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MULTIPLE SCLEROSIS IN PAKISTAN AND NEED FOR MULTIPLE SCLEROSIS REGISTRY

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ABSTRACT

BACKGROUND: Multiple sclerosis (MS) is an acquired chronic demyelinating disease of central nervous system is a leading cause of non-traumatic disability in young with significant socioeconomic impact.

The aim of this study was to provide a comprehensive review of all available data of MS in Pakistan.

METHODS: A comprehensive literature search was performed using Medline®, Scopus, Embase, Cochrane library and PakMedinet. There are no nationwide prevalence or incidence reports from Pakistan and no population based surveys.

RESULTS: 15 case series were analyzed. 708 patients were found. Revised McDonald criteria of 2010 was the most widely used diagnostic criteria in the studies. Female to male ratio of 1.6 was observed. The mean age of onset of disease was 29 years.

CONCLUSION: Population based surveys are lacking in Pakistan and most of its South Asian neighbors. Real world data in the form MS registries is being increasingly recognized as an important source of provision of epidemiological data of MS. Establishing MS registry can prove to be a milestone in formation of MS related health care policy and improving the standard of MS care in Pakistan.

Key words: multiple sclerosis; Pakistan; review; Randomized controlled trials, Registries

INTRODUCTION: Multiple sclerosis (MS) is an acquired chronic inflammatory demyelinating disease of the central nervous system.¹ MS is a leading cause of non-traumatic neurological disability in young patients, with a significant resultant social and economic impact, as well as potential life time dependence.^{2,3}

MS predominantly affects women. The estimated female to male ratio of MS incidence has increased from 1.4:1 to 2.3:1 as determined in a systematic review of epidemiological studies.⁴

There is considerable geographical variation in incidence and prevalence of MS. Kurtzke⁵ described three geographical zones according to prevalence of MS: (1) high frequency >30/100,000, (2) medium

frequency 5-25/100,000, and (3) low frequency <5/100,000. White populations constitute most of the high and medium risk areas⁵. The GBD 2016 Multiple Sclerosis Collaborators estimated the worldwide prevalence of MS to be 22,21188 in 2016.⁶ The highest reported prevalence was found to be in North America, Western Europe and Australia.⁶ A substantial increase of 10.4 % in prevalence was also noted since 1990⁶.

