

Epilepsy in China: major leaps in the last two decades

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Abstract

China has about 10 million people with epilepsy. A vast 'epilepsy treatment gap' in China mainly driven by deficiencies in healthcare delivery and social discrimination resulting from cultural beliefs about epilepsy. The WHO's Global Campaign against Epilepsy Demonstration Project in China, which showed that it was possible to treat epilepsy in primary care, was a significant milestone. The China Association against Epilepsy has been a vital force to stimulate epilepsy interest. Nearly 20 anti-seizure medications are available in China. Non-pharmacological options are available, but they are still unmet needs for epilepsy management. The Chinese epilepsy research portfolio is varied, but areas of concentration and thus, expertise are particularly in epidemiology and clinical research. The challenges remaining for further improvement for delivering care for people with epilepsy in China are primarily related to public health and to reducing inequalities within this vast country.

Introduction

China is a vast, diverse country with 1.38 billion inhabitants, half of whom live in rural areas. The 2018 Gross National Product per capita was reported as US\$ 9470, a ten-fold increase over the last two decades, attesting to the rapid economic growth of China¹. It is estimated that 10 million people in China have epilepsy, but only about a third of them are receiving appropriate or adequate treatment. The Global Burden of Disease Study estimated the burden of epilepsy in China as 1.6 million Disability Adjusted Life Years (DALYs), counting for 12% of that in global, and 95% of that in East Asia². From 1990 to 2016, a significant decrease of 41% (95% uncertainty intervals: -51%, -29%) was found in age-standardised DALY rates due to epilepsy in China mainly due to the ageing of the population³.

The first record of epilepsy in China was in the 'Inner Canon of Huangdi' over 2200 years ago⁴. In Chinese, epilepsy is termed 癫痫 (Dian Xian), the first character is the derogatory term for a person who has a mental disorder (crazy) and the second is the condition (seizures). Epilepsy imposes enormous physical, psychological, social and economic burdens on individuals, families, communities and countries, compounded by the misunderstanding, fear and stigma which has prevailed for millennia.

Many people with epilepsy could be seizure-free with relatively cheap treatment. Currently, in China, about two-thirds of those with epilepsy are either not receiving treatment or the treatment received is inadequate or inappropriate⁵; this proportion exceeds 87% in Tibet⁶. This vast 'treatment gap' is mainly driven by deficiencies in the delivery of healthcare and the social discrimination attached to epilepsy resulting from cultural beliefs.

In China, there is a small number of epilepsy specialists and neurological facilities, usually based in larger cities, and these are insufficient for the large number of people with active epilepsy⁷. There is also an uneven distribution of specialist and facilities among regions as medical resources are even rarer in the underdeveloped areas, particularly in Central and Western China. In rural areas, this is compounded by the high cost of long distances travel to healthcare facilities, often with limited transport options. In 2002, WHO sponsored the Global Campaign against Epilepsy (GCAE) Demonstration Project in China, which assessed the feasibility of delivering appropriate epilepsy management in primary care settings. The success of the project stimulated the Chinese government to expand the initiative to more sites throughout the country. This expansion was an explicit confirmation of an upgrade of care for epilepsy to a high priority tier for medical and health services in China⁴.

The last two decades, in parallel with economic growth, have seen a rapid improvement in the epilepsy scene in China, not only in clinical care but also in research. In 'traditional' parts of China, epilepsy is not perceived as a medical condition, and there is a vast treatment gap. In 'modern' China, epilepsy care has made inroads and state of the art clinical and surgical treatment is delivered side by side with research at the forefront of knowledge and science. Here, we review the current situation of epilepsy in China, from organisational aspects, management and research. We present the experience derived from the development of an effective and sustainable framework for epilepsy care and scale-up in resource-poor settings. We also discussed the challenges and opportunities for epilepsy research and strategies to promote epilepsy as a public health priority.

