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Multiple sclerosis in India – drivers of access and affordability

Abstract

Introduction: Multiple sclerosis (MS), a progressive autoimmune disease, is characterized by episodes of inflammation and degradation of the fatty myelin sheath surrounding the axons of the brain and spinal cord. Attacks of MS may lead to inflammation and injury to the myelin sheath resulting in blocked or slowed nerve signals that may lead to difficulty in controlling vision, muscle coordination, strength, sensation and other bodily functions. MS was characterized as a disease of the Western Hemisphere for several years. However, in the past few years, newer cases were seen in Asia, particularly in regions of China and India, since the presence of MS in these regions has been notable in the light of increasing access to MRI techniques, better detection and increasing numbers of specialized neurologists in these countries. Particularly in southern India, neuro epidemiological studies demonstrate that the prevalence of MS has more than doubled in the past thirty years (1.33 vs. 3 cases/100,000). MS-related hospital admissions have nearly doubled in the last decade (1.58% vs. 2.54%). While MS cannot be adequately treated, its symptomatology may be managed with existing pharmacotherapy. Medications to manage MS are specialty biologics, usually cost-prohibitive to patients even in high-income countries. India, being a Low Middle Income Country (LMIC), has few patients who can afford expensive out-of-pocket medications. Poor insurance coverage, lack of affordable medications and a developing health care system are a few of the factors contributing to access and affordability barriers for MS patients in India.

Methods: This study aimed to identify issues of access and affordability for Indian patients living with MS.

Results: Autoimmune disorders do not fall under the high priority areas for the National Health Mission of India. As such, focus areas for MS and other autoimmune diseases were classified as - affordability, societal support, and acceptance and physician competence.

Discussion: MS is a costly disease and in recent studies, treatments have shown little cost-effectiveness. Few MS drugs are manufactured in India and other brand entities have to be imported. As a result delays in the supply chain, price fluctuations, and unavailability of medications in certain areas may result in a lack of access to the medications in a timely manner.

Conclusion: There is almost no research in the literature examining access and affordability issues for patients living with MS in India. Lack of registries and surveillance data impedes any further research to determine whether these patients are being monitored for appropriate outcomes, whether therapeutic regimens are effective and more importantly, whether social conditioning and provisions are made when the disease progresses into disability. Further studies are needed to better understand the conditions of patients living with MS in India to drive policies for an improved health care system.

Keywords: Multiple sclerosis, India, epidemiology, disease progression, MRI technology, unmet needs, pharmaceuticals, access, insurance coverage

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Introduction

Multiple Sclerosis (MS), a progressive, autoimmune disorder resulting in damage to the myelin structure in the central nervous system is characterized initially by episodes of reversible neurologic deficits, followed by progressive neurological deterioration over time in most patients.[1,2] Depending on site of demyelination, there may be deterioration in the cognitive or emotional functioning and/or level of mobility. MS attacks may lead to inflammation and injury to the myelin sheath resulting in blocked or slowed nerve signals that may lead to difficulty in controlling vision, muscle coordination, strength, sensation and other bodily functions. MS was first described by French neurologist Jean-Martin Charcot in 1868 and more than 140 years later, there is still no known cause, nor cure, for the disease. Treatments to slow progression are available and may help with functioning. Onset of MS remains unclear, however, it is now recognized that MS can arise during childhood or adolescence.[3] MS affects roughly 2.1 million people worldwide with wide geographic variation. In general, observed prevalence is greater at higher latitudes with exceptions (i.e. low rates observed among Chinese, Japanese and Africans; high rates observed among Sardinians, Iranians and Palestinians).[4,5] Diagnoses and treatments: Patients may present with a range of symptoms from cognitive changes to ataxia, depression, visual impairments or hemiparesis. Commonly identified symptoms include:

a) Sensory loss (paresthesias)

b) Spinal cord symptoms: Weakness, spasticity and sensory symptoms

c) Optic neuritis

d) Pain and fatigue

e) Subjective difficulties

There are four categories of clinical MS:

i. **Relapsing-remitting MS (RRMS)**: Characterized by recurrent attacks where neurological deficits appear in different parts of the nervous system and resolve completely or almost completely over a short period of time, leaving little residual deficit. This is the most common type of MS and 85% of MS cases are patients with RRMS.

