Multiple sclerosis in US minority populations

Clinical practice insights

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Summary

The heterogeneity of multiple sclerosis (MS) characteristics among various ethnic minority populations is a topic of recent interest. However, these populations are consistently underrepresented in clinical trials, leading to limited data on the effectiveness of treatments in these groups of patients and lack of an evidence-based approach to treatment. In order to achieve optimal disease management in the ethnic minority MS populations, a better understanding of the regional, socioeconomic, and cultural influences that result in underrepresentation of these groups in clinical trials is needed. Furthermore, it would be beneficial to identify the genetic factors that influence disease disparity in these minority populations. Suggestions for the identification and implementation of best practices for fostering the trust of ethnic minority patients with MS and enhancing their participation in clinical trials are offered.

Multiple sclerosis (MS) is a presumed autoimmune disorder of the CNS characterized by inflammatory demyelination and neurodegeneration, affecting approximately 400,000 people across the United States and over 2 million people worldwide.^{1,2} Symptoms of MS, a disease typically diagnosed in adult women between the ages of 20 and 50 years, vary tremendously and may comprise diffuse symptoms such as depression, pain, cognitive difficulties, and fatigue, as well as focal

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Minority populations in the United States, such as African Americans and Hispanic Americans, have a higher incidence of MS compared with their ancestral countries of origin.

symptoms such as weak motor and sensory deficits, visual disorders, spasticity, bladder and bowel dysfunction, and dysphagia.^{2,e1}

Although the cause of MS is unknown, it is a heterogeneous disease thought to result from complex interactions among genetic predisposition, sex, and environment.¹ Race is another important factor, but due to its complexity and overlap with some of the above elements, there is uncertainty around its role in MS. Although MS has been reported in most ethnic/racial groups, many studies suggest that it is more common in Caucasians of northern European ancestry.³ Minority populations in the United States, such as African Americans and Hispanic Americans, have a higher incidence of MS compared with their ancestral countries of origin.⁴ However, minority populations are often underrepresented in clinical trials in the United States,⁵ which is also likely true for MS-specific studies. It is therefore difficult to assess treatment response in these populations, even in subgroup analyses, because of the small number of patients.⁵ Inadequate access to specialty care, mistrust of the health care system, and cultural and religious beliefs are some of the common factors that affect participation in the health care system.⁶ This review discusses the current understanding of the clinical disease expression and provides suggestions to address the needs of these underserved, ethnic minority, MS populations.

Overview of clinical and genetic influences on disease progression in minority patients with MS

A PubMed review conducted on January 13, 2014, revealed that there were nearly 60,000 published articles in total on MS, with nearly 52,000 written in English; however, only 113 focused on African American (or black) and 23 focused on Hispanic American (or Latino) patient populations with MS (136 total). While these represent less than 1% of the literature on MS, many of the articles have been published within the last decade, suggestive of a growing interest in the study of MS in minority patients. Although variations in the definitions for many of the ethnic minorities were presented in the literature, they have been standardized for the purpose of this review. Only 2 articles describe the incidence of adult-onset MS across several racial and ethnic groups within the United States,^{7,8} while others have evaluated specific comparisons between 2 ethnic patient groups.^{4,9,10} Among the studies reviewed, ethnic differences were noted in overall incidence of disease, characteristics at onset of MS including age at onset, length of diagnostic delays, and disability at diagnosis, as well as characteristics over the course of the disease. Although the level of evidence varies based on the study design and the numbers and cohorts of patients included, several generalizations can be made.

Historically, it was thought that the incidence of MS was less common in African Americans than Caucasian Americans.^{e2} However, results of recent studies showed that this may not be the case. In a retrospective cohort study of 496 patients newly diagnosed with MS, the incidence rate per 100,000 person-years was higher in African Americans (10.2) than in Caucasian Americans (6.9), Hispanic Americans (2.9), or Asian Americans (1.4).⁷ Furthermore, African Americans had a 47% increased risk of MS, while Hispanic Americans had a 50% lower risk and Asian Americans had an 80% lower risk of MS compared with Caucasian Americans.⁷ Likewise, a contemporary study of 2,691 Gulf War–era military veterans with MS found that the incidence rate per 100,000 was higher in African Americans (12.1) than in Caucasian Americans (9.3), Hispanic Americans (8.2), Asian Americans (3.3), or Native Americans (3.1).⁸ These findings