Networking and organisational aspect

The China Association against Epilepsy (CAAE) (www.caae.org.cn) was established and accepted as a chapter of the International League against Epilepsy (ILAE) and of the International Bureau for Epilepsy (IBE) in 2005⁸. By 2018, CAAE membership exceeded 10000 and they are now 28 provincial branches. In the last decade, CAAE has been a vital force to stimulate epilepsy interest in China. It has been a major drive to develop professional care, and conducted campaigns to reduce misconceptions, stigmatisation and discrimination of epilepsy, which may have lead to a narrowing of the treatment gap.

In 2007, CAAE launched the first epilepsy guideline in China⁹; this was revised in 2015¹⁰ and a further review is due in 2020. Since the publication of the first guidelines, expert opinion reports (see Box 1) focusing on various aspects of epilepsy management and prevention have been launched, helping to improve epilepsy care. CAAE also administer EEG training course nationally and nearly 2000 physicians, nurses and technicians have already been certified. The 'Going West Project', using telemedicine, brought case studies, ward-rounds, lectures and consultations to over 40 remote areas in the West of the country. Other initiatives, such as conferences, courses¹⁰, and an annual Epilepsy Summer School, have delivered training to thousands of physicians from all levels of health care.

International networking plays an important role in the development of epilepsy affairs in China. The Commission on Asian and Oceanian Affairs and the Asian Epilepsy Academy provide links between ILAE, IBE, WHO and CAAE. There are

also broad collaborations with epilepsy centres in North America, Europe and Australia. CAAE was instrumental in encouraging China's authorities to co-sponsor at the 68th World Health Assembly in 2015, a resolution on the burden of epilepsy and the need for coordinated action at the country level to address it. China also had an essential role in the approval of an intersectional **action plan on epilepsy and other Neurological Disorders**' at the 73rd World Health Assembly in November 2020. **These call for coordinated action at a country level to address epilepsy needs. These were the major epilepsy milestones in the history of the WHO.**

Epidemiology

Aetiology

Between a third and half of people with epilepsy in China have a symptomatic condition¹¹⁻¹³. Brain injury, at birth or later, vascular causes, and central nervous system (CNS) infection are the most frequent identified risk factors¹³⁻¹⁵. Perinatal injuries are the leading risk factor in children, while CNS infection and traumatic brain injury are most common in teenagers and young adults. In people aged over 40 years, cerebrovascular disorders, especially stroke, are the most common¹⁵. The most common comorbidities reported are sleep disorders, headache, anxiety, and depression¹². To date, however, no report of systemic comorbidities amongst people with epilepsy in China is available.

Prevalence, incidence and mortality

The burden of epilepsy in China was mostly unknown until 1983, when the first nationwide epidemiological survey was carried out in six urban areas and 22 rural

areas. A prevalence rate of 3.7-4.4 per 1000, and an incidence rate of 30-40 per 100000 person-years were reported^{14,15}. Population-based studies of epilepsy were, however, mostly limited until 2000 when recognition of the societal burden of epilepsy stimulated interest amongst clinicians and public health officials. Since the epidemiological survey at the onset of the demonstration programme in 2000, studies conducted in several sites have reported prevalence ranging from 0.9- 8.5 per 1000 and the incidence ranging from 22.4 to 53.4 per 100000 person-years⁵. As the population is rapidly aging in China, a prevalence peak in people over 60 years (4.7-6.2 per 1000)¹⁶ has been noticed and this is mostly due to cerebrovascular diseases.

The extent and nature of the risk of premature death in people with epilepsy in China has not been entirely ascertained as yet. An almost 4-fold increased risk of early death was observed in the GCAE Demonstration Project in rural areas. This was one of the first indications in China that epilepsy poses a threat, particularly to young people¹⁷.

