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REVIEW ARTICLE

Epilepsy in Southeast Asia, how much have we closed the management gap in past two decades?

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Abstract

The last review on epilepsy in Southeast Asian (SEA) countries was reported in 1997. This review aimed to update the understanding of epilepsy management in this region over the past 23 years. There has been significant increase in the epidemiological studies which reported a prevalence of 4.3-7.7 per 1,000 populations in this region. Reversible aetiologies of epilepsy such as head injury, birth trauma, cerebrovascular disease, and intracranial infections (neurocysticercosis or meningoencephalitis) are still prevalent, with a surge in autoimmune encephalitis. There was a surge in genetic studies which suggest ethnic variation. Treatment gap is still high especially in the rural and less developed areas, and the availability and affordability of newer anti-epileptic drugs (AEDs) is still a major challenge in SEA. Alternative medicine is a common practice but varies among different ethnic groups. AEDs hypersensitivity especially on the association between HLA-B*1502 and carbamazepine-related severe cutaneous reaction had been extensively studied and proven in nearly all SEA countries. However, HLA-B*1502 screening is not widely available in SEA and the cost-effectiveness of the screening is questionable. Stigma and its psychosocial consequences are still a major concern despite enormous efforts to study the public attitudes towards epilepsy and change of epilepsy naming in a few countries. The number and complexity of epilepsy surgery are progressing, but it is still under-utilized in many SEA countries, related to cost, cultural perception and lack of facilities. More resources should also be channelled in training adequate number of epileptologists who can spearhead epilepsy care around the region, as well as public education and research in epilepsy. In conclusion, there is an increase in epilepsy research in this region, gradual increase in trained neurologists and facilities, and efforts to reduce the knowledge and treatment gap, but the epilepsy management gap is still a battle to fight.

Keywords: Epilepsy, Southeast Asia

INTRODUCTION

Epilepsy is one of the most common chronic neurological conditions with major socio-economic burden. It is characterized by the predisposition to recurrent episodes of seizure associated with undesirable psychological, cognitive and social consequences. Despite sustainable health care and progressive economic development that has been achieved by the Southeast Asian countries, managing epilepsy remains challenging given the vast cultural, ethnic and political diversity among its members. This can be conceptualised as management gap, which includes the gaps in knowledge and training, diagnostic facilities and accuracy, medical and surgical treatment, as well as stigma reduction. Even with robust campaigns by worldwide healthcare authorities to make combating epilepsy a priority in the Southeast Asian region, there are only a handful of studies

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pertaining to it from this region. There is so much more to be done in generating more data, which is important for epilepsy to be included into the public policy priorities. A review on epilepsy in Southeast Asia was published in 1997[1], and over the past 23 years the number of epilepsy research in this region has increased exponentially.[2] Here, we provide a succinct and updated review on the various aspects of epilepsy care aiming to determine how much the epilepsy management gap in the Southeast Asian region has improved in the past 23 years.

Southeast Asia

Southeast Asia countries are located south of China and east of India, consists of 11 countries, of which most are members of the Association of Southeast Asian Nations (ASEAN). This is different from the Southeast Asian region as defined by World Health Organization in 2011. There are approximately 668 millions population (8.58% of the world population), with a GDP per capita of USD4,601 and most (7/11) countries are in the lower middle income category. Of which, there are three countries with large populations, i.e., Indonesia (267 million), Philippine (107 million), Vietnam (96 million). Furthermore, these countries practices various political ideologies, which affect the health system and policies. In sociocultural aspect, SEA is diverse in ethnicity with the 'Malay' as the largest group, followed by Vietnamese, Thais, Bamar, and later immigrants from China, India and Arabs. The culture is mainly Hindu-Buddhist, followed by Islam and Catholic, with the Chinese culture influence in Vietnam. These variations make it challenging yet interesting to understand the diversity in epilepsy management.

METHODS

Search strategy and selection criteria

In order to have a comprehensive understanding of the epilepsy management gap in this region, a standard systematic review methodology was employed to identified relevant papers, as previously described.[2] Additional 75 articles from 2nd March 2018 till 29th February 2020 were identified and added for review using the same search strategy, and selection criteria.