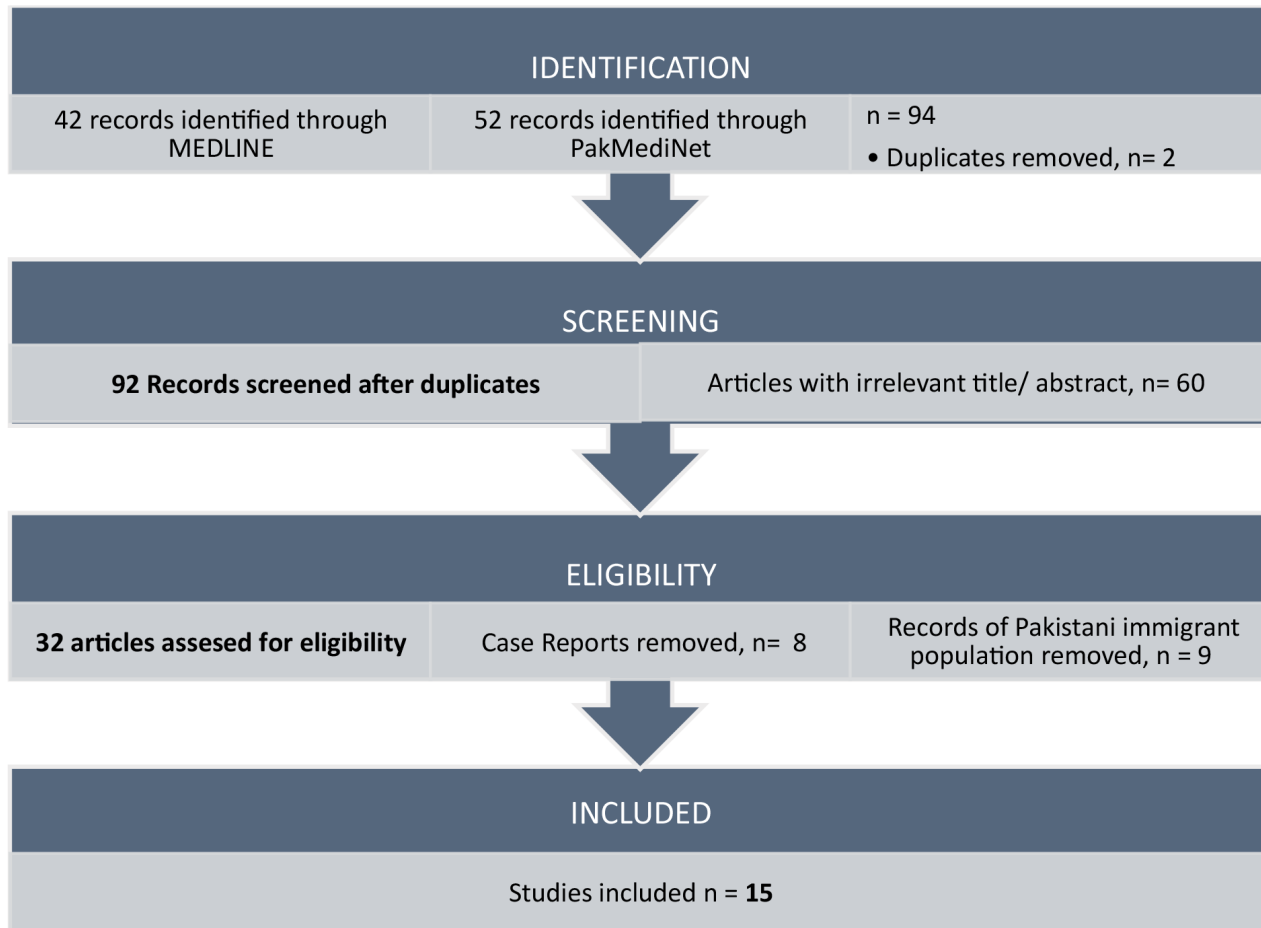
South Asia has been considered to be a low prevalence zone.^{7,8} However recent trials have shown an increasing prevalence in this region as well. Etemadifar M et al.⁹ in their systematic review demonstrated that incidence and prevalence of MS has increase in Iran, and ranges from medium to high frequency distribution and not in

the low frequency zone as previously suggested.⁹ In this review, we have tried to cover all studies conducted in Pakistan related to MS.

METHODS

A literature search of Medline ®, Scopus, Embase, Cochrane library and PakMedinet was made using keywords `multiple sclerosis, prevalence, incidence, epidemiology, Pakistan and its various cities. We searched for papers published before March 25, 2019. The title and abstract of all literatures recognized by the databases were reviewed. The data from various articles was entered into a tabulated form purpose of comparison with a focus number of patients, study setting, diagnostic criteria used, gender ratio and age of onset.

Fig. 1. Flow diagram of Methods



RESULTS

The result obtained a total of 94 articles (fig. 1). No population based study or registry was found. Duplicate entries were removed. 60 articles were assessed for eligibility after removing articles with irrelevant titles or abstracts. Case reports and records of immigrant population from Pakistan to various countries were excluded. 15 case series were included and data entered in tabulated form (table 1).