ii. **Secondary progressive MS (SPMS):** Approximately 50% of patients convert to a secondary progressive pattern within 10 years of disease onset. This pattern may or may not include relapses, but it is characterized by continued progression over the years.

iii. **Primary progressive MS (PPMS):** This pattern accounts for approximately 10% of all MS cases and function declines steadily without relapses.

iv. **Progressive relapsing MS (PRMS):** Persons with PRMS (<5%) have occasional relapses. 70% of patients with Clinically Isolated Syndrome (CIS) (defined as an acute neurological disease suggesting demyelination of the central nervous system but not fulfilling the criteria for clinically definite MS) if left untreated develop MS within 15years.

Diagnostic criteria is a wide differential diagnosis often has to be considered. Magnetic Resonance Imaging (MRI), electro-physiologic and cerebrospinal fluid studies can all contribute to an early definitive diagnosis. Currently, the McDonald diagnostic criteria are used for diagnosis of MS. MRI is the best tool for detection of asymptomatic dissemination of MS. In certain cases, MRIs may predict progression. Sensitivity of MRIs in detecting MS varies from 81-90%.[6,7] Treatments: Currently, there is no known cure for MS. Disease modifying agents are used to prolong demyelination and slow down disease progression. All disease-modifying agents are approved for RRMS and only Mitroxantone is approved for secondary progressive MS (Table 1).

Table 1 Disease modifying agents for RRMS

Agent (Brand)	Manufacturer	U.S. FDA approval	Administration	Frequency
Avonex (interferon beta-1a)	Biogen Idec	1996	IM	Once a week
Rebif (interferon beta-1a)	Merck	2002	SC	3 times a week
Betaseron (interferon beta-1b)	Bayer	1993	SC	Every other day
Extavia (interferon beta-1b)	Novartis	2009	SC	Every other day
Copaxone (glatiramer acetate)	Teva	1997	SC	Daily
Tysabri (natalizumab)	Biogen Idec	2006	IV	Monthly
Novantrone (mitoxantrone)	EMD Serono and OSI Pharm	2000	IV	4 times per year (lifetime limit of 8-12 doses)
Gilenya (fingolimod)	Novartis	2010	Oral	Daily
Aubagio (teriflunomide)	Genzyme (Sanofi)	2012	Oral	Daily
Tecfidera (dimethyl fumarate)	Biogen Idec	2013	Oral	Daily

Sources: National Multiple Sclerosis Society, Mayo Clinic, U.S. FDA
SC: subcutaneous IM: intramuscular IV: intravenous

Multiple sclerosis in India

During the mid-1970's, India was identified as a low MS-prevalent nation (<5cases/100,000people).[8,9] True estimates on MS prevalence are nearly impossible to find. Reporting is influenced by various factors, including surveillance, availability of skilled neurologists, MRI machines, and more.[8,9] In the 1980's, a crude prevalence rate of 0.77-1.33/100,000 was reported. However, record keeping and long term follow-up of patients remain limitations to data collection and analysis, excepting teaching hospitals. Poor awareness, lack of epidemiological monitoring, and limited diagnostic capabilities have severely limited the ability to identify, diagnose, and report MS in India. MRI coverage is restricted mostly to urban areas with teaching hospitals and private for-profit hospitals that get patients from the upper socioeconomic strata. MS-related neurology hospitalizations increased from 1.58% to 2.54% over a decade.[10] The MS International Federation's World Multiple Sclerosis Atlas projects a prevalence of 3/100,000; nearly triple the estimate of previous reports. With a current population of >1 billion, it may be simply calculated that the prevalence of MS in India could perhaps be higher than reported numbers (i.e. 35,000 cases per simple calculation). In patients of Indian and African origin, MS has a high optic and spinal cord involvement.[11,12] MS is attributed to genetic and environmental factors, though research has been sparse to identify specifics. Considering the fact, that MS will likely result in disability, the focus of health programs should be to help patients manage their disease toward preventing and/or prolonging disability. The longer a person can ward off full disability, the longer they may be able to contribute productively to the economy and society.

