Editorial

The Discrepancy of Neurological Diseases between China and Western Countries in Recent Two Decades

Jun Ni[1], Fei Han[1], Jing Yuan[1], Han Wang[1], Dong-Chao Shen[1], Yan Xu[1], Li-Ying Cui[1,2]

[1]Department of Neurology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China

[2]Neuroscience Center, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China

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Introduction

Neurological diseases are characterized by high frequency of disability and mortality with pathogenesis largely unknown. Genetic, refractory, and rare diseases account for a large proportion of neurological diseases; sympathetically, limited curable treatments are available. Hundreds of millions of people worldwide are affected by neurological disorders. The diagnosis and treatment of neurological disorders have made significant progress in recent years, especially in the past two decades with the rapid development of technology. For example, regarding acute ischemic stroke, the disability, mortality, and recurrence rate were notably decreasing with the improvement of intravenous and intra-artery treatment and with the emphasis on secondary prevention in recent years worldwide. More surprisingly, gene therapy is emerging as a powerful approach to help patients suffering from gene defects with the potential to treat and even cure the genetic disorders. Almost at the same time, remarkable changes have been made in terms of diagnosis, treatment, and prevention of neurological diseases in China. Even more importantly, China is a country having very large geographical areas with disequilibrium of economic development and having enormous population covering diversified cultures and customs. Therefore, risk factors and spectrum for some of the neurological disease are different from Western countries. Hereby in this paragraph, we reviewed the progression of neurological diseases in the recent two decades and further compared the differences between China and Western countries. The comparison will help medical practitioners and researchers to better understand the gap, to make better medical decisions for patients, and to encourage progress in research field.

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Stroke and Cerebrovascular Disease

Stroke is the second most common cause of death worldwide, and a major global cause of disability.[1] There are significant geographical differences in stroke burden by regions and country income levels. In the past two decades, within Western countries, there has been a great reduction in stroke incidence, mortality, mortality-to-incidence ratios, and disability-adjusted life years (DALYs) lost, which could be explained by the good health services and strategies for stroke prevention and medical care in these countries. Conversely, in China, stroke incidence has increased, and mortality-to-incidence ratios and DALYs lost are much higher than those in high-income countries. Although reductions in stroke mortality have taken place globally, compared to the high-income countries, a two-fold higher stroke mortality rate was observed in the low-income and middle-income countries.

In 2017, the up-to-date stroke epidemiology survey in China was published in *Circulation*.[2] The age-standardized stroke prevalence, incidence, and mortality rates were 1114.8/100,000 people, 246.8/100,000, and 114.8/100,000 person-years, respectively. Stroke burden in China has increased over the past three decades and remains

Address for correspondence: Prof. Li-Ying Cui, Department of Neurology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China
Neuroscience Center, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China
E-Mail: pumchcuily@sina.com

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particularly high in rural areas. This might be explained by the westernized lifestyle and sociodemographic changes in China which may have had an impact on the prevalence of common stroke risk factors. Geographical gradients (North to South) of stroke burden within China were observed as well. The highest incidence and mortality of stroke were in the Northeast region, while Central China ranked second, and the regions with lowest incidence and mortality rates were in South China.

Compared with populations of European and US origin, Chinese populations have a higher proportion of strokes attributable to intracerebral hemorrhage (ICH). It has been reported that there is a twice higher rate of ICH incidence in Asian people compared with that in other ethnic populations.[3] Chinese also have an apparently different distribution of ischemic stroke subtypes, in comparison with Caucasian populations. There are higher overall proportions of small vessel disease (lacunar) and large artery atherosclerotic ischemic stroke in Chinese and a lower proportion of cardioembolic stroke.[4] The frequency of ischemic stroke due to intracranial atherosclerotic stenosis seems to be higher in Asian people (30–50%) than in Caucasian populations (5–10%).[5]

Previous studies investigating the epidemiology of asymptomatic cerebral small vessel disease (CSVD) in the general population were mainly carried out in Western countries, including the Framingham study, the Rotterdam scan study, and the Cardiovascular Health study. The prospective community-based Shunyi Study, which was conducted in 2013 in the rural area nearby Beijing, supplemented the epidemiological data of CSVD in Chinese population. When comparing participants in the same age group from Western world region, a higher burden of lacunas but a relatively lower prevalence of cerebral microbleeds was observed, which might be attributable to the very low awareness, treatment, and control rate of vascular risk factors (data from our team, not published).