Data collection and analysis

A total of 777 articles from SEA countries were found. Articles up to 1st March 2018 were assessed as previously reported[2] and the subsequent articles from 2nd March 2018 were assessed by the first four authors. The articles were divided into the following categories: epidemiology and mortality, aetiology, medical treatment and health economics, stigma and psychiatric comorbidities, and epilepsy services.

EPIDEMIOLOGY

Approximately 4 billion people (50% of the global population) live in Asia, of whom about 23 millions have epilepsy.[3] The lifetime prevalence of epilepsy varied among Asian countries from 1.5 to 14.0 per 1000.[4]

The prevalence of epilepsy in Thailand was estimated at 7.2 per 1,000 population with the highest two peaks in the age groups of 5-9 and 25-34 years (17.0 and 17.4/1,000, respectively).[5] In Singapore, two epidemiological studies were performed in 1993 and 1999. Puvanendranon *et al*. reported a lifetime prevalence of 3.8 per 1,000 populations in Singapore.[6] A second study in Singapore by Kun et al who surveyed 20,542 Singaporean men prior to their pre-enlistment screening for military service discovered 89 patients with epilepsy, indicating a lifetime prevalence of 4.9 per 1,000 males by 18 years.[7] In 2006, the prevalence of epilepsy in a rural district of central Lao PDR was reported as 7.7 cases per 1,000.[8] Nguyen *et al*. conducted field surveys 3 years apart in year 2005 and 2008 yielding a prevalence of 4.02 and 4.29 per 1000 populations in Vietnam respectively.[9] A recent study in Cambodia reported a prevalence of 5.8 per 1,000 population.[10] However, there is no epilepsy prevalence study in Indonesia, Philippine or Malaysia, which consist of 400 millions or 60% of the SEA population. (Table 1)

Based on the current available data, the prevalence rate of epilepsy in South East Asia is considerably lower than those reported in other less-developed continents of the world (e.g., 15 per 1000 in sub-Saharan Africa and 18 per 1000 in Latin America, with as high as 57 active epilepsy per 1000 in Panama City).[11,12] The reasons for the high prevalence in those regions were mainly due to the parasitic infections, particularly neurocysticercosis. intracranial bacterial or viral infections, perinatal brain damage, head injuries, toxic agents, and hereditary factors.[13]

For specific subgroups, 92.9% of children with febrile seizures in Malaysia had the first seizure before the age of three, 33.3% had complex

Table 1: Prevalence of epilepsy in Southeast Asian countries

Country	Reference	Year	N	Prevalence /1000	Method
Singapore	6	1993	*	3.8	Army recruits
Singapore	7	1999	20,542	4.9	Army recruits
Thailand	5	2002	2,069	7.2	All residents in a rural sub-district
Vietnam	9	2005	47,269	4.02	Door-to-door survey in a rural district
Lao PDR	8	2006	4,310	7.7	Door-to-door survey in a rural district
Vietnam	9	2008	48,968	4.29	Door-to-door survey in a rural district
Cambodia	10	2011	16,510	5.8	Door-to-door survey in a province

* Full text is not available.

febrile seizure and 26.5% with family history.[14] In Thailand, the incidence of febrile seizure in thalassemic patients was 1.10 per 1,000 person-years, less than that of the general population.[15] In Indonesia, 37.3% of patients with cerebral palsy had epilepsy.[16] Catamenial epilepsy was reported to be 98.5 per 1,000 female patients with regular menstruation in Thailand.[17]

MORTALITY

The risk of premature death in people with epilepsy is 2-3 times higher than the general population. Some of the increased risk is related to the cause of epilepsy, a smaller number of people die in circumstances around a seizure and some have sudden unexpected death in epilepsy (SUDEP).[18]

Data on mortality rate among people with epilepsy in Southeast Asia is scarce. One meta-analysis showed there is an association between epilepsy and suicide, including Korea and Japan, but none reported in this region.[19] In Singapore, a higher hospital mortality was reported amongst older patients with ertapenem-related seizures (33.3% vs. 9.1% of those without seizures).[20]