Data of the cause-specific proportional mortality ratios (PMRs) in people with epilepsy was only available from studies in rural China^{17,18}. The major cause of premature death is injury and accident, among which drowning is relatively common^{18,19}. Living in a waterside area, higher baseline seizure frequency, and uncontrolled seizures were reported as risk factors^{19,20}. Studies of Sudden Unexpected Death in Epilepsy (SUDEP) are also limited in China. There have been some Chinese case reports with autopsy²¹, as well as PMR estimations (1%-14.7%) in cohort studies¹⁷⁻¹⁹. Post-mortem examinations are rare in China, especially in rural areas, which causes difficulties in investigating SUDEP. The only available data showed the incidence of probable and possible SUDEP as 2.34 (95% CI 1.36–3.77)

per 1000 person-years in a prospective cohort in rural China²². The SUDEP incidence was relatively higher than reported from high-income countries. SUDEP may, kill over 20000 people with epilepsy yearly in China based on the incidence and the huge number of people with epilepsy. Risk factors for probable SUDEP identified were childhood onset of epilepsy, high seizure frequency, and uncontrolled seizures²³. **A whole exome sequencing in samples from incident cases of SUDEP found rare variants in SCN5A, KIF6, and TBX18 genes that support the hypothesis that underlying heart disorder may be a driver of SUDEP risk**²⁴.

Global Campaign Demonstration Project

In 1986, a feasibility pilot of the project 'Community Control of Epilepsy' was conducted in rural areas adjacent to Beijing and in the Western province of Sichuan. This showed that epilepsy management in primary care settings was viable and sustainable. This project was the precursor of the WHO sponsored GCAE Demonstration Project in China. The GCAE was launched in 1997 to address global issues affecting people with epilepsy⁴. China was seen as an ideal candidate for hosting a demonstration project to assess the feasibility of delivering epilepsy management in primary care settings as well as to evaluate different models for this delivery. The GCAE Demonstration Project started in 2000, initially in six provinces covering a total population of over three million (**Figure 1**, black coloured areas). This was one of the most successful demonstration projects of the GCAE and was a major milestone in epilepsy care in China. The three-year intervention led to a significant reduction of the treatment gap^{5,25}. This was achieved by training local primary-care physicians, enhancing awareness and education in the intervention areas and the initial provision of free basic ASMs. In 2005, another large scale national epilepsy

project 'the Epilepsy Prevention and Control Management Project in Rural Areas' was approved by the National Health Commission. This national project was fully funded by the central government, confirming that epilepsy care had been upgraded to a higher level of priority. Since, over 200000 people in 18 provinces (Figure 2, dark grey coloured provinces) have been screened and diagnosed by neurologists and, of those, over 11500 people with convulsive epilepsy were treated by primary care physicians with anti-seizure medications (ASMs), free at the point of delivery²⁶. The programme was successful in implementing management of convulsive epilepsy in rural areas using the existing primary care facilities. It has now been expanded to more sites and has consolidated epilepsy care in vast areas of China.

Stigma and psychosocial aspects

Local beliefs vary throughout China, but commonly epilepsy is seen as a **mental disorder** rather than a neurological condition. Often this **'mental disorder'** has negative connotations, and this is an essential contributor to social stigma. The translation of stigma in Chinese, is 病耻感 (**Bing Chi Gan**), 'feeling of disgrace because of the condition'. Enacted stigma is almost universal among people with epilepsy affecting not only the individuals but also their families, causing 'loss of face' and decreased self-esteem²⁷. Social issues may aggravate the situation, e.g. a lack of accurate knowledge of epilepsy by the general public, exacerbated by incorrect information in the media, and there is limited legislation concerning the rights of people with epilepsy²⁷.

In parallel with the demonstration project, researchers conducted a knowledge, attitude and practice survey. It covered various topics on the views of people with epilepsy, their family members, neighbours, teachers, employers, community

administrators, and health workers. The survey found that stigma had a major negative impact on the individual²⁸. The most significant difficulties encountered were education and employment opportunities; marriage and childbirth were also major concerns²⁸. A survey in 20 cities reported that nearly two-thirds of teenagers and young adults with epilepsy had kept epilepsy secret from others. More than two-thirds of children, teenagers and young adults expected epilepsy to hinder their future, affecting their chances of getting a job, continuing their education, and getting a partner²⁹.

