is independent of patient location (within or outside Africa) [19], which suggests a

genetically driven explanation. Kissani also shared the results of a questionnaire he sent to his African colleagues—in an attempt to understand the true prevalence of MS in African countries—highlighting not only the low number of MS cases reported, but also the comparably high incidence of neuromyelitis optica (NMO) and the problematic lack of resources and therapies (in most cases, the only treatments available were corticosteroids). Kissani finished his presentation by underpinning the necessity of more studies (supported by robust collaborations) to understand—and tackle—the MS low prevalence/high severity dichotomy in Africa.

Fu-Dong Shi (Tianjin Medical University General Hospital, China) discussed the MS landscape in China, focussing on the latest advances in the diagnosis and treatment of both MS and NMO Spectrum Disorder (NMOSD). The prevalence of MS in China is unknown; however, when data from Hong Kong and the neighbouring countries of Japan and Korea are taken into consideration, MS prevalence in China is estimated to be between 5 and 10 cases per 100,000 inhabitants, while the ratio of MS:NMOSD seems to be 2:1. Regarding treatments, while not all currently used drugs are available in China, the scenario is quickly changing, and drugs such as fingolimod, dimethyl fumarate and dalfampridine are in the pipeline for a quick approval. According to Shi, one of the greatest diagnostic dilemmas concerning MS in China is the prediction of conversion after a clinical isolated syndrome (CIS) in the presence of changes in white matter. In this respect, Shi presented BioMind, a diagnostic support system that uses deep learning technology to analyse MRI and computed tomography images, increasing the accuracy of diagnosis by 20% (when compared to the human eye). Other ongoing projects mentioned by Shi included the utilization of OCT to discern between MS and NMOSD [20]; the identification of immune markers able to predict CIS conversion; the responsiveness to a reduced dose of rituximab in NMO patients [21]; the utilization of bortezomib in NMOSD patients [22]; and the efficacy and safety of tocilizumab in NMOSD patients.

Regina Papais-Alvarenga (Federal University of the State of Rio de Janeiro, Brazil) discussed the prevalence and risk factors for MS in Latin America (LA), a region characterized by an heterogeneous and genetically complex population. Although LA comprises 20 countries, most MS studies published to date have been conducted in only six of these—Brazil, Argentina, Mexico, Colombia, Chile and Cuba. Overall, LA seems to be an area of low to medium MS prevalence, with rates varying from 0.83 to 21.5 cases per 100,000 inhabitants [23]. More specifically, in Brazil, a systematic review by Pereira et al. reported MS prevalence rates varying between 1.36 (in the northeastern region) and 27.2 (in the southern region) per 100,000 inhabitants [24]. This distribution is likely driven by genetic factors, although environmental risk factors may also play a role in the dynamics of MS prevalence [25, 26]. Familial MS cases seem to be rare in the countries of LA, with values ranging from 3.3% (in Mexico) to 10.5% (in Buenos Aires). However, the relative frequency of NMO in NMO + RRMS cases in LA is higher than that reported for Europe and Australia: in fact, a multicentre study involving 1917 patients revealed NMO relative frequencies ranging from 2.1% (in Argentina) to 43.3% (Venezuela) [27]. This variation was related to ethnicity, with higher frequencies found among non-white populations, a finding which confirms results from previous studies.

Jan Hillert (Karolinska Institutet, Sweden) presented the Swedish MS Registry and discussed the implications of registry data for research. The Swedish MS Registry was started on 2000 and became web-based in 2004: it currently includes data pertaining to 17,000 patients (of the 20,500 MS patients in Sweden) from all 64 neurology units that exist across the country [28]. At the start of a consultation, by opening a patient's registry, the physician has immediate access to a set of data providing valuable information, including a temporal line representing patient progression [according to the EDSS and MS Severity Score (MSSS)], current and past DMDs and other treatments, MRI results, MS attacks and functional tests, among other information [28]. Importantly, the long-term clinical data in the Swedish MS Registry