The increased number of cases may be partly due to increasing availability of MRI equipment and better-trained neurologists, particularly in urban areas. In India, public and/or teaching hospitals usually receive patients from lower socioeconomic backgrounds with gender inequality contributing significantly to data collection

and analysis from these settings.[3,8] It was assumed for a long time that MS was a disease of the West, since geography may play a role in disease incidence. Geographically, northwest India (above 15°N latitude) has an incidence of an average of 4.15 compared to 3.2 in South India (below 15°N latitude). India saw an influx of Persians (now Iranians) in the 8th to 10thcenturies. This population, known as Zoroastrians or Parsis, has an observed prevalence of 26/100,000. Several epidemiological studies have indicated high prevalence rates of MS among Iranians, especially in the Ishfahan province adjoining Pars. Most neurologists base their diagnoses on the older Poser's criteria. It is estimated in several reports that there may be about 100,000-200,000 people living with MS in India. With an improved MRI coverage, including governmental plans for expansion of facilities in rural areas, better estimates of prevalence and incidence may come about in following years, indicating perhaps a greater need for services.[13] The landscape of clinical MS in India can be expected to change, albeit slowly, with the advent of expanding neurological services and wider availability of magnetic resonance imaging (MRI).

There have been relatively few studies on MS in Asia and particularly in India. Asian MS has been traditionally thought of as a distinct entity characterized by high incidence of visual involvement at onset, more severe visual involvement at follow up, prevalence of recurrent acute transverse myelitis, high incidence of optico-spinal involvement, severe involvement of spinal cord with functional disability and less frequent involvement of cerebellum.[8,12,14–17] In April 2005, the Indian Government launched a comprehensive National Health Mission (NHM) to address health challenges in the country. The NHM addresses several communicable and non-communicable diseases. However, inclusion of autoimmune and other disorders in a separate category may provide much needed impetus to adequately survey and record cases for better incidence/prevalence estimates.

Cost of MS

The total cost of MS in India remains unknown. Disease modifying agents cost approximately $60,000 each year in the U.S. with varying insurance coverage.[18] India's average per capita annual income was around $1820 in 2015.[19] Currently, India is a low insurance market. Approximately 15% of the population has some coverage with the other 85% paying out-of-pocket. Most of the population's insurance coverage comes through government schemes and is available to governmental employees per the Insurance Regulatory and Development Authority (IRDA). According to the World Health Organization (WHO), in 2015, India spent only 4.0% of its Gross Domestic Product (GDP) on the health sector (lowest among the BRICS countries – Brazil, Russia, India, China and South Africa).[20] By contrast in the U.S., approximately 20.9% of GDP is spent on healthcare, with health insurance estimated to be nearly at 80-85% coverage. India's planned healthcare spending increase to 2.5% from 1.4% of GDP aimed toward free medications at government facilities, setting up free ambulances in rural areas, doubling the number of trained workers, and lifting millions of young children and women out of chronic malnutrition and preventable deaths.[21] However, autoimmune and other neurological disorders remained unaddressed.

Biosimilars

Given the high cost of MS drugs, Indian life sciences companies have developed biosimilars or biopharmaceutical products that have similar properties as their patented counterparts. Many biosimilars are now available for MS treatment. Biosimilars, unlike generics consist of human and/or animal materials and are processed through complex biotechnological processes. Biosimilars are follow-on biologics. Each country has a different mechanism for regulatory approval of biosimilars. The Central Drugs Standard Control Organization (CDSCO), which is the regulatory authority for drug approvals in India, has approved as many as 50biosimilars for various diseases and provides detailed guidelines for approval of biosimilars. Safety concerns with biosimilars and biologics involve the potential risk of immune-based adverse reactions and it is important to develop adequate pharmacovigilance measures to adequately address issues of safety and alleviate risks.[22]