Epilepsy is strongly associated with significant psychological and social consequences for everyday living³⁰. Some of these psychological issues may reflect innate ability or secondary effect from upbringing or stigma. Several studies examined the negative impact of maladaptive personalities of people with epilepsy on psychological adjustment. They were found to have more labile emotions and be more introverted than controls without epilepsy³¹. Deficits may cause the impaired empathy ability of individuals with idiopathic generalised epilepsy in frontal lobe function³². A comprehensive study of the psychosocial issues of people with epilepsy, such as the associations of harm avoidance, self-directedness, cooperativeness, social skills, anxiety, and depression, was also conducted³³. The findings suggest that personality traits and social skills are significant predictors of psychological morbidity, and that clinical services include psychotherapeutic approaches and psychoeducational programs to help people with epilepsy to cope³³.

Quality of life (QOL) has been extensively assessed. Factors affecting children's QOL include educational level, mental development, age at diagnosis seizure frequency,

seizure duration, and the number of ASMs³⁴. Age epilepsy of onset, seizure unpredictability and fear of injury were all significantly associated with QOL in adolescents with epilepsy³⁵. Perceived side effects and number of ASMs exerted greater effects on QOL in women, while anxiety and seizure-related variables had a stronger impact on QOL among men³⁶. Subjective anxiety, depression, and sleep disturbance exerted a greater effect than short-term seizure control on the QOL of individuals with epilepsy³⁷. Among seizure-free adults with epilepsy, those who had withdrawn ASMs experienced better QOL than those continuing ASM treatment³⁸. Sexual dysfunction has not been extensively assessed. One study, however, reported that most women with epilepsy had sexual dysfunction, mainly associated with poor economic status, anxiety, and poor medication adherence³⁹.

Children with childhood absence epilepsy (CAE) and benign childhood epilepsy with centrotemporal spikes (BECTS) showed cognitive deficits in intelligence and executive function but normally performed in language processing. Impairment in visual attention was specific to those with CAE, whereas impaired spatial ability was specific to the children with BECTS⁴⁰. School-aged children with idiopathic or probably symptomatic epilepsy may have significant ecological executive function impairment including aspects of the behavioural regulation index, inhibition and working memory, which were significantly related to their reduction of social adaptive function⁴¹.

Studies of stigma and psychosocial aspects in China highlighted the important issues and challenges facing people with epilepsy and their families. CAAE has conducted a series of activities to reduce the misconceptions, stigmatisation and discrimination of epilepsy, including improvement of medical services at primary care level and raising epilepsy awareness amongst the public especially to students and school teachers. The 28th of June is "Epilepsy Caring Day", and various activities take place often in collaboration with national mass media channels. For reasons entrenched in history and culture, though attitudes toward people with epilepsy have improved over the years, for many people with epilepsy, stigma continues to influence adversely psychological well-being and QOL. Further strategies are being developed focusing on policymakers, to improve legislation for epilepsy and to lobby governments and health authorities to improve health insurance policies to cover epilepsy treatment costs, especially for children and in rural areas²⁷.

Management approach and costs

Treatment with anti-seizure medications

In the early 1950s, treatment for epilepsy was limited to phenobarbital and phenytoin sodium. Currently, **18 ASMs are available in China**¹⁰ (see Box 2).

In line with WHO's recommendation⁴², phenobarbital was selected as the standard initial monotherapy during the demonstration project. The tolerability and long-term efficacy of phenobarbital was rigorously assessed in a large study which enrolled 2455 people with convulsive seizures between 2001 and 2004. Seventy percent of

those who completed 2 years' treatment had a reduction of seizure frequency of at least 50% and a quarter remained seizure free, with good tolerability⁴³. An extended 6-year follow-up assessment confirmed the initial reports and showed that the long-term probability of retention was comparable with newer ASMs⁴⁴.

Phenobarbital was well tolerated; drowsiness, dizziness, and headache were the most common initial adverse events (AEs), but these declined over time⁴³. AEs seem dose-related and taking over 180mg per day was a predictor of tolerability issues⁴⁵. A controlled assessment of cognition during treatment did not show a negative impact on performance or mood ratings in adults with convulsive seizures⁴⁶. It is possible that the cognitive gains resulting from improved seizure control were greater than impairments potentially caused by phenobarbital itself⁴⁶. In China, the yearly cost of phenobarbital, established during an economic assessment of the intervention, can be as low as <US\$5 per person. Other expenses such as health care visits, investigations and travel to and from clinics ranged from US\$26 to 179 per person, which is most acceptable to health care service providers and also to most people with epilepsy, even in low-income areas⁴⁷. This expense was, however, still prohibitive to some people, emphasising the need to take this into account if the treatment gap is to be reduced further.