can be used to improve our understanding of MS. In this context, Hillert provided several examples in which the Swedish MS Registry was used as the basis of pertinent investigations in the field. Among these was the identification of MS progression trends in Sweden (namely, a tendency towards a slower progression and a decreased risk of reaching EDSS 3, 4 and 6 [29]; a decrease in MS costs [30]; and a lower incidence in primary progressive MS [31]). Moreover, registry data have also been used to identify risk factors and predict secondary progressive MS [32] and to identify socioeconomic consequences of disease progression [33]. Finally, the Swedish MS Registry was useful to show that the risk of MS progression can be ameliorated by the utilization of DMDs [34], as well as by an early introduction of these therapies [35, 36], and that smoking cessation can slow down disease progression [37]. Hillert also mentioned that an unification of several national Swedish MS registries has recently taken place, allowing the integration of data and making available larger cohorts for investigational studies (three of which are currently ongoing) and for post-approval safety studies (also being launched).

MS-RELATED DISEASES AND DIFFERENTIAL DIAGNOSIS

Despite the remarkable advances achieved in the fields of imaging, pathology and immunology in recent years, MS diagnosis remains challenging [38]. One important—and many times puzzling—step is to differentiate MS from other neuroinflammatory disorders, namely those of a demyelinating nature. Two renowned neurologists—Francesc Graus and Jacqueline Palace—were invited to the 5th International Porto Congress of Multiple Sclerosis to discuss the diagnosis, outcomes and therapeutic options of two neuroinflammatory disorders other than MS.

Francesc Graus (University of Barcelona, Barcelona) discussed the physiopathology of autoimmune encephalitis, highlighting the need to loosen the boundaries between the fields of autoimmunity and neurodegeneration. Starting with a retrospective overview of the topic, Graus mentioned that the relationship between limbic encephalitis and cancer has been known for over 50 years, with Corsellis et al. first describing patients (n = 3) with this form of encephalitis and small-cell lung cancer in 1968 [39]. The subsequent identification of antibodies reacting with both intracellular brain and tumour antigens suggested that limbic encephalitis was actually immune mediated, although by then this immune attack was considered to be mainly driven by T-cell infiltrates [40]. Finally, the identification of different antibodies reacting against intracellular and neuronal surface antigens led to the current belief that these antibodies are, indeed, the main pathogenic agents, a finding which supports the development of different forms of encephalitis. Importantly, serological tests should not be mandatory when considering the diagnosis of autoimmune encephalitis and starting the treatment. An initial diagnosis of autoimmune encephalitis can be made on the basis of the patient's clinical symptoms and using conventional tests, as described in Graus et al. [41]. Still, the identification of which antibodies are present is important to confirm the diagnosis and determine patient prognosis and the likelihood of cancer development. Anti-LGI1 is one of the most common antibodies related to encephalitis: patients with this form of the disease are mostly men (60–70%) and between 50 and 70 years of age and, in most cases (87%), have the limbic phenotype. Importantly, patients with anti-LGI1 encephalitis develop faciobrachial dystonic seizures before encephalitis itself and can therefore be misdiagnosed. Anti-NMDA receptor (NMDAR)-associated encephalitis, which mainly affects young women and children, is another important form of the disease. Interestingly, patients with this form of encephalitis typically present with psychiatric symptoms, with the neurological signs following shortly thereafter. It should also be taken into consideration that autoimmune encephalitis, and namely anti-NMDAR encephalitis, can be triggered by herpes simplex encephalitis [42]. The best therapy for these diseases is still under discussion: the development of clinical trials is hindered by the low number of cases and,

therefore, all knowledge gathered to date is of a retrospective nature. Steroids are the most common first-line therapy for anti-LGI1 encephalitis (with rituximab as the most common second-line therapy), and most patients have positive outcomes. Still, around 25% of patients become fully dependent or acquire severe cognitive deficits [43]. The scenario is similar with the anti-NMDAR forms of encephalitis, with approximately 80% of patients showing a good outcome after immunotherapy or tumour removal [44]. Importantly, patients who switched therapy after an unsuccessful first-line treatment had better outcomes that those who did not switch, suggesting the importance of considering alternative treatments in difficult cases [44].