Supplemental Data

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challenge the notion that MS is less common in African Americans than Caucasian Americans,^{e2} and support the increasing awareness of MS among other minority populations.⁷

Regarding clinical manifestations of disease, African Americans are more likely to have an older age at disease onset, whereas Hispanic Americans may have an earlier age at disease onset compared with other patient cohorts. However, the actual mean age at disease onset among the various ethnic patient populations varies between studies. For example, African Americans had a mean age at symptom onset of 38.3 years in the retrospective cohort study,⁷ and 30.8 and 29.9 years for African American men and women, respectively, in the study of Gulf War–era military veterans.⁸ Notably, although the ages at symptom onset and MS diagnosis vary between patient populations, the length of diagnostic delay appears to be consistent between groups in the various studies. Mean time from symptom onset to diagnosis was 2.0 years in the retrospective cohort study⁷ and 2.6 years in the military veterans study.⁸ While the earlier onset of disease adds to the concern that Hispanic Americans may also develop increased disability at an earlier age than other populations, the more aggressive disease course experienced by many African American patients also places them at an increased risk for disability. In support of this, African Americans were found to have a higher average Multiple Sclerosis Severity Score (MSSS) compared with Caucasian Americans (5.6 vs 4.5; $p < 0.001$) at diagnosis.^{9,e3}

Disease presentation and disease course have also been shown to vary among ethnic populations. African American patients may experience a more aggressive disease course and are more likely to have transverse myelitis, more frequent relapses, worse postrelapse recoveries, faster transition from relapsing-remitting MS (RRMS) to secondary progressive MS, and more severe ambulatory impairment compared with Caucasian Americans (table 1^{4,9}; figure 11).^{9,11} Furthermore, African Americans, Hispanic Americans, and Asian Americans are more likely to present with opticospinal MS, which is a distinct form of MS that is restricted to the optic nerves and spinal cord.^{9,e1} MRI results indicate that African Americans with MS have higher T2 and T1 lesion volumes, lower *N*-acetylaspartate values, and lower brain magnetization transfer ratios (figure e-1 at Neurology.org/cp).⁹ A higher CSF immunoglobulin G (IgG) index has also been reported in African American patients with MS compared with Caucasian patients with MS, although this was shown to not be a predictor of early disease progression.^{e4} However, in another study, elevated CSF IgG index was also observed in African Americans with MS compared with Caucasians with MS.^{e5} Furthermore, the elevated CSF IgG index negatively correlated with brain gray matter volume in African Americans with MS but not Caucasians with MS.^{e5} These observations raise at least the possibility of a more pronounced CSF humoral response in African Americans with MS and warrant further investigations.

Although fewer studies exist comparing Hispanic Americans with Caucasian Americans, research suggests that Hispanic Americans demonstrate a higher frequency of optic neuritis and transverse myelitis at presentation and have lower vitamin D levels compared with Caucasian Americans (table 1^{4,9}).^{4,7,12,e6} The higher rates of optic neuritis and transverse myelitis and the lower incidence rates of MS in Hispanic Americans may be related in part to their Asian ancestry.^{4,7} For example, longitudinally extensive spinal cord lesions (LESCLs), which occur predominantly with opticospinal MS and are associated with increased disability, have been observed with similar prevalence in both Asian Americans and Hispanic Americans (14%–31% and 19%, respectively), and it has recently been demonstrated that an increasing proportion of patients with non-European ancestry are at risk for LESCLs ($p = 0.03$) in addition to increased disability ($p = 0.05$).^{e7} Despite these differences, female preponderance, RRMS, and disease progression following diagnosis have been reported to be similar between Hispanic Americans and Caucasian Americans.^{4,7,10}

The role of genetics in the development of MS is a topic of intense research. Recent studies have implicated dysregulation of both immunologic pathways (e.g., cell-mediated immune mechanisms) and neuronal pathways (such as those involved in axonal guidance and long-term potentiation) as having potential roles in MS susceptibility.^{1,13} Genetic admixture mapping studies uncovered a direct correlation between the degree of African ancestry at the human leukocyte antigen region and disease severity as measured by MSSS.^{9,e3} Additional analyses revealed that