India has the 3rd largest pharmaceutical industry in terms of volume in the world. The tremendous capacity to develop and manufacture biosimilars amidst generics is hailed by watchdog and civil society groups, including Medicines Sans Frontieres, toward improving affordability and accessibility for a vast percentage of the world's poor population. Take for example, Avonex (Interferon Beta 1a 30 mcg prefilled syringe) that costs around INR 30,000 per syringe (USD $500). Patients would have to inject Avonex once a week putting monthly costs at ~INR 120,000 (USD $2,000). Average incomes in India fall under INR 10,000 per month[23] thereby making this drug highly unaffordable. A bio similar called Relibeta (30mcg prefilled syringe) made by Reliance Life Sciences, an Indian biopharmaceuticals company is sold for INR 5,623 (USD $93) per syringe. At 4 syringes a month, the treatment would come to approximately INR 22,492 (USD $374) that may still be beyond the reach of many patients, but probably affordable by some. In the absence of feasible solutions for MS, the alternative remains management and prolonging disability. Table 2 below shows the various MS agents available in India and their prices.

Associated costs

Along with MS medications, recurring costs for hospitalizations, MRI scans, check-ups, and disability related services must be considered in an economic analysis. Adding up these costs in India is difficult due to the varying prices offered by service providers, varying insurance coverage and lack of standardized databases where such information may be captured.

Off-label use

In recent years, off-label medications have found use for managing symptoms in MS patients and are often used when patients have exhausted all MS medication treatments, are unable to pay the cost of MS treatments (including biosimilars), are looking for cheaper alternatives, or are looking for a different side effect profile. Some studies in the scientific literature have shown value and promise with the use of certain immune suppressing medications toward managing MS in patients. Off-label medications, such as Rituximab, Modafinil (Provigil), and Azathioprine, are reportedly used by patients who may or may not have exhausted all standard-of-care options (personal communications with MS patients). However, in the absence of scientific rigor and an U.S. FDA indication, outcomes are difficult to assess. Autoimmune diseases may require heavy monitoring for immune-mediated responses thereby necessitating neurologists and patients to take charge with extensive follow-ups to maximize utility and minimize risks. Chemotherapeutic agents and other immune modifying drugs will continue to be studied for other uses including managing MS.

Table 2 MS biosimilar agents available in India

Agent	Biosimilar/ Manufacturer/ Distributor*	Price per unit**	Frequency
Avonex (interferon beta-1a)†	Biogen Idec	INR 9557 (USD 144.3)	Once a week
Relibeta (interferon beta-1a)	Reliance Life Sciences	INR 6785 (USD 102)	3 times a week
Betaseron (interferon beta-1b)	Zydus Cadila	INR 116 (USD 1.93) [0.25 mg vial]	Every other day
Glatimer (glatiramer acetate)	Natco Pharmaceuticals	INR 975 (USD 16.25)	Daily
Glatira (glatiramer acetate)	Cipla Pharmaceuticals	INR 350 (USD 5.83)	Daily
Tysabri (natalizumab)	Biogen Idec	INR 76,894 (USD 1,161)	Monthly
Mitozan(mitoxantrone)	VHB Life Science	INR 385 (USD 6.41) [20 mg vial]	4 times/year (lifetime limit of 8-12 doses)
Oncotron (mitoxantrone)	Sun Pharmaceuticals	INR 401 (USD 6.69) [2 mg vial]	
Gilenya (fingolimod)‡¶	Novartis	INR 31 (USD 0.47)	Daily
Aubagio (teriflunomide)¶	Genzyme (Sanofi)	~INR 1500-2000 (USD 22.64 – 30.2)	Daily
Tecfidera (dimethyl fumarate)¶	Biogen Idec	~INR 12,000-16,000 (USD 181.87-241.2)	Daily

*Any manufacturer or distributor licensed in India.
**All prices are based on information obtained through distributors or the MedIndia website. Prices for imported goods may be higher due to customs and other expenses incurred. Prices may also fluctuate according to the USD exchange rates. The exchange rate used for the above table is USD 1 = INR 66.23 as of December 31, 2015.
†Avonex is imported into India from surrounding countries through a distributor.
‡Novartis lost a patent battle against Indian company Torrent Pharmaceuticals based on non-novelty and non-obviousness of fingolimod.
¶Prices computed from 2015 import data on total quantities and total costs.