Jacqueline Palace (University of Oxford, UK) gave an overview of myelin oligodendrocyte glycoprotein (MOG) antibody disease, focussing on its distinctive features and diagnosis criteria. MOG is a structural glycoprotein found at the surface of myelin in the central nervous system (CNS). Anti-MOG disease, which is distinct from MS and mutually exclusive from anti-aquaporin 4 (AQP4) disease, can be classified into multiple clinical phenotypes, including acute disseminated encephalomyelitis, transverse myelitis, optical neuritis (ON) and cortical disease. Two large cohorts of anti-MOG patients have been recently characterized and shown to have a remarkably similar distribution of features, namely the female:male ratio (57 and 49% females), the incidence of relapsing disease (46 and 42%), the percentage of Caucasian patients (85.8 and 92.9%) and the predominance of ON (unilateral or bilateral) as the main disease manifestation [45, 46]. The results of these studies are utterly important to our understanding of the epidemiology of anti-MOG disease, and are referred to several times by Palace, as seen below; however, it should be kept in mind that both studies were carried out in "Caucasian" countries and, therefore, the possibility of having different trends in countries where the percentage of Caucasian people is different from those noted above cannot be excluded. Regarding diagnosis, Palace highlighted the Matthews criteria of "at least one lesion adjacent to the body of the lateral ventricle and in the inferior temporal lobe; or the presence of a subcortical U-fiber lesion; or a Dawson's finger-type lesion" for distinguishing patients with MS from those with NMOSD with a sensitivity of 92%, specificity of 96%, 98% positive predictive value and 86% negative predictive value [47]. These imaging findings may, however, be similar in anti-MOG disease. With respect to the course of disease, both cohorts mentioned above were again very similar, with 41 and 43% of patients relapsing within 24 months [45, 46]. Interestingly, most of these patients relapsed in a rather early phase of the disease. Additionally, no relapses were reported for those patients who became anti-MOG negative (28% of the initial patients, 88% of whom stayed negative until the end of the follow-up), and therapy for periods longer than 3 months seemed to reduce the risk of relapse [45]. Disability seemed to affect patients with anti-AQP4 disease more severely than those with anti-MOG disease, irrespective of the severity of the relapses [45, 46]. Still, a considerable number of anti-MOG patients developed sphincter-related disability, namely permanent bladder dysfunction (28%), bowel dysfunction (20%) and erectile dysfunction (21% of male patients) [45]. The best treatment for patients with anti-MOG disease is still under discussion: a possible algorithm, recently published, includes testing for anti-MOG antibodies after an initial 6-month course of corticosteroids and considers extra courses for patients who test positive; patients with late relapses are candidates for long-term immunosuppression [48]. The best immunosuppressive drug for these patients, however, is yet to be identified: in fact, two recent studies that examined the relapse rate of patients with anti-MOG disease on different treatments yielded distinct values for similar therapies [49, 50].

MEDICAL MANAGEMENT AND PATIENTS' DAILY LIFE ACTIVITIES

The impact of MS and other demyelinating diseases, such as NMOSD, on patients' QOL is both devastating and complex. The importance

of setting thresholds to define an early and effective medical intervention was the theme of one of the talks discussing this topic; others were focused on the cognitive impairment associated to MS, and on family planning and pregnancy in patients with MS and NMOSD.

Jeremy Hobart (University of Plymouth, UK) presented the MS Brain Health Initiative (https://www.msbrainhealth.org/), which is based on the importance of a time-efficient approach to the different stages of the disease, with the ultimate aim to improve MS care at an international level. Importantly, whereas the dysfunction generated by other diseases can be ameliorated or cured with organ transplantation, MS patients have no such option: the accumulated damage to the CNS is mostly irreversible. As such, a time-wise care strategy able to prevent the accumulation of such damage would represent an immense benefit to MS patients. In this context, the "Brain Health—Time Matters in Multiple Sclerosis" report details a series of explicit recommendations pertaining to the urgency of care at every stage of MS [51]. Following the publication of this report, and in an attempt to turn these recommendations into tools that can be used in daily clinical practice, a group of neurologists carried out a Delphi methodology-based study to define the optimal time frames that should be met in different stages of the disease [52]. These time frames were divided into 'core', 'achievable' and 'aspirational', reflecting minimum, good and high standards of MS care, respectively. For example, the time frame within which a diagnostic workup should be completed after referral to a neurologist is 2 months (core), 4 weeks (achievable) or 7 days (aspirational) [52]. Clinical teams are thus provided with international standards against which they can compare their own performance, thereby enabling them to identify their own strengths and weaknesses, and to focus on areas that need improvement. To further facilitate this, quality improvement tools—based both on physicians' and patients' reports—are being developed and tested (pilot phase).