Table 1 Demographic and clinical characteristics of Caucasian American vs ethnic minority patients with multiple sclerosis

Characteristics (CA vs AA patients) ^a	CA (n = 717)	AA (n = 673)	p Value
Female sex, %	77.5	80.1	0.12
Mean age at onset, y (SD)	29.9 (8.6)	32.8 (9.7)	<0.001
Mean disease duration, y (SD)	9.9 (8.4)	9.7 (7.8)	0.62
Disease type, n (%)			
RRMS	513 (71.6)	402 (59.7)	0.001
SPMS	155 (21.6)	182 (27.0)	
PPMS	33 (4.6)	46 (6.8)	
PRMS	6 (1.5)	24 (1.8)	
Unknown course ^b	5 (0.7)	17 (4.6)	
Median time from disease onset to diagnosis, y (mean)	1 (3.4)	1 (3.1)	0.33
MSSS, mean (SD)	4.47 (2.6)	5.6 (2.8)	<0.001
Time to cane dependency, HR ^c		1.96	<0.001
Opticospinal MS, n (%)	53 (7.4)	72 (11.0)	0.02
Transverse myelitis, n (%)	84 (11.7)	180 (27.0)	<0.001
Motor onset, n (%)	138 (19.2)	209 (31.0)	<0.001
Seropositive for anti-aquaporin 4, n (%)	3 (4.2)	8 (6.2)	0.55
Characteristics (CA vs HA patients) ^d	CA (n = 76)	HA (n = 119)	p Value
Female sex, %	75.0	58.0	<0.05
Mean age at first symptom, y (SEM) ^e	32.6 (1.15)	28.5 (1.01)	<0.05
Mean age at first diagnosis, y (SEM) ^e	32.9 (1.48)	29.7 (0.98)	
Diagnostic lag, y (SEM) ^e	0.3 (0.12)	1.2 (0.26)	<0.05
Mean disease duration, y (SEM)	11.4 (1.07)	8.8 (0.75)	<0.05
Optic neuritis, %	19.7	31.5	<0.05
Sensory, %	27.9	13.9	<0.10
Motor, %	14.7	13.0	<0.10
Transverse myelitis, %	13.1	25.0	<0.05
Other, %	18.0	16.7	

Abbreviations: AA = African American; CA = Caucasian American; HA = Hispanic American; HR = hazard ratio; MS = multiple sclerosis; MSSS = Multiple Sclerosis Severity Score; PPMS = primary progressive multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis.

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^bPatients could not be classified into one of the preceding categories.

^cExpanded Disability Status Score = 6.

^dAdapted with permission of SAGE from Amezcua L, Lund BT, Weiner LP, Islam T. Multiple sclerosis in Hispanics: a study of clinical disease expression. Mult Scler 2011;17:1010-1016. Copyright© 2011 SAGE Publications.⁴

^eAnalyses were restricted to 113 Hispanic Americans and 65 Caucasian Americans.

Figure Distribution of African American and Caucasian American patients with multiple sclerosis across EDSS grades and benign and malignant categories

Box boundaries indicate the 25th and 75th quartiles, the line within each box is the median, and the 2 outer bars indicate the largest and smallest observed values that are not outliers of Expanded Disability Status Score (EDSS) differences $p < 0.001$. The dashed horizontal line across the 6 grades represents the expected percentage of patients in each grade (16.7%). Adapted with permission from Lippincott Williams & Wilkins/Wolters Kluwer Health: Kister I, Chamot E, Bacon JH, et al. Rapid disease course in African Americans with multiple sclerosis. *Neurology* 2010;75:217-223.¹¹

the classic/multifocal subtype of MS is associated with DRB1*15 alleles in African American patients (figure e-2).⁹ The lower risk for developing MS in Hispanic American patients may be related, in part, to the increasing proportions of Asian ancestry in the admixed population.⁷ The prevalence of opticospinal MS in Hispanic Americans and Asian Americans may underlie a potential link between the genetic variations in these ethnic populations with manifestations of demyelinating disorders.