Sudden unexpected death in epilepsy (SUDEP) is a significant cause of mortality with an estimated overall crude annual incidence rate of 1.16 cases per 1000 patients, which was only second to stroke in terms of mortality burden from neurological diseases.[21] In Malaysia, Fong *et al*. reported that parents of children with epilepsy expressed positive feelings after SUDEP information provision and reported no increase in depression, anxiety and stress after SUDEP discussion.[22] This study provides valuable insights into provision of accurate information on SUDEP in this region.

AETIOLOGY

There are very few studies on the cause of epilepsy in the Southeast Asian population. Although genetic factors have a strong association with idiopathic (genetic) epilepsy, the reversible aetiologies such as head injury, birth trauma, asphyxia, cerebrovascular disease, and intracranial infections (neurocysticercosis or meningoencephalitis) seem to be more relevant in Southeast Asia. Other emergent and re-emergent aetiologies of epilepsy in the tropics include viral encephalitis and tuberculous meningitis.

In Cambodia, 44.8% of PWE had idiopathic epilepsy, and symptomatic in 17.8%, of which, head trauma, neurocysticercosis and vascular epilepsy were among the common causes.[10] Recently, neurocysticercosis has also become a common cause in Singapore due to influx of immigrants from developing countries.[23] In Vietnam, infectious diseases and trauma were common causes in children with epilepsy.[24] In Malaysia, CMV IgG was found to be associated with epilepsy.[25] Perinatal insults dominate among those with symptomatic epilepsy in Laos.[8]

Other than infectious disease, autoimmune encephalitis is emerging in the tropics, for example, anti-NMDAR and anti-LGI-1 encephalitis are evident in Malaysia and Thailand.[26-28] A case with glycine receptor antibody-associated progressive encephalomyelitis with rigidity and myoclonus (PERM) was reported in Singapore.[29]

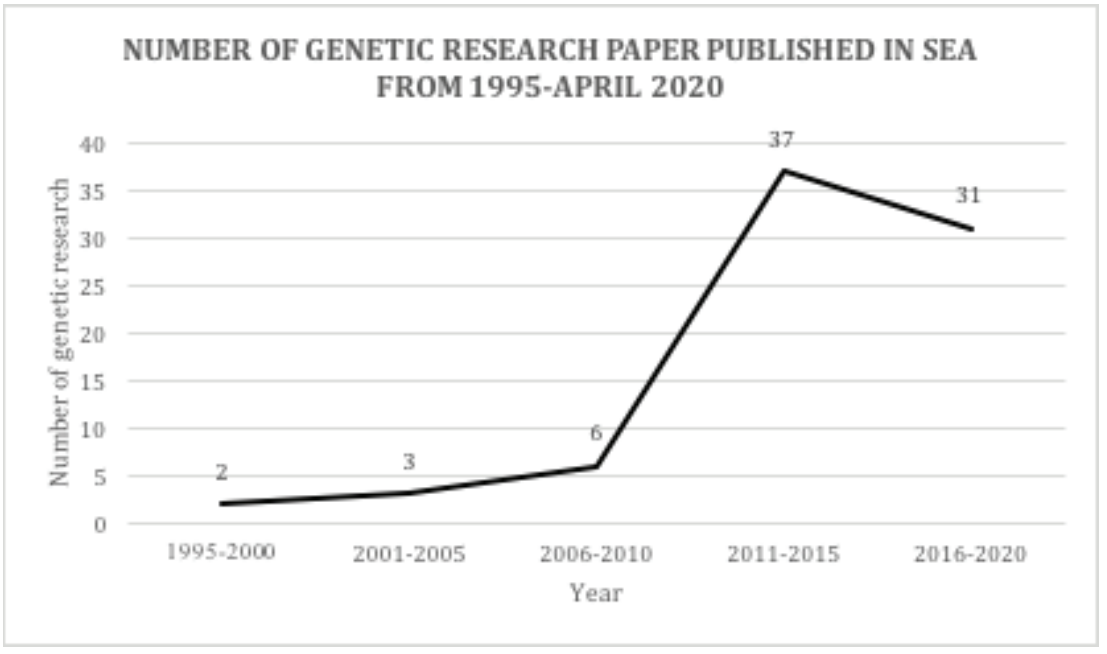

Figure 1. Number of research paper published on genetics in epilepsy from 1995-2020