Insurance coverage

Currently, only governmental employees have insurance coverage for MS medications. Medications are not widely available and have to be ordered through a distributor. Under the Central Government Scheme, employees and their families have access to a network of providers. Health insurance in India stood at 34% in FY 2016-17, indicating a low penetration in the market, particularly the healthcare market where expenses are likely to be high. Most private insurers rule out MS as a pre-existing condition for coverage.

Societal support

Complex neurological disorders are not stigmatized in India. Therefore, societal support and acceptance is less problematic. However, areas of concern include reasonable disability laws and accommodations to protect from discrimination. Social service programs and disability centers that can address specific disabilities from MS along with long term care and support are much needed.

Limitations

Issues of access and adherence to MS medications remain unknown in India. Access and adherence, along with healthcare outcomes--particularly Economic, Clinical and Humanistic outcomes for MS patients living in India--need to be further investigated for a deeper understanding so that clinical programs may be optimized. Critical questions of access and affordability remain, making MS an expensive condition. In the absence of drug databases and outcomes reporting in India, all information procured is usually through patients or neurologists willing to discuss treatments. Some online websites like Med India serve as guides for drug information, pricing etc. A compilation of information from multiple sources presented in Table 2serve as the starting point for future discussions around access and affordability of MS treatments.

Discussion

Affordability

MS medications are very costly entities usually requiring a procedure administered by a clinician. While most medications are self-injectable, patients may still require a healthcare provider to administer them, and surely to monitor the care closely for cost management and improved outcomes. MS disease modifying agents' costs exceed USD $50,000 per patient per year. According to Blue Cross/Blue Shield in the U.S., the average annual MS drug cost was $28,152, while all other health costs were $13,608. Yet, another study looked at the total all-cause healthcare related costs for MS and found that these costs ranged from $8,528 - $54,244 per patient per year. Direct costs ranged for more than 60% (64-91%) of the total healthcare costs for MS. Prescription drugs accounted for a majority of the direct costs.[24] In India, currently there are no provisions for subsidizing medications for patients hence; most treatments for MS are out-of-pocket. Only patients who work for the government and have insurance coverage are currently covered for specialty prescriptions. However, a vast majority of the Indian workforce is employed in the private sector with very low insurance coverage rates (most insurances do not cover MS as a pre-existing condition; some insurers will cover MS medications, but have a 5 year wait period—a patient must be continuously insured by the insurer for 5 consecutive years as a precondition for coverage, thereby leaving them with little option for accessing their medications at least initially). Added to that are financial costs associated with consultations, diagnostics, and disability support among others.[24] Insurance is offered through various schemes–governmental (central and state), private, NGOs and Employers. The lack of a fair and adequate system has led to low participation in insurance schemes. Healthcare spending in India is expected to increase by around 12% annually with an

increasing aging population in need for services. Coverage of MS and other autoimmune diseases as pre-existing conditions for those previously diagnosed as well as new diagnoses remains to be seen.[25] An evolving regulatory environment along with safe guarding the insured populations' interests is likely to make India a high insurance market in the future.[25,26] Multinational insurance firms have been targeting India for this market potential as its health care system and economy develop rapidly[26]. McKinsey & Company particularly sees the pharmaceutical sector's great potential for multinational firms, including specialty pharmacy.[27,28]