Challenges to providing optimal treatment for minority patients with MS

Differential response to first-line treatments Multiple sclerosis is a chronic disease and patients must make a long-term commitment to drug therapy. In the last 20 years, interferon- β -1 and glatiramer acetate have been used as disease-modifying therapies (DMTs) for RRMS.¹⁴ There is some evidence that interferon- β -1 is relatively less effective in African American patients compared with Caucasian Americans. In a post hoc study investigating interferon- β -1a (EVIDENCE trial), the subset of African American patients ($n = 36$) experienced more MS exacerbations, were less likely to remain exacerbation-free, and developed more new MS lesions at 48 weeks ($p = 0.04$) while on interferon- β -1a therapy than Caucasian American patients.¹⁵ However, the trial was not designed to investigate the effect of race/ethnicity, and it has not been determined whether the reduced clinical response is a result of a treatment effect or differences in the natural history of the disease in this population.¹⁵ In a retrospective chart review of patients with MS treated with conventional DMTs (interferon- β -1a or -b, glatiramer acetate, or natalizumab), African American patients ($n = 66$) demonstrated an increased median Expanded Disability Status Scale (EDSS) score difference ($p < 0.001$), suggestive of poorer response to DMTs than

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Caucasian American patients.¹⁶ The limited representation of minority patients in clinical trials makes it difficult to determine the effect of treatment, including DMTs, in patients with MS.

Socioeconomic barriers Many minority patients in the United States with complex chronic diseases and physical disabilities may have difficulty accessing and utilizing specialty care because of barriers such as lack of or limited insurance, low income, lower education levels, and language and computer literacy barriers.^{17,18} In a large-scale study of 21,557 patients with MS enrolled in the North American Research Committee on Multiple Sclerosis (NARCOMS) registry, not only were African Americans found to have increased odds of severe disability, but they were also more likely to be in the lowest income and education levels and less likely to have private insurance compared with Caucasian Americans (table 2).¹⁰ When socioeconomic status was included as a covariate in data analysis, disease severity between African Americans and Caucasian Americans was reduced, indicating that failure to account for socioeconomic status leads to overestimation of the differences in disease severity.¹⁰ A related NARCOMS study revealed that significantly fewer Hispanic American patients received mental health or rehabilitation care compared with African Americans or Caucasian Americans, whereas fewer African Americans received care at an MS clinic than Caucasian American or Hispanic American patients.¹² In contrast, patients with MS who are cared for by a neurologist are more likely to undergo diagnostic and treatment-related testing; receive DMTs, alternative therapies, and palliative care for symptoms; have shorter durations of illness; be less disabled; and see other specialists such as physical therapists, mental health specialists, ophthalmologists, and urologists.¹⁷

Lower-income ethnic minority patients tend to have poorer health and worse outcomes for a spectrum of diseases.¹⁸ A study conducted on low-income minority patients with MS determined that cultural and socioeconomic factors affect MS management and quality of care.¹⁸ A major finding was the general lack of adequate education and understanding about treatment, known resources, and realistic expectations about treatments among Hispanic American and African American patients with MS.¹⁸ Moreover, a significant determinant of ambulatory disability in Hispanic Americans is timing of migration to the United States. Hispanic Americans who were older when they migrated (>15 years) had a >threefold increased risk of having ambulatory disability compared with those born in the United States (odds ratio [OR] 3.61; 95% confidence interval [CI] 1.1–12.2).⁴ The differences between the migrants and nonmigrants may have been a result of health care disparities that could, in turn, reflect economic, educational, or environmental elements not yet understood, but nevertheless important to the modification of disease disability.