Genetics and ethnic variation

Genetic studies in epilepsy was lacking in Southeast Asia until year 2010. There was an abundance of published paper from year 2011-2020 as shown in Figure 1. The most studied gene is the SCN1A gene. Mutation in this gene lead to a range of seizure disorders with varying severity. This was also studied among Vietnamese Children with Dravet Syndrome and 13 were found to have pathogenic or likely pathogenic SCN1A variants.[30] In Malaysia, Tan *et al*. research on GEFS+ patients, identified mutations of SCN1A in 9 out of 36 (25%) cases, of which two were novel mutations.[31] However, in Indonesia, it was found that majority of GEFS+ patients were not associated with SCN1A mutations.[32]

A cross sectional study in Malaysia of 392 patients with genetic generalized epilepsy (GGE) found that Chinese had the lowest percentage of GGE among those with epilepsy (12.3%), as compared with Indian and Malay (25.3% and 21.3%).[33] This could be attributed to the fact that consanguineous marriage is common in certain cultures, as reported previously among Indians with epilepsy in Malaysia that 29.5% of them had a parental consanguineous marriage.[34]

STATUS EPILEPTICUS

In Thailand, the incidence of status epilepticus is 5.10 per 100,000 population, and as high as 8.78 patients per 100,000 among the elderly.[35,36] A recent study in Philippines reported 16% of patients with SE were refractory.[37]

Hyperglycaemia was found to be a common cause (48%) in epilepsia partialis continua in Thailand but not in European countries[38] and encephalitis was common aetiology in Thailand as compared to stroke in developed countries.[39]

The mortality rate of status epilepticus in SEA ranged from 8.4-26.7%[35,39,40] and 11.7% among children with convulsive status epilepticus.[41] Factors positively associated with mortality in patients with SE were central nervous system (CNS) infection, cancer, heart diseases, chronic renal failure, septicemia, pneumonia, respiratory failure, acute renal failure, and shock.[42] In Thailand, a 9-year longitudinal data showed pulmonary complications are common in patients with status epilepticus. 32.3% suffered from respiratory failure while 9.7% developed pneumonia during the course of hospitalization.[35]

Nonconvulsive status epilepticus (NCSE) is not uncommon in SEA but might impose a diagnostic challenge due to lack of EEG facilities and incorrect interpretation. An Electroencephalography (EEG) study in Singapore reported 9.8% of all EEGs requested to exclude NCSE found to have NCSE.[43] Another study in Singapore on the ictal and interictal EEG in those with subtle and NCSE, reported a large variations in interictal and ictal localisation, duration of

seizure and EEG patterns.[44]

Delay in treatment is a challenge in SEA. The median duration of SE before treatment was reported to be three hours in Thailand.[39] This was related to incorrect diagnosis and management, lack of appropriately trained personnel and limited facilities, long distances and difficulties in transportation, and lack of essential intravenous AEDs in certain primary care hospitals. Moreover, in southern Thailand, it is not possible to treat SE in ambulances with first-line AEDs, with the exception of diazepam.

MEDICAL TREATMENT

In Singapore, 21.5% of the people with epilepsy were reported to be drug resistant, while 40.9% drug responsive.[45]

The efficacy and tolerability of AEDs in Asian population might be different from other non-Asian population, possibly due to pharmacokinetic and genetic variation. Therefore, clinical trials on newer AEDs in Asian population are required for drug registration in certain Asian countries. However, only a few AED-related studies in SEA are investigator-initiated.