There is, however, currently a different picture, particularly in urban areas. A multicentre survey of 11 tertiary hospitals across China reported that half of people were treated with monotherapy, with the rest taking two or more ASMs. One-quarter of those on monotherapy for focal seizures took oxcarbazepine. In contrast, one-third of those with generalised seizures took valproic acid, the most commonly prescribed

ASM in China, either as monotherapy or part of combination therapy¹². The defined daily dose of ASM monotherapy ranges from 33% to 70%⁴⁸; however, this inadequate dosage is recognised as the leading cause of uncontrolled seizures, which account for 80%¹².

ASMs, particularly those with aromatic ring structures such as carbamazepine (CBZ), lamotrigine (LTG), and phenytoin (PHT), are among the most common causes of severe cutaneous adverse drug reactions (cADRs). The association between HLA-B*15:02 allele and cADRs has been preliminarily confirmed in Chinese people with epilepsy in south and central China⁴⁹⁻⁵⁵. It is suggested that screening for HLA-A *24:02 in addition to HLA-B*15:02 should be considered before prescription of aromatic ASMs⁵⁵. The HLA-B*15:02 screening policy has yet **to be** established in China due to the inadequate evidence from large-sampled clinical studies. The cost-effective of the screen should also be considered as the point-of-care genotyping is still very high.

Surgery and other treatments

As the economy developed, equipment such as Video-EEG, Ambulatory EEG, functional and structural Magnetic Resonance Imaging (MRI), Positron Emission Computed Tomography (PET), Single-Photon Emission Computed Tomography (SPECT), and magnetoencephalography (MEG) were deployed. Epilepsy surgery programmes have rapidly developed using the various approaches to locate the epileptogenic zone and now offer neurosurgical treatment following comprehensive pre-surgical evaluation in several centres. A national survey suggests that the number

of epilepsy surgeries procedures in the large cities has increased from 20 cases per centre yearly before the year 2000 to 100 cases per centre in 2017^{56,57}. A nationwide multicentre study on resective surgery in a large cohort of people with tuberous sclerosis complex, for instance, reported high postoperative seizure freedom rates at the long term⁵⁸. The situation in rural areas, however, is not so positive. A community-based study found that over one-third of people with chronic epilepsy in rural have potentially epileptogenic lesions with two-thirds meeting the definition of pharmacoresistance⁵⁹. This suggests a large unmet needs in terms of potential surgery candidates in rural China.

Vagus Nerve Stimulation (VNS) is used in many centres particularly, since 2008⁶⁰. From 2015 to 2018, on average, 100 VNS devices were implanted yearly in Beijing alone. Recently the tendency has been to use a Chinese made device (PINS) instead of the original VNS. Deep Brain stimulators have also been used in China since 2013⁶¹. Use of low-frequency high-intensity Transcranial Magnetic Stimulation (rTMS) as a treatment for epilepsy has also been reported⁶². The ketogenic diet, which is used mostly in children⁶³, is a non-pharmacological treatment also available in China.

Complementary and alternative medicine treatments

The use of Traditional Chinese Medicine (TCM) is widespread in China. Chinese patent medicine and herbal concoctions commonly used often include grass-leaved sweetflag, rhizome gastrodiae, arisaema with bile, pinelliaternata, poriacocos, uncaria, and scorpio to treat seizure¹⁰. The last 20 years have seen increase research into the properties of such products. It's possible that some of these traditional remedies may

hold anti-seizure properties. Other forms of traditional medicine such as meridians and points, acupuncture, embedding thread, digital point pressure, and massage are often used in combinations with herbals⁵⁷. Obtaining solid evidence of efficacy is, however, challenging due a number of issues such as difficulty in randomising, dosing and consistency.