Cultural influences as potential barriers in MS Cultural influences, such as religious beliefs and societal distrust, are thought to be potential barriers with respect to participation of some minority patients in clinical trials. For example, deeply religious patients may have a direct conflict between their faith and the study treatments and medical procedures required by the study, such as the use of concomitant therapy, acceptance of blood products, or receiving immunizations or antibiotics.^{e8} A review of published medical and social research from 1995 to 2008 demonstrated that minority patients reported mistrust of the medical community, especially of researchers and sponsoring agencies (in contrast with physicians and nurses), and were fearful of the concept of experimentation and feeling “like a guinea pig.”¹⁹ In a survey conducted on 776 older African Americans and Caucasian Americans, higher levels of societal distrust have been reported for African Americans than Caucasian Americans because of perceived discrimination in health care (table 3).⁶ Previous studies have also suggested that

Table 2 Socioeconomic characteristics in Caucasian American vs African American patients with multiple sclerosis in the NARCOMS registry

Characteristic	Patients		p Value
	Caucasian American (n = 20,540)	African American (n = 1,017)	
Married/cohabitating, n (%)	13,047 (68.7)	415 (43.9)	<0.0001
Education, n (%)			
<12 y	677 (3.3)	48 (4.8)	0.002
High school diploma	8,391 (41.2)	434 (43.3)	
Associate degree	3,460 (17.0)	190 (18.9)	
Bachelor degree	4,697 (23.0)	203 (20.2)	
Postgraduate degree	3,168 (15.5)	128 (12.8)	
Annual income			
<\$15,000	3,008 (16.6)	310 (33.4)	<0.0001
\$15,000	3,691 (20.4)	245 (26.4)	
\$30,000	4,831 (26.7)	213 (23.0)	
\$50,000	5,082 (28.1)	135 (14.6)	
>\$100,000	1,465 (8.2)	24 (2.6)	
Insurance			
VA/CHAMPUS	640 (4.1)	62 (7.9)	<0.0001
Medicaid	437 (2.8)	70 (8.9)	
Medicare	1,523 (9.7)	113 (14.4)	
Medicare and Medicaid	749 (4.7)	76 (9.7)	
Private	12,386 (78.7)	463 (59.1)	
Region			
West	5,255 (25.6)	255 (14.1)	<0.0001
Midwest	4,652 (22.6)	143 (26.1)	
South	5,373 (26.2)	411 (40.4)	
East	5,260 (25.6)	198 (19.4)	

Abbreviation: NARCOMS = North American Research Committee on Multiple Sclerosis.

Adapted with permission from Marrie RA, Cutter G, Tyry T, Vollmer T, Campagnolo D. Does multiple sclerosis-associated disability differ between races? *Neurology* 2006;66:1235-1240.¹⁰

African Americans may be more distrustful of clinical research as compared with Caucasian Americans, thereby suppressing participation in clinical trials.⁶ This societal distrust may be warranted in light of the Tuskegee Syphilis Study, which was conducted from 1932 to 1972 on African American men who were not properly informed of the true intent of the study and who did not receive adequate treatment for their disease.⁹ Similarly, research has demonstrated that Hispanic Americans are less likely than Caucasian Americans to use preventive care and are also less likely to have entered the health care system for any type of care.²⁰ At this time, no data exist related to MS health outcomes in Hispanic Americans.

Clinical practice insights for improved management of minority patients with MS

Disease-modifying therapies for MS are intended to reduce the frequency and severity of acute relapses and slow or prevent further disease progression and disability. Programs that promote

Table 3 Types of distrust in clinical research in Caucasian Americans vs African Americans

	Survey responders		
	Caucasian American (n = 481)	African American (n = 295)	p Value
Sociodemographics			
Mean age, y (SD)	76.0 (9.0)	69 (10.0)	<0.001
Education: college graduate or higher, %	56	34	<0.001
Has current health insurance, %	98	98	0.5
Has personal doctor or nurse, %	95	93	0.2
Experimental factors, %			
History of discrimination in health care	15	43	<0.001
Awareness of Tuskegee Syphilis study	41	64	<0.001
Previous trial participation	59	52	0.07
Trust in physician, n (SD) PCAS trust subscale ^a	77.1 (15.3)	77.6 (14.9)	0.7
Individual distrust index items, %			
Likelihood that you/people like you will be used as guinea pigs without permission	27.7	54.2	≤0.05
Frequency that doctors, in general, prescribe medications to experiment on people without their knowledge	40.6	60.0	≤0.05

Abbreviation: PCAS = primary care assessment survey.

^aThe PCAS trust subscale is scored from 0 to 100.