The efficacy of Vigabatrin in Asian children with infantile spasms was studied in Thailand and Singapore and was reported to be similarly effective and tolerable.[46-48] A small randomised double-blinded trial on oxcarbazepine in refractory epilepsy was performed in Thailand, which support its effectiveness and tolerability.[49]

Pharmacokinetics

Pharmacokinetics of older AEDs in Southeast Asians were found to be different from other populations and also varied among the races in SEA, but there was no study on newer AEDs. In Singapore, it was reported that Chinese patients required higher doses of phenytoin to reach the therapeutic range compared to studies reported elsewhere.[50] Similar trend was also reported in children with epilepsy in Singapore who needed to be given higher doses of phenobarbitone to reach therapeutic range.[50] However, it was found that Indian patients in Singapore required a lower dose of phenobarbitone as compared to the Chinese and Malays[51], and similar ethic variation was also found among Malaysian population.[52] For carbamazepine, slow clearance was reported in a Malay woman in Malaysia, correlated to CYP3A5*3/*3 and ABCB1 3435-CC genotypes.[53] A study on transporter gene (G2677T SNP of the ABCB1 gene) identified an association with CBZ resistance among the Malaysian.[54]

A Thai study reported high correlation between serum and salivary phenytoin levels, supported the use of saliva in place of blood for phenytoin drug monitoring[55], which was subsequently supported by a similar finding in UK.[56] However, therapeutic drug monitoring of most newer AEDs are not available in many SEA countries.

Repetitive transcranial magnetic stimulation

Repetitive transcranial magnetic stimulation (rTMS) has become an important non-invasive clinical tool for neuronal perturbation.[57] In Malaysia, rTMS was found to be effective in selected patients with a 33% respondent rate and improvement in depression.[58]

Alternative medicine

Alternative or complementary medicine is commonly used in SEA for most diseases, including epilepsy. This is probably related to the Asian cultural and religious practices, and the belief that complementary medicine is natural with fewer side effects. Multivitamins, traditional herbs, and acupuncture were common forms of complementary medicine used in 27.5% of paediatric patients in Singapore. Christians/Catholics were more likely to give their children multivitamins while Buddhists were more likely to use acupuncture and traditional herbs, and surprisingly caregivers with a higher education level were 3.52 times more likely to use alternative medicine.[59] Alternative medicine is also practised in the Western countries[60,61] but the types of alternative medicine practised in SEA are different. For example, among the Malay PWE in Malaysia, it was found that 26.7% had consulted Malay traditional healers (bomoh) and/or homeopathic practitioners in addition to modern treatment.[62] A systematic review reported a correlation between the use of alternative medicine and non-adherence to AED among PWE.[63] Thus, studies on the use of alternative medicine among PWE in various SEA populations are recommended to understand the variation of medical practice and the impact on seizure outcome, in order to guide local clinical practice.

TREATMENT GAP

Treatment gap is the difference between the number of people with active epilepsy and the number whose seizures are being appropriately treated. It has been proposed as a measure to

evaluate access to, and quality of care for people with epilepsy across different populations. Serial reports showed dramatic global disparity in the treatment gap of epilepsy between high- and low-income countries. Similar disparity is also observed between rural and urban settings.[64] Untreated epilepsy not only leads to a lifetime of disability and premature death but also carries significant social stigma and economic burden to the country.

In Asian countries, the treatment gap is between 29-98% with values for most countries between 50-80%.[4] Particularly, treatment gap in developing countries in this continent was estimated to have a mean of 64%.[65] In South East Asia, the earliest study was performed in rural Malaysia in 1996, based on antiepileptic drug consumption in Sabah and patients seen in Kuala Lipis, Pahang. The study has shown a high treatment gap of more than 90%.[66] Similar finding was observed in Lao Peoples' Democratic Republic (Lao PDR) with only 1 out of 33 people with epilepsy in rural district of Hinheub, and 12 out of 2350 in the capital city Vientiane receiving antiepileptic drugs.[67] This high treatment gap was largely due to low availability of phenobarbital, misconception and stigma on epilepsy, and insufficient health care infrastructure and human resources. (Table 2)

A recent study in rural Vietnam reported a treatment gap of 84.7% among patients with active epilepsy. The main reported reason is the perception that their seizures were too few to justify the trouble and costs associated with treatment.[68] A population-based study in a rural setting in Prey Veng province, Cambodia showed a treatment gap of 65.8%, which was the lowest among the available studies in South East Asia.[65,69]

The treatment gap in most Southeast Asian countries are high, especially in the rural region. These figures are particularly alarming and reflecting the urgent need to study the treatment gap in other SEA countries and the associated psychosocial, cultural, economic, political and organizational factors.