Non-standard and illegal 'epilepsy hospitals' and 'clinics' have appeared, mostly in the underserved areas, mainly as result of the lack of proper specialist health facilities.

They often enhance the efficacy of TCMs by adding ASMs to traditional concoction⁶⁴.

These 'clinics', usually run by non-qualified health professionals, have become extremely popular in some areas, regularly causing unnecessary physical and emotional harm, as well as economic loss to people with epilepsy.

Cost

Epilepsy is a cost-intensive condition particularly in urban China, with most of the direct cost due to ASMs. The average cost of outpatient ASM treatment is about US\$800 per person per year⁶⁵. The average inpatient cost is US\$150 per person per day for people with epilepsy and US\$ 225 per person per day for people with Status Epilepticus (SE)^{66,67}. In addition to regular medical treatment, people in China often resort to traditional medicines (either initially or concomitantly with conventional treatment) and this also attracts a cost. Some estimates suggest this can be almost half of the total direct cost⁶⁸. The cost of loss of productivity of people with epilepsy and

caregivers is US\$208 per year; this accounts for the vast majority of indirect costs.

Based on the Gross Domestic Product (GDP) in 2012, the total annual cost of epilepsy is estimated at US\$11.35 billion, which is equivalent to 17.5% of the average GDP per capita in China⁶⁹. The cost of ASMs, particularly newer ones, is not affordable by many. Among the 20% of households with the lowest income, ASM treatment costs 107% of the family income⁶⁵. Only part of the treatment costs is covered by medical insurance, and reimbursements vary widely depending on the insurance scheme and provincial rules. In Shanghai, for example, 30% of the cost of ASMs is reimbursable which is better than reimbursement rates in Sichuan and Shanxi provinces⁶⁵.

Quality of clinical management

In 2017, the Clinical Quality Control System for Epilepsy management was set up by the National Health Commission and aims to provide data to allow the derivation of key performance indicators for epilepsy care. Initial results suggest that the average person-days of hospitalisation for epilepsy is about 30000 per year in tertiary hospitals in China. The average length of stay is 7.5 days, with 9.6 days for people with SE. In-hospital mortalities of epilepsy and SE are about 2 per 1000 and 14 per 1000 per year⁷⁰. Initial assessment suggests that, in hospitals integrated into the system, seizure frequency and drug information (including AEs) were recorded in almost all cases. Over two thirds had basic diagnostic tests, including neuroimaging and EEG. Only one third of individuals were screened for psychiatric comorbidities and a very small number of women of child-bearing age were advised on reproductive issues including

teratogenicity⁷⁰. The quality of epilepsy management would be improved by refining examinations, identifying comorbidities, individualising care, and improving the referral system. Continuous efforts are needed to implement evidence-based approaches, and future policies and strategies must address the unmet needs^{66,67}.

Epilepsy Research

The Chinese epilepsy research portfolio is varied, but areas of concentration and thus expertise are particularly in **epidemiology and clinical research including psychosocial issues**, genomic research, imaging and functional connectivity, and experimental neurology. Epilepsy genetics and precision medicine have made rapid progress in research and clinical application. Genetic research in China has developed rapidly with the application of new generation sequencing technology. Advances in genetic aetiological diagnosis not only bring new opportunities for the study of mechanisms and functions, but also contribute to genetic counselling⁷¹⁻⁸¹. Human brain connectivity is time-dependent, dynamic, and associated with ongoing rhythmic activity.

Disruption of this activity through pathological processes (e.g., the generation of epileptic spikes) may be a significant mechanism underlying the pathogenesis and cognitive deficits in epilepsy. Centres in China have engaged in research in this field and some pioneering findings have been reported⁸²⁻⁹⁰. Temporal lobe epilepsy (TLE) with hippocampal sclerosis is the most common type of drug-resistant epilepsy.