Dawn Langdon (Royal Holloway, University of London, UK) discussed the importance of cognitive impairment in MS and its impact on patients' QOL. Cognitive deficits are common among MS patients and are known to interfere in different life domains [53, 54], with perhaps one of the most important being employment status [55, 56]. Moreover, cognitive impairment also affects the patient–doctor relationship and the shared process of therapeutic decision-making, as recent therapies and DMDs often carry with them an intricate network of risks and benefits that is notoriously hard to perceive. Interestingly, cognition is an important predictor of neurological outcomes and morbidity/psychosocial risks among MS patients. In terms of neurological outcomes, cognitive impairment is known to be related with the risk of conversion to MS after CIS [57], while cognitive deficits assessed immediately after diagnosis can predict the degree of disability and disease progression several years later [58, 59]. Regarding morbidity risks, cognition is known to be related with medication adherence [60], decision-making ability and speed [61, 62], symptom management [63], fear of falling and actual falls [64–71] and driving safety [72–75]. Finally, with respect to psychosocial risks, cognition has been reported as being linked to employment and working status [76], psychiatric disturbances and associated co-morbidities [77, 78], financial abilities [79, 80], participation in domestic, leisure and outdoor activities [81–85], social cognition and emotional awareness [86, 87] and caregivers' QOL [88, 89]. Given all of the above, the importance of neuropsychological assessment in MS patients is indisputable. However, Langdon highlighted that cognition self-report is often unreliable, being confounded by a number of different factors (such as depression, anxiety, fatigue, conscientiousness, perceived stress and self-efficacy) [90–93]. In this context, a committee of experts has analysed and recommended a set of tools—named the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS)—that aims to allow a fast cognitive assessment of MS patients in small centres (which may lack neuropsychological experts) at an international level [94].

Maria Isabel Leite (University of Oxford, UK) discussed the implications of pregnancy in patients with NMOSD, focussing particularly on

those with anti-AQP4 antibody disease. Pregnancy is a matter that should be taken into account because most NMOSD patients are female and of child-bearing age: in fact, according to Kim et al., 84–90% of NMOSD patients are female, and the average age at onset varies from 33 to 43 (being slightly lower for Asian and African-American/African-European patients) [95]. Leite divided her presentation into two main topics, with the first focussing on the effects of pregnancy on NMOSD disease activity, and the second focussing on the influence of NMOSD on pregnancy outcomes and foetal development. With respect to the former, several retrospective studies have shown that the relapse rate may increase slightly during the third trimester of pregnancy (although in a non-significant manner) and is generally higher in the 3- to 6-month post-partum period [96–98]. Moreover, Simizu et al. reported that suboptimal immunosuppression seems to increase the risk of pregnancy-related relapses [99]. Regarding the impact of NMOSD on pregnancy outcomes, the studies available to date suggest an increased risk of miscarriage that seems to be independent of maternal age and miscarriage history (at least for pregnancies initiated after or up to 3 years before NMOSD onset) [100]. Additionally, patients with NMOSD have also an increased risk of preeclampsia, which is apparently independent of NMOSD onset but instead related with the presence of other autoimmune disorders [100]. On the other hand, and with the exception of a few reports on pre-term births without major complications, there are very few reports of complications in children born from NMOSD-afflicted mothers. Leite also highlighted that, although there are no studies on the safety of drugs used during pregnancy in NMOSD patients, one can extrapolate from what is known in other diseases that azathioprine, cyclosporine, tacrolimus, prednisolone, intravenous immunoglobulin and plasma exchange are safe therapeutic options. Conversely, methotrexate, mycophenolate and rituximab should be used with extreme caution. Overall, in Leite's opinion, NMOSD should not be considered to be a contraindication for pregnancy, but rather patients should be thoroughly informed and closely monitored. Moreover, the choice of an adequate and effective treatment is a crucial step towards a positive outcome.