Adapted with permission from Durant RW, Legedza AT, Marcantonio ER, Freeman MB, Landon BE. Different types of distrust in clinical research among whites and African Americans. J Natl Med Assoc 2011;103:123-130. JNMA© 2011 reprinted by permission of the NMA whose permission is required for further use.⁶

patient education, medication adherence, symptom management, and a healthy lifestyle are all important in the overall management of MS, regardless of ethnicity.¹⁴ A recent multisite study of Italian patients found that educational attainment (OR 5.0; 95% CI 1.7–14.4) and exposure to information aids (OR 3.3; 95% CI 1.6–6.9) were main predictors of MS knowledge.^{e10} Minority patients may also have poor communication with their physician or have difficulty finding educational materials written in their primary language.¹⁴

Clinical best practices that address patients' ethnic and cultural differences, as well as potential language or educational barriers, should be recognized and implemented by health care professionals to help gain the trust of their patients and ensure their patients' unique needs are being addressed. Whenever possible, all patients with chronic diseases such as MS may benefit from having a chronic disease manager or nurse navigator due to the complexity of the health care system, although it is recognized that these services are not reimbursed. For example, a recent study of patients with chronic obstructive pulmonary disease (COPD) reported that the integration of a COPD nurse navigator who educated patients and their families and transitioned these patients through various points of care resulted in a significant decrease in emergency department visits and hospital stays, which can improve patient outcomes.^{e11}

For patients treated in clinics that do not have resources to address the needs of minority patients, patient referral to neurologists who specialize in MS, in private or academic settings including MS centers, may be considered. In some cases, the health care professionals at these centers may have a wider range of experience with disease differences in ethnic/racial minority

patients and increased familiarity with the clinical research concerning disease course and ethnicity. Educational resources need to be readily available outside of the clinic for minority patients with MS. Partnering with patient advocacy groups such as the National MS Society's Hispanic Latino Advisory Council and African American Advisory Council can modify the minority experience as well as provide support on the best approaches to reaching and engaging patients in these MS communities. Coordinated efforts by these multidisciplinary health care groups should be made to direct patients to these important resources.

In light of the growing recognition that there is considerable variability in the clinical expression of MS in minority populations, more data are needed to optimize the clinical management of these patient populations, including an understanding of whether currently approved DMTs available for the treatment of RRMS have the same observed response in minority patients. Despite inclusion of minorities in clinical trials mandated by the NIH Revitalization Act of 1993, the participation of African Americans and members of other minority populations is disproportionately low in MS trials compared with Caucasian Americans.⁶ This underrepresentation may hinder the ability to not only identify differences in treatment response, but also support the need for epidemiologic studies to incorporate cultural, environmental, or physiologic factors unique to that population. Because MS differs both in incidence and clinical expression, prospective cohort studies that incorporate race/ethnicity need to be conducted if we are to better understand MS and establish the best standard of care specific to each patient's needs.⁵ The increased recruitment and inclusion of ethnic minority patients in MS research are essential to overcome these issues.¹⁹ Minority populations have been successfully recruited and retained in randomized controlled trials to increase breastfeeding among ethnically diverse, low-income women,¹² and the strategies employed in these studies should be applied to future MS research.

Phase 4 studies with health economics and outcomes research components, as well as large, observational, prospective, cross-sectional studies with prospectively designed subgroup analyses of minorities, will provide a more comprehensive, data-driven analysis of the obstacles and outcomes prevalent in the minority MS community. Moreover, studies in patients with aggressive disease at trial sites with a high minority population and studies investigating breakthrough disease combined with an assessment of adherence would provide evidence-based criteria upon which treatment decisions could be made. In the absence of prospective clinical trial data, registries in the real-world setting, as well as coordinated retrospective analyses of relevant datasets, could also provide valuable insight into the unique disease characteristics and treatment approaches and outcomes in minority patients with MS.

DISCUSSION

In order to optimize disease management and treatment outcomes for minority patients with MS, increased awareness and understanding of their variable genetic, pathophysiologic, environmental, sex, socioeconomic, attitudinal, and demographic factors are required. The development and delivery of appropriate educational material, the cultivation of patient trust, and the promotion of research and clinical trial participation are essential for addressing the needs of these underserved ethnic minority patients with MS.

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DISCLOSURES

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