In 2005, with the enactment of patent laws on pharmaceutical products, India lost its advantage to reverse engineer pharmaceutical molecules. Since all the MS drugs are currently patented, there is virtually little to any incentive for multinational pharma firms to reduce drug prices in lieu of affordability. The global MS therapeutics market is projected to grow at a CAGR of 3.16 percent over 2012-2016, but lack of therapies available to manage the progression of the disease poses a challenge to this growth.[29–31] Incomes in India vary significantly by sector, so it is practically impossible to compute the actual cost of MS treatment due to its chronic nature. While most reports have identified costs of MS drugs as significantly high with expected future increases, there is currently very little push from authorities in India to regulate or monitor specialty drug prices, though stands against multinationals are being taken on certain issues. Another parallel and significant issue is the use of off-label prescription drugs to prolong disability amongst MS patients. Long term costs and effects of these treatments are unlikely to be known. Issues of switching medications and longer-term effects remain unknown.[32,33] Clinical programs: Patients living with MS may respond well to medications if diagnosed and treated early. Currently, the quality of care is not accounted for. It is unclear how much actual training is provided to neurology residents and neurologists on MS. In fact, the four-year Bachelors of Medicine curriculum (M.B.B.S) does not list neurology as one of the core topics. MS and other autoimmune disorders are covered post-graduation under General Medicine or Neurology specializations. The quality and quantity of information provided to medical graduates may vary by universities and colleges; it remains unclear as to how much actual information is passed down to practitioners. It is important for physicians to identify and make referrals for MS patients since most of the signs and symptoms are not specific and may be confused with other autoimmune or neurological disorders. This condition within the medical profession reveals how few epidemiological assessments hinder both disease prevention and eradication in larger populations.

Identifying quality of care parameters, outcomes measures and assessing disability will be among the most challenging necessities in terms of developing skilled tertiary care centers for auto-immune diseases in India. MS is a chronic disease and patients need to take their medications as prescribed for several years to respond to treatment and slow its progression. As such, costs of living with MS may well exceed costs of living thereby leaving fewer options for patients and their caregivers. Multiple sclerosis may not be a priority on India's growing list of health care concerns, but there are thousands of Indian patients currently living with MS who require programmatic interventions to relieve their suffering and maintain their functioning as productive citizens. The ability to procure medications for these patients at reasonable prices is a challenge that legislators and healthcare advocates alike need to consider toward improving these patients' lives. Moreover, there is a critical need for a system for monitoring post-marketing of adverse drug reactions. Different reactions to the agents can be expected in varying population groups provoking the need develop a clinical evidence database.[34,35] Outcomes for this condition require compliance to high cost and high-risk drugs thus necessitating data-driven surveillance to assure clinical and economic outcomes for MS treatment among Indians. This monitoring mechanism could be facilitated along with such cost and quality observation over other critical population health conditions.

Conclusion

MS is a costly disease where people in India suffer physically, emotionally, and financially; families are greatly affected also. There are very few studies that address actual costs of living with MS in India. While MS prevalence appears low in India now, there are several rural and urban areas where MRI capacities have not been extended. In coming years, we may see prevalence estimates increase as a function of better diagnostics, along with provider and public awareness. Most patients are able to continue their regular activities while battling MS with access to proper healthcare and medications. However, in the current state, MS treatments may be out of reach for many patients. While India has been extremely successful in developing a generic pharmaceutical industry with the ability to provide medications at lower costs that compete in international markets, the paradoxical issue of prohibitive access to patented drugs due to costs is appalling. We found that cost was one of the major barriers to access MS medications, along with the need for education, awareness, and support. The authors hope that additional studies will illuminate new directions for public policy and advocate for remedies. The U.S. CDC recently announced launching of a National Neurological Conditions and Surveillance System (NNCSS) to help increase understanding of neurological disorders and to further support neurologic research. Perhaps in a future trade negotiation with India a comparable database can be provided to the Indian Ministry of Health (Rosenberg, 2018).[36] Further studies are needed to better understand long-term adherence and outcomes of patients living with MS in India. MS is a complicated disease with progression into disability, and patients have very few options towards affording medications. From a health policy standpoint, issues of cost, access and insurance coverage remain of great concern with regards to MS patients in India.

Authors' contributions

Aruru MV developed concept, contributed to 50% of writing, developed bibliography, edited and proofread manuscript and Salmon JW contributed to 50% of writing including discussion and conclusions. Edited and proofread manuscript, developed bibliography.

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Conflicts of interest

The authors hereby declare that there are no conflicts of interest associated with this study. The authors did not receive any funding for this study and conducted this study solely out of academic interest. A previous version of this manuscript was presented at the Business and Health Administration Association (BHAA) 2014 to solicit feedback.

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