Elisabeth G. Celius (Oslo University Hospital, Norway) also discussed pregnancy and family planning, but with a focus on MS patients instead of patients with NMOSD, highlighting the increasing rate of pregnancy among MS patients in recent years [101]. Interestingly, MS does not seem to impact fertility, although it might be associated with sexual dysfunction. However, pregnancy itself causes a number of major immune changes, one of which is an increased immune tolerance. The clinical implications of this increased immune tolerance on the disease course were described in 1998 by Confavreux et al. [102] and confirmed 20 years later by Bsteh et al. [103]. As in NMOSD, it would appear that the rate of MS relapses decreases during pregnancy and increases in the post-partum period [102, 103]. That the same pattern was observed in cohorts separated by 20 years shows that the availability of modern treatments has had little impact on these pregnancy-related variation in relapse rate. As shown in the MSBase registry, the number of pregnancies initiated while on DMDs has increased over the last 12 years. The median time of DMD exposure is 30 days, suggesting that most women interrupt treatment when pregnancy is confirmed [104]. Interrupting treatment because of a planned or confirmed pregnancy carries an increased risk of rebound of disease activity, which is particularly relevant when therapy with fingolimod and natalizumab is interupted. In addition, some of the more commonly prescribed hormonal treatments meant to increase fertility in women who are trying to conceive might trigger disease activity. In contrast, glatiramer acetate may now be continued until pregnancy is established, and interferons also seem to be safe. Interferons and glatiramer acetate may be appropriate choices for women with mild to moderately active disease, whereas immune reconstitution therapy, using alemtuzumab or cladribine, should be considered for women with high disease activity before conception. Regarding alemtuzumab, a preliminary study reported by Celius et al. at the 34th Congress of

the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS 2018) has shown some promising results, particularly in terms of the absence of disease activity during pregnancy and post-partum in women with pre-treatment high disease activity [105]. Exclusive breastfeeding might offer some protection against MS relapses, although the reports published to date on this subject are conflicting [106, 107]. While none of the drugs are approved for use during breastfeeding, interferons, glatiramer acetate and alemtuzumab seem to be safe. Overall, future pregnancies should be taken into consideration when initiating therapy in women of childbearing age, and women should be informed of the possible risks related to a pregnancy that are associated with each of the different therapies available and the need for contraception. After giving birth, breastfeeding should be encouraged, and an MRI should be performed 4–6 weeks post-partum to assess disease activity. In the absence of disease activity, patients may consider continuing breastfeeding, but this decision should be re-evaluated after 3–4 months. Conversely, the detection of disease activity requires treatment re-initiation and usually the interruption of breastfeeding.

BASIC AND APPLIED MOLECULAR RESEARCH

Molecular research is a key field of MS investigation. As it would be impossible to discuss the multitude of interesting projects currently exploring MS-related molecular issues, two aspects were chosen to be presented at the 5th International Congress: the role of Epstein–Barr virus (EBV) infection in MS development, and the importance of identifying biomarkers and their potential in MS diagnosis and monitoring.