Recent research in China focused on potential mechanisms involved in TLE, especially on the regulating effect of microRNA (miRNA)⁹¹⁻⁹³. Chinese researchers have been active in developing new and improved animal models of epilepsy as this could advance the understanding of epileptogenesis and lead to improved therapies

Research into seizure disorders has made significant inroads in China in the last two decades. The first research publication in English appeared in 1985 but since then rates have increased and in 2018 there were over 5000 reports on epilepsy from China in English and as many more in Chinese language journals. China is now amongst the top ten countries in terms of epilepsy research output which is mostly funded by the National Nature Science Foundation, Key Research Project Programme of the Ministry of Science and Technology and by the National Health Commission.

Following the United States, Europe, Japan and South Korea which each launched billion-dollar brain initiatives since 2013, the China Brain Project is expected to complement these projects with a universal goal of understanding the neural basis of human cognition, which is the central pillar of the project. The 'one body, two wings' scheme of the China Brain Project implies that the basic research on the neural circuit mechanisms underlying cognition provides input to, and receives feedback from, the two applied wings of brain disease: diagnosis/intervention and brain inspired intelligence technology⁹⁷. The project, entitled 'Brain Science and Brain-Inspired Intelligence', is formulated as a 15-year plan (2016–2030), with the first five years coincident with China's 13th five-year development plan. This is already providing great opportunities for epilepsy research mainly focusing on genomics diagnosis as a tool to enable individualised treatment and to elucidate comorbidity mechanisms for epilepsy and related disorders. Another important area of research is the early prediction of outcome as a possible tool for the prevention of drug resistant refractory epilepsy⁹⁸. This approach requires gathering longitudinal data (clinical records,

biological samples, brain imaging, brain tissues and genomic data) from large populations of healthy people, individuals at high-risk of developing epilepsy and people with established epilepsy. In view of the numbers, China is in a unique position to do this.

Epilepsy and COVID-19

In December 2019, an outbreak of coronavirus disease 2019 (COVID-19) had its onset in Wuhan, Hubei province. After that, it becomes a pandemic across the world. On the 19th of February, 2020, CAAE announced the 'Recommendations for the Management of People with Epilepsy During the COVID-19 Outbreak' with suggestions on maintaining safety, avoiding excessive panic, maintaining adherence, and providing guidelines for online medical consultants. A recommendation on children with epilepsy was also published in response to early studies showing that children were at low risk of COVID-19⁹⁹. A nationwide expert consensus suggested that regular ASMs supplies, medical and psychological support were the most urgent needs of people with epilepsy¹⁰⁰. Online surveys of people with epilepsy in Wuhan and Chengdu suggested that stress, anxiety, and inappropriate change in ASM regimen were associated with increased seizures during the COVID-19 outbreak¹⁰¹. More attention should be paid to mental health of people with epilepsy, especially those with drug-resistant epilepsy¹⁰². Chinese neurologists firstly reported neurological complications in people with COVID-19^{103,104}. A large study of people with COVID-19 in Hubei and Sichuan province and in Chongqing municipality established that neither acute symptomatic seizures nor status epilepticus were major issue amongst people with COVID-19 and found no evidence that people with epilepsy are more vulnerable to it¹⁰⁵. The long-term impact of COVID-19 to the epilepsy

community in China needs further monitoring and investigation.

Conclusions and future directions

China has the world's largest number of people with nearly all major brain disorders, including ten million people with epilepsy. The unmet needs for epilepsy management include improving diagnostics, identifying comorbidities, individualising care, and improving the referral system. The challenges of further epilepsy control are largely related to public health, including differences in medical resources and services for epilepsy in western, central and eastern China; misconception and discrimination of epilepsy; lack of prevention strategies for epilepsy and premature death; under-development of public health research in epilepsy. Strategies to promote epilepsy as a public health priority should be urgently developed (Panel). China has come a long way from traditional to modern epilepsy care, but epilepsy-induced discrimination and stigma formed over thousands of years will not be eradicated completely without sustainable education to future generations. Hard work is still needed towards the end goal: no one should endure the burden of epilepsy unnecessarily in China.

Contributors

DD, DZ, JWS and ZH conceptualised the Review. DD and DZ conducted the literature search, data collection and analysis. DD, DZ and JWS evaluated the quality of the included studies, and drafted the manuscript. All authors were involved in the interpretation of data, critically reviewed the manuscript and approved the final version.

Declaration of interests

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