Compliance to medication

AED compliance is crucial in controlling seizures. Non-compliance leads to an increase in morbidity as well as hospitalisation, and poorer quality of life.[70] In European countries, non-compliance rates have been reported at about 35-40% (North Carolina 39%, Finland 34%, and the UK 36.4%), and lower in the United States (26%).[71] In SEA, the non-compliance rates varied; for example, Singapore reported a rate of 27.7%, while Malaysia and Lao reported higher rate of 61.4% and 32.3-57.6% respectively.[72-74]

The two key factors associated with non-compliance reported in this region were socio-economic factor especially the cost of treatment especially in low-middle income countries, and patient's perception and attitudes toward epilepsy. Other factors included demographic and clinical factors, including type of epilepsy, complexity of regimes, side effects and efficacy of AEDs.[72-75]

AEDs HYPERSENSITIVITY

A strong genetic predisposition of carbamazepine induced adverse reactions in Asian populations possessing the HLA-B* 1502 allele was first reported in Han Chinese in Taiwan. Such strong association has also been validated in the SEA populations including the Thai, Singaporean Chinese and Malays, Malaysian Malays, Chinese and Indians, Vietnamese, Indonesia and Myanmar.[76-81] HLA-B* 1502 has also been implicated in phenytoin induced SCAR in the Malay population.[82]

HEALTH ECONOMICS

Health economics studies the relationship between health care and economy and attempts to achieve an effective allocation of limited health care resources in a given society. Corresponding to improvement and development of general economy in this region, economical evaluation of the healthcare sector provides pragmatic insights into how health care can be delivered in the most organized, consistent and cost-effective manner.

Table 2: Treatment gap in Southeast Asian countries

Country	Reference	Year	Treatment gap (%)	Population
Malaysia	66	1996	>90	Rural
Lao PDR	67	2008	>90	Urban and rural
Vietnam	68	2009	84.7	Rural
Cambodia	65, 69	2012	65.8	Rural

Cost of illness

Cost of illness (CoI) is a study of all cost related to a disease and serves as a baseline for further economical evaluations.[83] In Asia, the direct cost of epilepsy is estimated to be USD625 in China over 6 months[84] and USD344 in India annually.[85] As a comparison, the annual cost was reported as USD1376 in Italy and USD2384 in France.[86,87] In Malaysia, the CoI study was performed on newly diagnosed children with structural-metabolic epilepsy, which reported USD541 per year.[88] The main factors influencing the cost are the choice of antiepileptic drugs and the frequency of seizures. Another study on children with epilepsy in Malaysia reported an annual direct cost of USD367 and indirect cost of USD149 due to loss of parent's productivity.[89] The cost of illness is relatively high in Malaysia or Asian countries, when the cost is compared with the country gross domestic product (GDP). However, data from South East Asian region was scarce and more studies are needed to reflect this economic challenge in epilepsy management.

*Cost-effectiveness of HLA-B*1502 screening*

There are a few studies in this region measuring the cost-effective of HLA-B*1502 Screening. A study in Singapore reported that it is cost-effective to screen Chinese (USD 37,030/QALY gained) and Malay patients (USD 7,930/QALY gained), but not the Indians (USD 136,630/QALY).[77] Another study in Thailand supported the conclusion that HLA-B*1502 genotyping is cost-effective.[90] On the contrary, 2 later studies from Thailand and Malaysia concluded that screening would not be cost-effective due to the rarity of SJS/TEN among HLA-B*1502 positive cases, higher cost of alternative AEDs and poorer seizure control with alternative AEDs.[91,92] Nevertheless, lack of newer AEDs in some regions, significant morbidity of SJS/TEN, possible cost reduction in mass HLA-B*1502 screening and potential rapid test kits in development may improve the cost-effectiveness of the screening.