Gulfaraz Khan (United Arab Emirates University, UAE) dedicated his talk to the discussion of the role of EBV infection in MS immunopathology. EBV is an ubiquitous double-stranded DNA virus known to have tumourigenic properties. Its detection has been improved by a very specific and sensitive in situ hybridization technique developed by Khan and colleagues, which is based on the recognition of two small RNAs—EBER1 and EBER2 (EBV-encoded RNA 1 and 2)—that are expressed in all forms of infection known to date [108–110]. The association between EBV infection and MS has been studied for a long time, and numerous studies, such as those of Cepok et al. [111], Haahr et al. [112] and Ponsonby et al. [113], have provided indirect evidence suggesting the existence of a relationship. In fact, individuals with EBV immunoglobulins are at an increased risk of developing MS, and virtually all (99.5%) patients with MS are EBV seropositive. Moreover, the levels of anti-EBV antibodies and specific T cells are higher in MS patients when compared to controls both before and after disease onset. The first direct evidence of the EBV–MS link came from the study of Serafini et al., who detected EBV infection in brain-infiltrating B cells and plasma cells in 21 of 22 patients with MS [114]. Interestingly, at least three studies published afterwards found no evidence of such a link [115–117], which has been suggested to be a consequence of technical issues and different sampling procedures [118]. Khan's group has recently examined 1055 samples extracted from MS and non-MS patients and shown that EBV is present in 91 of 101 (90%) MS patients, but in only five of 21 (24%) patients with other neurological conditions [119]. Moreover, none of the samples were positive for other common herpesviruses [HSV-1 (Herpes simplex virus 1), CMV [Cytomegalovirus], HHV-6 [Human Herpesvirus 6]) [119]. Interestingly, the virus was transcriptionally active in only a few of the cells, being latent in the majority of them, which may be a mechanism by which it escapes immune surveillance [119, 120]. Another interesting finding made by this group was that the virus was not only present in B cells, as expected, but also in astrocytes and microglia [119]. Khan and collaborators are currently working with an animal model of EBV infection [121], and the promising results from this study will certainly contribute to a better understanding of the impact of EBV in MS immunopathology.

Inês Mendes Pinto (International Iberian Nanotechnology Laboratory, Portugal) discussed the pertinence of using biosensors in

neuroimmunological diseases and presented a device, designed and fabricated in her laboratory, that is able to detect different MS biomarkers. A biosensor is a device conceptually composed of a sensing module that is able to selectively recognize a given biomarker (i.e. anything from nucleic acids to entire cells) and a transducing module that translates the recognition reaction into a measurable signal. Ideally, a biosensor should be highly specific and sensitive, have minimal requirements in terms of sample volume and technical expertise and be efficient in terms of detection limits and time [122]. In the context of neuroimmunology, and particularly in the case of MS, there is a high demand for new diagnostic methods: the conventional platforms are usually ELISA (enzyme-linked immunosorbent assay)-based, restricted to central laboratories (as they require technical expertise), time-consuming (around 24 h from sampling to output reading) and costly. Other limitations include the requirement of large samples (50 μL) and the impossibility to detect and monitor different biomarkers simultaneously (i.e., multiplex). In this context, Mendes Pinto's team has developed a portable biosensor that overcomes most of these limitations. This device is an electrochemical-based system able to detect different MS biomarkers using 1 μL of body fluid (either cerebrospinal fluid, blood serum, tears or others) in less than 10 min and without requiring technical expertise. Specificity of the biomarkers is ensured by the chemical irreversible immobilization system used to cross-link the antibodies to the chip. Sensitivity depends on the biomarker(s) being detected, but is generally higher than that obtained with conventional tests (e.g. those for the detection of tumour necrosis factor α is around 40-fold more sensitive than the ELISA-based assays) [123]. Moreover, this biosensor can be integrated into a reader and connected to a computer or to a smartphone, from which the results can be directly read. All of the above characteristics make this chip a convenient and user-friendly bedside diagnosis and monitoring tool. In terms of cost-efficiency, this device can be produced in batches, which lowers its production cost. Overall, this biosensor—which is currently in its clinical validation stage—is a promising tool to diagnose and monitor MS patients in a rapid, cheap, time-efficient and minimally invasive fashion.

ADVANCES IN MRI AND OTHER IMAGING TECHNIQUES

Magnetic resonance imaging remains a pivotal tool in MS diagnosis and monitoring. Importantly, advances in this and other imaging techniques are improving the diagnostic ability and monitoring capacity in MS medical care. Issues discussed in this section included MRI itself, other complementary approaches and the value of applying artificial intelligence to three-dimensional (3D) image analysis and automated segmentation.

