Multiple sclerosis in resource-limited settings

Research opportunities in an unequal world

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Neurology® 2019;93:176-180. doi:10.1212/WNL.00000000000007837

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This position piece is meant to extend the humanitarian argument for assisting people with multiple sclerosis (MS) in resource-limited settings, in this case, through research. It is also meant to highlight areas of strength of some low- and middle-income countries (LMICs), and therefore emphasize how the field of MS could best be served globally by more research with and for resource-limited populations. Possible areas of particular strength include (1) ethnicity, genetic diversity, and migration studies; (2) analysis of possibly emerging environmental and lifestyle-related risk factors; (3) understanding the immune system when exposed to novel pathogens and various infectious agents; (4) reverse innovation to promote better point-of-care diagnostic tests; (5) high participation rates in clinical registries and research; (6) appreciation of MS in special populations including a higher focus on pediatrics and pregnancy; (7) culturally adept means of treatment and rehabilitating disability; (8) models of care delivery for chronic, complex neurologic diseases; and (9) use of off-label, generic, and less commonly implemented disease-modifying therapy sequences. Strategies for strengthening the MS research landscape include (1) creation of centers of research excellence in LMICs and twinning of institutions between high- and low-income countries; (2) standardization of research procedures and reduction of bureaucracies; (3) consensus meetings and network building; (4) opening additional avenues for publications and expanding the types of available publications; (5) identifying and establishing dedicated funding mechanisms; (6) focus on local relevance; and (7) setting expectations to include patients from LMICs in international clinical trials. These underutilized opportunities build an argument that global partnerships for research and knowledge coordination could better reach across populations, geographies, economies, and expertise.

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Glossary

DMT = disease-modifying therapy; LMIC = low- and middle-income country; MS = multiple sclerosis.

Multiple sclerosis (MS) is often considered to be a disease of higher-income countries. While this is generally true, an emerging global literature reminds us that multiple sclerosis exists in most countries and populations. In the 2008 *Atlas of MS Resources in the World*, all 112 countries surveyed reported the presence of MS.¹ Although the majority of the world's population lives in low- and middle-income countries (LMICs), the vast majority of the medical literature, especially in MS, still derives from high-income populations.

Since many resource-limited settings lack both neurologists and neuroimaging facilities, the precise, modern diagnosis of MS remains elusive for thousands of people with MS worldwide. Paradoxically, traditional tests that would be most helpful in resource-limited populations, such as CSF testing, also remain difficult to obtain in LMICs due to time constraints, limitations on the range of available laboratory supplies, and a general lack of coordination within health systems for complex neurologic patients. In lowest income populations, the cost of a single brain MRI can equate to what the World Health Organization defines as a catastrophic health expenditure, or expenditure of >40% of one's disposable income on health, before acute or chronic treatment options are even considered.²

Thus in many low-income settings, MS disease-modifying therapies (DMTs) are used in a fluctuating manner, contingent upon procurement in a country, agreements between governments and suppliers, ability of health care workers to refer to specialized centers, and the opportunity for each patient to gather personal money for out-of-pocket medical costs. Some countries have drug supplies that reflect the situation that occurred in high-income countries 25 years ago: interferon- β and glatiramer acetate.³ People with more severe MS are forced to alternate between lower efficacy agents, failing to take advantage of the massive strides that the MS field has made in the last 2 decades and not reaping the benefits that accompany successful drug development, particularly for relapsing-remitting MS and clinically isolated syndrome. As there are many stakeholders on the international stage, the logistical hurdles to distribute DMTs to LMICs at times have been exacerbated by limited public health advocacy for neuroimmunologic conditions in LMIC settings.

The humanitarian argument to extend health services and clinical care to people with MS globally is clear. However, the neurology community must also look beyond clinical care. This brief position piece is meant to extend the humanitarian argument for assisting people with MS in LMICs, in this case, through research. It is also meant to highlight areas of strength of some resource-limited settings, and therefore emphasize how the field of MS could best be served globally by more

research with resource-limited settings. The following is a list of possibilities of what can be learned through strengthening partnerships for research and coordinating knowledge across populations, geographies, economies, and expertise.

Ethnicity, genetic diversity, and migration studies

Many LMICs have a magnitude of ethnic and racial diversity that exceeds that of high-income countries, including various periods of large in-migration and outmigration that can be analyzed for risk factors for MS. For example, comparative studies between European-born and immigrants of varying ancestries have been performed,⁴ but less work has been done comparing these populations to populations of the same ethnic backgrounds who have not emigrated. Other countries with MS registries may lend new insights into familial MS. For instance, a recently reported Egyptian registry found consanguinity of parents of patients with MS was common between first cousins in 11% and second or third cousins in 6%.⁵

Analysis of possibly emerging risk factors for MS

Several risk factors are postulated for either the development or evolution of MS, but others are yet to be identified. Although many examples exist, a more robust understanding of recognized factors such as serum vitamin D levels and smoking cigarettes could be performed, both because there are distinct variations and because the prevalence of certain risk factors is either much higher or much lower than places where they have already been well-studied. New risk factors such as alternative tobaccos, environmental toxins such as air and water pollutants, and dietary constituents could be better understood in several LMICs, particularly if there are dose-dependent effects. Another example of this is the reported relationship between some vaccines and later occurrence of MS, such as yellow fever vaccine.⁶ Since some vaccines and infections are uncommon where they are studied, but common where they are not studied, opportunities to rectify this situation remain.