Intravenous thrombolysis (IVT) for acute ischemic stroke represents one of the most important and recent breakthroughs in medicine. Recombinant tissue-type plasminogen activator (alteplase, rtPA) was first approved by the Food and Drug Administration in the United States in 1996.[6] The safety and efficacy of rtPA when administered within the hyperacute time frame after ischemic stroke onset are solidly supported by combined data from multiple randomized controlled trials ever since then. It is strongly recommended in Chinese guidelines, and its efficiency has been confirmed by extensive clinical experiences in China. Endovascular thrombectomy with stent retrievers for acute ischemic stroke has evolved substantially after 2015, which could significantly reduce disability for patients with large vessel ischemic stroke.[7] Based on the best evidence currently available in the Chinese guideline for the early management of patients with acute ischemic stroke, mechanical thrombectomy, in addition to IVT, is recommended for treatment of acute stroke in patients with large artery occlusions in the anterior circulation up to 6 h after symptom onset. Intensive efforts have been made by Chinese health systems and neurologists to minimize delays of hyperacute phase management and thus to maximally improve the efficacy and safety of stroke reperfusion therapies. According to the official government report, increase of both IVT and thrombectomy rates, as well as a reduction of door-to-needle time has been observed year by year in the experienced stroke centers of China.

China is also making great progress in the aspect of stroke secondary prevention. The government has supported the organization and publication of several national stroke prevention guidelines to improve standards of care. The cluster-randomized, guideline-based, structured care program, known as the Standard Medical Management in Secondary Prevention of Ischemic Stroke in China (SMART) study, demonstrated that using a program of guideline-based structured care and patient education in China is feasible, which could increase the patient adherence to the medical therapy and further reduce the recurrent stroke risk and improve patient health status.[8] Furthermore, the subgroup analysis of SMART study showed that implementation of the structured program can improve the 6-month functional outcome in low-educated patients[9] and also demonstrated that elevated fasting blood glucose was found to be predictive of poor functional outcome in nondiabetic stroke patients.[10] Analysis for prescription of traditional Chinese medicine (TCM) for the acute stroke patients found that nearly one-third of the hospitalized patients were prescribed TCM at discharge.[11] Findings from Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial, which was conducted in China, showed that, among patients with high-risk transient ischemic attack or acute minor ischemic stroke, treatment with a combination of clopidogrel with aspirin for 21 days, followed by clopidogrel alone for a total of 90 days, is superior to aspirin alone in reducing the risk of subsequent stroke events.[12] The CHANCE study has made a great international impact and updated the current guidelines for the management of acute ischemic stroke published by both Chinese Medical Association and American Heart Association/American Stroke Association.

Dementia

Dementia is one of the leading causes of disability in the elderly population across the world. Given the huge social burdens put by this devastating disease, efforts to elucidate the mechanisms and find optimal treatments have been made for decades; however, challenges still exist.

In recent years, the prevalence of dementia in China has been reported to be similar to that in Western countries.[13] Moreover, with the aging of the population in China, the prevalence of dementia increased slightly based on recent population-based study compared to that of 20 years ago.[13,14] Jia *et al.* reported the prevalence of dementia, Alzheimer's disease (AD) and vascular dementia (VaD)

were 5.14%, 3.21%, and 1.50%, respectively,[13] compared to that of 5.0% for dementia, 4.8% for AD, and 1.1% for VaD reported by Prof. Zhang's study conducted in 1997 and to that reported in a systematic review of studies conducted from 1980 to 2004 in China.[14,15] Both studies found that AD ranks the most common type of dementia and that VaD ranks the second, which is similar to the pattern of dementia observed in Western countries. Jia *et al.* also found that the prevalence of dementia and AD in rural populations is significantly higher than that in urban populations in China, and divergence in education might be an important explanation for this observation, which is different from Western countries where urban-rural areas exhibited no such big differences. In China, the crude incidence in persons' 65 years was 12.1/1000 person-years for dementia, 8.2/1000 person-years for AD, and 3.1/1000 person-years for VaD, which are comparable with those reported previously in Europe and the United States.[16] However, recent reports from the Framingham Heart Study and the Einstein Aging Study in the United States revealed decreased trends in the incidence of dementia, although the factors contributing to the decline have not been completely identified.[17,18]