Claudia Chien, who represented the Dr Friedemann Paul laboratory (Charité-Universitätsmedizin, Germany), presented the latest advances in imaging tools for application in neuroimmunological disorders, namely those related to MRI and OCT. Regarding MRI techniques, analysis of the central vein sign represents an important development: the presence of more than 50% perivenular lesions in the brain enables MS to be distinguished from other inflammatory vasculopathies with 100% diagnostic accuracy [124]. Another major improvement to the field may be the utilization of cortical thickness atlases coupled with the mapping of myelin content [125, 126], as this approach may facilitate the analysis of the typical cortical and juxtacortical lesions in MS, which are often difficult to visualize using standard MRI. The analysis of functional visual networks by resting-state functional MRI has also brought some interesting results: the presence of ON was associated with a stronger connectivity in the visual network of patients with NMOSD or those who had suffered a CIS [127, 128]. Finally, the improvement of automated techniques for the assessment of spinal cord atrophy, as well as the inclusion of this assessment into the routine monitoring of patients with MS and NMOSD, has now been pinpointed as an important research area for the future [129]. In this context, Gros et al. have

recently published a method to segment spinal cord (and intramedullary) MS lesions on a variety of MRI sequences [130]. There have also been some advances in OCT recently: this high-resolution imaging technique enables thickness analysis of individual retinal layers, two of which have proven to be particularly important in the context of MS—the retinal nerve fibre layer (RNFL) and the ganglion cell/inner plexiform layer (GCIPL). In fact, in one study, the most conspicuous differences between the eyes of MS and control patients were the peripapillary RNFL and the macular GCIPL [131]. Zimmermann et al. have also demonstrated that the thickness of the GCIPL may inform on future disease activity and risk assessment of conversion to MS in CIS patients [132]. As for NMOSD research, OCT-based studies have shown that GCIPL loss occurs independently of ON attacks in AQP4-positive patients [133] and that the presence of prior ON can be assessed with a relatively high sensitivity using thresholds of 6 and 3 μm differences in RNFL and GCIPL thickness, respectively [134]. Overall, Chien considered that multi-modal imaging is the future, with the integration of different techniques allowing for a more accurate diagnosis and monitoring of neuroinflammatory diseases.

Darin Okuda (UT Southwestern Medical Center, USA) argued on the possibilities offered by artificial intelligence in the field of medical imaging, focusing on the potential of automated 3D analysis of white matter lesions in MS. MRI, by itself, has revolutionized the diagnosis and understanding of MS pathology. Moreover, it can inform on disease progression risks: the number of lesions after an isolated attack is known to be related with the risk of conversion to MS, whereas the temporal profile by which lesions accumulate over the initial years of the disease is helpful in predicting the risk of secondary progression later on. However, neurologists are often confronted with clinico-radiological paradoxes, i.e. patients whose MRI examination reveals devastating lesions but who are neurologically well, and patients who are in a poor neurological state but whose examination reveals nothing but small radiological changes. Indeed, it is now accepted that CNS lesions do not necessarily inform on the patients' clinical condition at the moment: these lesions are very dynamic and may not have clinical manifestations until several years later. Accordingly, Kantarci et al. have followed 453 subjects who suffered radiologically isolated syndromes; of these, 128 progressed to symptomatic MS, 15 of which evolved to PPMS [135]. According to Okuda, the value of 3D analysis of white matter lesions may reside in an improved ability to diagnose, distinguishing different types of lesions and providing patients with fine-tuned and personalized medical care. The automatic segmentation of the lesions, as opposed to the manual procedures, is often criticized; however, as these processes rely on the distinction of subtle shades, machine learning systems tend to perform better than the human eye. Whereas previous attempts at automatic segmentation focussed on lesion volume, the newest techniques can accurately determine shape and surface structure. These characteristics may inform on the origin of disease, provide insights into the extent of injury and even deliver some information on the capacity for self-remyelination. Additionally, 3D data may allow the identification of different pathologies within the brain of a single patient, resulting in more accurate and effective medical care.

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