Understanding the immune system when exposed to novel pathogens and various infectious agents

There are multiple hypotheses on the causation of MS, some of which involve exposure to specific infections, such as Epstein-Barr virus, and others that depend on the absence of specific microbial exposures, such as the "hygiene hypothesis." One

hypothesis that helminth administration can ameliorate disease activity in experimental autoimmune encephalomyelitis provides a curious example of this novelty.⁷ More recently, the microbiome could be understood across populations exposed to various sets of pathogens depending on geographic location, sanitation, ambient temperature, and other unique environmental features.

Reverse innovation to promote better point-of-care diagnostic tests

There is a high need for a point-of-care MS biomarker, beyond the current use of MRI. The use of ancillary tests that could be helpful for the diagnosis of MS and its mimickers would likely be most useful in LMICs although arguably would be useful for all populations. The importance of tests such as neurofilament light chains in the serum, portable optical coherence tomography, visual evoked potentials, and portable MRI are important to understand. Research into less invasive ways to understand the immune system, for example through the identification of oligoclonal bands in tears,⁸ holds promise for LMICs as well.

High participation in clinical registries and research

The high number of people living in many countries designated as LMICs suggests that even though MS may be less common, the populations living in supercities lead to a high number of findable cases nonetheless. The situation of having only a few MS specialists centralizes care and allows registries and research to be organized rather quickly with adequately powered sample sizes for future studies. Participation rates for research studies in MS across LMICs are not well-reported but would likely meet and exceed participation rates in high-income countries.

Appreciating MS across the lifespan and in special populations

MS pregnancy registries are important to the understanding of the effect of MS and its therapies on maternal and fetal outcomes. Where pregnancy is more common with a higher number of births per woman, the implementation of pregnancy registries could yield important data for the MS field. Similarly, since many LMICs have overall very young populations, the number of pediatric patients with MS and associated understanding of pediatric MS in LMICs could provide new insights into MS in the youngest age groups.

Culturally adept ways of treating and rehabilitating disability associated with MS

Physical activity including aerobic exercise, dance, and other individual and community-based activities are commonly

considered ways to combat disability in MS. For example, whereas the United States has performed clinical studies of yoga for MS,⁹ countries where yoga originates would be equally well-suited to perform such studies and likely with even higher numbers of participants.

Determining models of care delivery for chronic, complex neurologic diseases

MS provides a model for working age adults to interface with neurologists in a chronic disease model. Some health systems succeed at caring for people with MS while others fail. The roles of MS allied health care providers, including nurses, physical therapists, and community health care workers, vary depending on health systems. In times of political instability, poor health systems negatively affect people with MS, including affecting their coping ability and their mood as well as their physical outcomes.¹⁰ Analyzing the role of the larger system in which people with MS cope provides incisive knowledge on how cost, expenditures, and human resources can affect patient outcomes.

Off-label, generic, and less commonly used DMT sequences

Since many people with MS in LMICs cannot reliably access typical DMTs and may not be able to afford them consistently, several have experience with other medications that may have immunosuppressive effects, such as medications used post-transplantation. Although this may not be ideal for patients when other more proven therapies exist elsewhere, their experiences could still be understood and reported since they have value in understanding the efficacy, effectiveness, safety, and tolerability of more complicated regimens that are being used in the real world. Alternating therapies and medication sequences that would not be typical in high-income countries may be used in LMICs and little is reported on these situations. Since the World Health Organization's Essential Medicine List does not yet include high-efficacy DMTs, use of drugs on this list for other conditions, namely rituximab, mycophenolate mofetil, and azathioprine, has been noted.^{3,11} Medication safety in environments where the differential diagnosis may not have been fully vetted, such as compared to neuro-myelitis optica and other demyelinating white matter conditions, could be similarly reported.

Since the range of resources can differ greatly across LMICs, the feasibility of basic science, translational, clinical, and epidemiologic research will vary. Although the above examples are meant to reflect pragmatic ways in which we can collectively learn about MS in partnership with resource-limited populations and investigators, the list is not exhaustive. The following are possible strategies to implement research ideas, including the study of the above concepts. These

strategies may be already implemented in some form for clinical care or used for research more broadly, or in other disciplines, but each could be advanced to strengthen MS research globally.