Table 1: Characteristics of MS in Pakistan

First Author	Year of Publication	Method	Study setting	Diagnostic criteria used	Number of Cases	Female: Male ratio	Mean age of onset (years)
Raza SQ¹⁰	1998	Retrospective	Hospital based	-	25	1.5:1	27.8
	Siddiqui T¹¹	2002	Retrospective	Single center, Aga Khan University Hospital, Karachi	-	15	-
Wasay M¹²	2007	Retrospective	Multicenter, hospital based	Poser criteria, Thompson criteria	142	1.45:1	27
Shahwar H¹³	2008	Prospective	Single center, Jinnah Post Graduate Medical Center, Karachi	Poser's criteria	20	2:1	25.8
Kazim SF¹⁴	2010	Retrospective	Single center, hospital based	-	46	2.5:1	-
Saleem K¹⁵	2011	Prospective	Single center, Mayo Hospital, Lahore	-	30	1.30:1	-
Khatri IA¹⁶	2012	Retrospective	Single center, Shifa International Hospital, Islamabad	-	24	1.66:1	-
Javid MA¹⁷	2012	Prospective	Multicenter, hospital based	2010 Revised McDonald criteria	64	1.56:1	36
Wasay M¹⁸	2013	Prospective	Multicenter, hospital based	-	100	1.5:1	-
Ahmad A¹⁹	2013	Prospective	Single center, Shifa International Hospital, Islamabad	-	4	3:1	27.7
Zaidi NR²⁰	2014	-	Single center, Mayo Hospital, Lahore	-	30	1:1	-
Javed MA²¹	2014	Retrospective	Single center, Mayo Hospital, Lahore	2010 Revised McDonald criteria	23	1.09:1	29.5
Ali A²²	2017	Prospective	Single center, Jinnah Post Graduate Medical Center, Karachi	-	85	1:1.07	-
Javid MA²³	2017	Retrospective	Multicenter, hospital based	2010 Revised McDonald criteria	15 (pediatric patients)	1.5:1	-
Pechuho SI²⁴	2018	Prospective	Single center, Chandka Medical College Hospital, Larkana	2010 Revised McDonald criteria	85	1.36:1	-

A net total of 708 patient's data was available. Four out of the 15 records were multicenter hospital based studies, whereas the rest were all single center studies.

Revised McDonald criteria of 2010 was the most widely used diagnostic criteria in the studies. Poser criteria was used in one study. There are no nationwide prevalence or incidence reports from Pakistan. Female predominance was seen consistently in most of the records, with a net female to male ratio of 1.6. Ali A et al.²² showed a slight male predominance and another study showed equal distribution amongst males and females.²⁰ The mean age of onset of disease was available in only 6 records and was estimated to be 29 years.

DISCUSSION

This article provides a systematic review of all existing data which has been published and is available online regarding Multiple sclerosis in Pakistan. Unfortunately like most other non-infectious diseases, there has been no epidemiological study conducted in south Asia to determine prevalence, incidence, gender and age distribution of MS.²⁵ The data available is only hospital based case series and only one such study was multicenter with over 100 patients.¹² All other patient cohorts are of much lesser number. It has also been found that since these were not targeted epidemiological studies, their utilization for extracting any meaningful epidemiological data is severely restricted. Pakistan's largest south Asian neighbor, India also lacks any large epidemiological study.²⁵ Similar gender distribution and mean age of onset was found by Pandit L et al.²⁶ in India as seen in our article (table 2).

Table 2: Comparison of characteristics of MS in Southern Asia in internationally published Multicenter Cohort studies from Pakistan, India and Iran

Country	First Author	Study Period	Study setting	Number of Cases	Female to male ratio	Mean age of onset	Prevalence in 100,000	Incidence
Pakistan	Wasay M ²⁵	2009-2010	Multicenter hospital based	100	1.5:1	32	-	-
India	Pandit L ²⁶	2011-2013	Multicenter hospital based	35	1.6:1	35	8.35	-
Iran	Etemadifar M ²⁷	2013	Ministry of Health report	42,200	3.48:1	-	54.5	5.87