According to World Alzheimer's Report 2015, there were 9.5 million dementia patients in China, accounting for 20% of the world's dementia patients and are expected to increase to 16 million by the time of 2030.[19] Recent study reestimated the socioeconomic costs of AD in China, demonstrating that the total costs were US $167.74 billion in 2015 and are predicted to reach US $507.49 billion in 2030 and US $1.89 trillion in 2050, much higher than the previous estimation made by the World Alzheimer's Report 2015.[20] Hence, China is facing an enormous challenge and disease burden of dementia.

Research and medical care on dementia have progressed greatly in these two decades in China with the enactment of guidelines on diagnosis and treatment,[21] more establishment of memory clinics,[22] the employment of new technology for early detecting biomarkers,[23] and the development of new drugs.[24,25] New investigational product developed in China, octohydroaminoacridine succinate, is under Phase III trial for the treatment of AD,[24] and DL-3-n-butylphthalide, a drug for acute ischemic stroke, demonstrated its efficacy for vascular cognitive impairment without dementia with good safety.[25] However, challenges still exist. Given the huge population in China, proper diagnosis and treatment are still unavailable to many dementia patients because of a lack of specialists in dementia and memory clinics, especially in underdeveloped areas, compared to Western countries.[22] To confront the difficulties and raise the countermeasures, the Chinese government has launched several national projects in these recent years.

Parkinson's Disease and Movement Disorders

Parkinson's disease (PD) is a movement disorder and the second most frequent neurodegenerative disease in China. Age-dependent prevalence of PD is found in worldwide populations, ranging between 41/100,000 inhabitants between 40 and 49 years and 1903/100,000 inhabitants older than 80.[26] A study from Beijing, Xi'an, and Shanghai of China, published in 2005, showed that the prevalence of PD was 1.7%, suggesting that the prevalence of PD in China was similar to that in developed countries.[27] Another meta-analysis revealed that the prevalence of PD in China was about 1.99 million in 2005, and it is estimated to reach to 4.94 million in 2030, with an increased proportion of the patients in selected countries arising from 48% to 57%.[28] Since PD predominantly affects older adults,[29] as populations' age, PD is expected to impose an increasing social and economic burden on societies, especially in economically developing countries. There is increasingly need to develop strategies to meet the health-care needs of patients with PD.

In contrast to the high prevalence, much lower incidence of motor complications in Chinese populations was identified than that in Western countries.[30-32] Many of the PD patients in China were treated with low-dose levodopa and combination of low-dose antiparkinsonian agents, which might be influenced by Chinese cultures.[32] Further investigation is also warranted to identify the possible mechanism and optimal treatment for PD.

Recently, there is also progress in genetic movement disorders. Chinese neurologists and reserachers identified some new causative genes for single gene disorder. For instance, *PRRT2* was identified by Chinese neurologists as the causative gene of paroxysmal kinesigenic dyskinesias (PKD) as well as other paroxysmal dyskinesias.[33-35] While genetic etiology may not show great differences in movement disorders of Chinese from other ethnic groups, abundance of patient resources would facilitate the identification of novel pathogenic genes. With collaboration, other potential causative candidates for *PRRT2*-negative PKD patients had recently been spotted by Chinese researchers such as *KCNMA1*, *SLC9A1*, and *SCN8A*.[36] Today, the gene therapy has become the potentially promising strategies for treatment of neurological diseases; further work is inevitably needed for treatment of genetic movement disorders.

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS), as a progressive neurological disease that causes disability and death, is catching great attention recently. The aim of the establishment of the ALS International Executive Committee is to promote the clinical and research work on the diagnosis of ALS. Epidemiologic data from Europe, America, and Japan showed that the peak age of ALS onset is between 60 and 70 years.[37,38] Unfortunately, there are no epidemiologic data about ALS in the mainland of China so far.[39] However, our ALS national collaboration team collected data from ten ALS centers in seven cities of China. The results indicated that the mean age of onset was 52.4 ± 12.1 years. The peak age at onset was 55–59 years for men and 45–49 years for women.[40] Genetic backgrounds and environmental factors may account for the differences.