Ways forward

Centers of Excellence in LMICs and institutional twinning

One strategy is through the concentration of resources, even if limited, in Centers of Excellence. This can strengthen infrastructure and research training for MS in at least some resource-limited locations. Centers can serve as hubs of expertise for other facilities and be charged with organizing larger scale and multinational research efforts. These Centers can be certified, just like in high-income countries, but have a set of standards that reflects local resources and priorities. On the African continent, for example, a group of MS Centers of Excellence may initiate the creation of a continental registry for MS and provide a hub for neuroimmunology subspecialty training. Scholars in MS from LMICs could rotate through such a center, or train there, and create new relationships. All topical training initiatives in MS could also emphasize research ethics and research skills advancement unique to MS. Partnerships with high-income countries' institutions, or "twinning," with these Centers could reciprocally cultivate expertise in MS research and allow more continuous exchanges of ideas, resources, and personnel between high- and low-income settings.

Standardization of procedures and reduction of research bureaucracies

Removal of unnecessary research bureaucracies and logistical barriers is especially important in LMICs to advance MS research. This may require negotiation across locations for vulnerable populations and patients. For instance, central institutional review boards for review of multisite studies in LMICs can obviate complexities that come with variable processes that differ by location. Creation of standardized documents for MS research programs, including fillable electronic databases, templated consent forms, and patient-focused informational brochures about MS research, translated in multiple languages could remove the burden foisted upon individual investigators who already possess limited resources. Online registries, teleconferences, and new software applications can leapfrog ahead in LMICs.

Consensus meetings and network building

Consensus conferences and network-building workshops, held in LMICs for LMICs, could influence research stakeholders' decisions on urgent needs and emphasize regional priorities. These could build upon existing regional efforts but have a distinct focus on countries with fewer resources. Such meetings will require both junior and senior

neurologists and possibly representatives from other fields such as physical therapy, ophthalmology, psychiatry, and radiology. Afterwards, a published consensus statement could be submitted to high-impact relevant medical journals.

Opening additional avenues for publication and types of publication

Through open-access publication, published statements of consensus meetings from LMICs could reach a wide audience, including early career physicians who are considering neurology and MS as a career pursuit. In the 2017 revisions to the McDonald criteria for the diagnosis of MS,¹² an influential position paper in the MS field, high priority areas for research were articulated. A specific call for the use of the updated criteria in diverse populations was identified as an unmet need, specifically "in Asia, Latin America, the Middle East, Africa, and other relatively less studied geographical locations," as well as across comorbidities. They included a need for practical, nonacademic settings to be included. An intent to publish such literature should follow, including on challenges and barriers to MS research in the field,¹¹ in the same way that publishing negative results is important to understand the full range of research that is actually performed. MS-focused journals may consider theme issues dedicated to the topic of MS in resource-limited and vulnerable population groups, such as providing MS care in humanitarian settings,¹³ creating a platform for investigators that may be otherwise unavailable.

Identifying and establishing dedicated funding mechanisms

Encouraging MS funders, particularly pharmaceutical companies, to consider both humanitarian efforts and investment in MS research that improves global equity is important. Investment in point-of-care diagnostic tests or registries for drug safety in new environments would help both people in LMICs and patients in remote and low-resourced high-income country settings. In high-income countries, national MS societies, private foundations, and patient philanthropy have played a pivotal role in supporting MS research beyond traditional funding schemes. These same groups explicitly aim to influence health policies through data-driven advocacy. Higher income national MS societies and regional chapters could also partner with LMIC MS societies, including setting up new groups and advising on the structure of research funding, grant opportunities, and other forms of investigator support.

Focus on local relevance

Research in LMICs should focus on the relevant epidemiology of the settings in which it is performed. In some cases, incorporation into syndromic or symptomatic presentations will be of highest yield. For instance, a study of transverse myelitis or optic neuritis and its range of etiologies can be most important to local clinicians beyond more disease-specific publications.

Setting expectations for international trials

A minimum number, or quota, of lower-income country participants or sites in large, international clinical trials of different phases would improve the representativeness of clinical trials data from both safety and effectiveness perspectives. The generalizability of trial results would also be improved globally.

Ideally, a multisector effort would ensue, allowing the purview of no one stakeholder to overcome the clear general needs. Honesty on realistic strengths of different sites, capacity of investigators, and time commitment to advance major efforts by teams is paramount. Finally, focusing on low-cost initiatives, tests that can actually be performed, medications that are within health systems' real budgets, and incorporation into local, ongoing, and culturally usual efforts make sense and could be realistically scaled up. Although there remain many inequities in the world, resource-limited settings have several ways in which they can and should contribute to the global knowledge base on MS.

Study funding

No targeted funding reported.

Disclosure

F. Mateen has served on medical advisory boards on multiple sclerosis for Genentech-Roche and Biogen and received

consulting fees from Oxford Pharmagenesis Ltd., unrelated to this work. Go to Neurology.org/N for full disclosures.

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DOI 10.1212/WNL.00000000000007837

This information is current as of July 22, 2019

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