No published data from neighboring Afghanistan was available for comparison.²⁵ Pakistan's other neighbor from Southern Asia Iran has the largest database of MS patients in this region.²⁵ Iran's largest data cohort published by the Ministry of health, has shown a medium frequency prevalence of 8.35 in 100,000 and a large female to male ratio of 3.48 to 1.^{25,27}

The highest level of evidence for clinical decision making in MS comes from randomized control trials (RCT), systematic reviews and meta-analyses.²⁸ They provide evidence on efficacy and safety and are crucial for regulatory approval. In situations where it might not be feasible to perform an RCT, high quality evidence can be generated from data collected in the real world clinical settings such as registries and health administrative databases.²⁸ Registries are databases that result from prospective, observational cohort studies aimed to collect individualized disease specific data. The main purpose of establishing a registry is to improve the delivery of health care and enhance our knowledge regarding the disease by collecting information on a standardized format. Randomized control trials (RCT) although provide the highest quality of data but their application gets limited in real world in several situations because of strict inclusion and exclusion criteria, cost of conducting an RCT and preferential focus of RCT on treatment efficacy vs provision of health care. Registries have the advantage of following up patients for a longer duration of time as compared to RCT.²⁹ [fink 2016] Data variables in MS registries range from personal data, clinical phenotypes, account of relapses, radiological data, MS related clinical outcome measures, treatment adverse events and quality of life measures and data of comorbidities.^{28,30} Registries do have their own sets of limitations. Problems with registries require active participation on the part of patient and the health care provider. Registries are also filled with inherent biases due to non-randomized sample collection. Over 700,000 patient of MS have been collected in various registries across Europe.³¹ MSBase is the biggest multinational MS registry which started enrollment back in 2003.^{32,33} It is active across 35 countries with over 60,000 patients included in the registry. (table. 3)

Table 3. Examples of MS registries

Name of MS registry	MSBase^{32,33}	OFSEP³³	MS-Register der DMSG³³	SMSreg³³	The Danish Multiple Sclerosis Registry³³
Country	Multinational, Australia ^a	France	Germany	Sweden	Denmark
Institution	MSBase Foundation Ltd	EDMUS Foundation, Université Claude Bernard, Hospices Civils de Lyon	MS Forschungs- und ProjektentwicklungsgmbH	Karolinska University Hospital, Stockholm	The Danish Multiple Sclerosis Center, Rigshospitalet, Copenhagen
Centers	35 Countries	41	181	64	
Enrolment started	2003	2010	2001	1996	1956
Patients enrolled	63534 ^b	68,097 ^c	48,000 ^d	19,257 ^e	25,000 ^f

a. Home to MSBase

b. www.msbase.org (accessed March, 2019)

- a. Home to MSBase
- b. www.msbase.org (accessed March, 2019)
- c. www.ofsep.org (accessed October, 2018)
- d. www.msregister.de (accessed January, 2017)
- e. https://vap.carmona.se/open/msvap/tabell/antal_reg/ (accessed December, 2017)
- f. www.rigshospitalet.dk/english/departments/neuroscience-centre/departments-of-neurology/research/the-danish-multiple-sclerosisregistry (accessed January, 2017)

The MS registries not only provide a solid clinical platform for MS research, but also helps in management of MS patients. Just to give an example, the Swedish MS registry (SMSreg), has provided data for over 100 scientific publications and had provided real world evidence in long term effective MS disease modifying agents.³⁴

There has been a global trend towards formation of national MS registries in most of the developed countries. Formation of an MS registry in a resource limited and densely populated country like Pakistan can serve as the first step in the long journey towards managing MS as per the established standards of care. Determining local MS epidemiology will assist in prognostication of disease, resource allocation and planning of national health services for MS and other acquired demyelinating diseases.

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Haris Majid; concept, data collection, data analysis, manuscript writing, manuscript review

Mohammad Wasay; data collection, data analysis, manuscript writing, manuscript review

Mazhar Badhshah; data analysis, manuscript writing, manuscript review

Mohammad Hassan; data analysis, manuscript writing, manuscript review