The genetic features of ALS in the mainland of China are distinct from that in Caucasian populations.[41] In Europe, the most common mutations were the C9orf72 repeat expansions, for both familial and sporadic ALS patients, followed by *SOD1*, *TARDBP*, and *FUS* mutations.[42] Since ALS patients carrying *C9orf72* mutation often present with frontotemporal dementia concomitantly, this might be the reason that the incidence of dementia in ALS patients in Europe and America is much higher than that in China and other Asian countries. In contrast, *SOD1* is the gene with highest mutant frequency in Chinese ALS patients, followed by *FUS* and *TARDBP*, while the repeat expansion in *C9orf72* is very rare.[43,44]

Inflammatory Demyelinating Diseases of the Central Nervous System

Inflammatory demyelinating diseases (IDDs) of the central nervous system, for example, multiple sclerosis (MS) which predominantly affects young adults, are characterized by disease relapses and progressive disability. The significant difference of IDD between China and Western countries is the incidence and prevalence of MS and neuromyelitis optica spectrum disorder (NMOSD). For MS, the incidence and prevalence vary geographically, higher latitude correlating with increased prevalence, incidence, and mortalities.[45] The high-frequency areas of the world include all of Europe (including Russia), Southern Canada, the Northern United States, New Zealand, and southeast Austria. In these areas, the prevalence ranges from 60 to 300/100,000.[45-47] China, Japan, and Korea belong to the low-frequency areas. A population-based survey suggested that the prevalence of MS in Shanghai, the South part of China, is 1.39/100,000.[48] For the past 20 years, many studies investigated the pathophysiology and mechanism of actions of the disease-modifying drugs (DMDs) for treatment of MS, to reduce the frequency of episodes, disability accrual, and severity of irreversible nerve damage.[49,50] Although availability of DMD increase, there is still the need to personalized DMD since only some of the patients respond satisfactorily to a given treatment based on evidence from clinical trials and daily clinical practice.[49]

Contrast to MS, the incidence and prevalence of NMOSD in China is much higher than that in Western countries. Prevalence rates (/100,000) of NMO/NMOSD were reported to be 3.9 in the United States,[51] 4.4 in Denmark,[52] 2.0 in South East Wales,[53] and 0.7 in North West England.[54] Until now, there was no epidemiological study about NMOSD in China. However, data from the MSNMO database, collected from an observational and prospective cohort organized by Peking Union Medical College Hospital (PUMCH),[55] showed that the ratio of MS: NMOSD is about 1:2–3. A study from North East Tuscany showed that this ratio is 42.7:1.[56]

Syphilis and Neurological Syphilis

Epidemiology and disease spectrum of syphilis have changed greatly in recent decades. Based on the data from Chinese Center for Disease Control and Prevention, the incidence of syphilis has been increasing significantly since the 1980s, especially during 1995–2000s. Latent syphilis increased by more than 50%, while the rate of primary and secondary syphilis had declined in recent years, which was different from that of the 1950s.[57] The data of neurological syphilis from PUMCH showed that notable increasing trend was present since 1980s. In detail for stages and clinical types of syphilis, compared to that of the 2001–2010, the prevalence of third-stage neurological syphilis including tabes dorsalis (syphilitic myelopathy) and general paresis increased significantly after 2011 (28% vs. 69%). Contrastly, meningovascular syphilis decreased from 36% to 0% (data from our team, not published). These changes make clinical challenges to physicians for the diagnosis and prompt treatment of syphilis.

Syphilis still remains a major popular public health issue in China and national measures according to the epidemiological features are urgently warranted to control the disease.

In conclusion, with dramatic growth of the economics and significant transformation of lifestyle for the past two decades, the epidemiology and spectrum of neurological disorders are potentially changing and imposing great challenges for neurologic practice in China. Enormous clinical researches and population-based studies are emerging for understanding the risk factors, disease progression, management, and prognosis of certain neurological diseases, and the spontaneous development in neuroscience advance the understanding of pathogenesis of neurological disorders. Chinese neurologists would need to balance the domestic and international challenges and opportunities and to be part of the world force for imminent discoveries and development of neurologic practices.

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