Cost-effectiveness of therapeutic drug monitoring in epilepsy

Therapeutic drug monitoring among children with structural-metabolic epilepsy is cost-effective, as reported in Malaysia. The incremental cost-effective ratio (ICER) was USD 731 per one additional patient that achieved a ≥50% reduction in seizure frequency, and USD 9,196 per one additional patient with a 3-month seizure free period.[93] However, the cost-effectiveness in SEA country depends on the availability of the TDM services.

Cost-effectiveness of video-electroencephalography (VEEG) monitoring followed by surgery

A study in Thailand on patients with drug-resistant focal epilepsy concluded that VEEG followed by surgery was more cost-effective than continued medical treatment, as evident by higher QALY gained (13.80 years compared to 12.30 years), and higher ICER of USD 1,236 per one QALY gained for the VEEG over no-VEEG.[94]

STIGMA AND PUBLIC ATTITUDES TOWARDS EPILEPSY

Many studies have reported a genuine lack of awareness and limited knowledge, accompanied by false beliefs and negative attitudes toward epilepsy, leading to higher stigma among PWE in SEA.[95] Study as early as 1999 by Lim *et al*. has already reported high awareness of epilepsy in Malaysia and repeated studies since then have consistently reported high awareness among different populations.[96] Despite the high awareness rate, the stigmatizing nature of epilepsy is still evident in this region; for example, average half would object to having their children marrying a person who has epilepsy and 20-30% of the study population still thinks that epilepsy is a form of insanity or psychiatric disorder over the years.[97-100] Similar results are also echoed in Indonesian, Thai and Vietnamese studies.[4] A qualitative study in Philippines on the stigma experienced by PWE as well as people with mental health problems identified cultural traits related to stigma, suggesting that existing stigma-reduction strategies might have limitations in their effectiveness across cultural settings.[101]

Social stigma of epilepsy leads to long-term stress and discomfort, and psychosocial consequences including unemployment and psychological disorders.[102] A study in Malaysia showed high unemployment rate among PWE.[103] People with uncontrolled seizures were shown to encounter greater difficulties in employment in Malaysia compared with those with controlled seizures.[104] A systematic review showed that the mean adjusted employment rate was only 58% (range, 14%-89%).[105] Reducing the stigma of epilepsy is the key to reducing its impact and improving quality of life. There has been a proliferation of work assessing epilepsy related

stigma in Southeast Asia. Lim et al examine the origin, types, causative factors and implications of stigma allowing better understanding on how prejudicial believes are translated into discriminatory behaviours towards people with epilepsy.[106]

In 2012, the Public Attitudes Toward Epilepsy (PATE) scale[107] was developed in Malaysia to address the need for a quantitative measurement of epilepsy stigma across different cultures. It consisted of 14 items and was divided into the general and personal domains. The general domain did not require considerations of long-term personal commitment, contrary to the personal domain. This scale was subsequently translated and validated in various languages, including Malay, Chinese, and Indonesian language[108-110], and was used in various populations, including the urban general public, teachers, students and the indigenous people in East Malaysia.[107-113] Despite the varied magnitude of stigma in different populations, one consistent finding in all studies was the poorer attitudes in the personal domain and its dissociation from the education level. This finding supported the postulation during the scale development, which stated an isolation between knowledge-based attitudes and interpersonal, emotional-based attitudes toward epilepsy. Thus, these findings could lay as a foundation to prompt further studies in the individualistic, psychological factors that cause stigma in epilepsy, especially in the SEA region.

One of the factors affecting epilepsy stigma is the names of epilepsy in various Asian languages.[114] Epilepsy in Chinese (癫痫*dian xian*, madness; 羊癫风*yang dian feng*, goat madness) is associated with insanity and animals. The names of epilepsy in certain East and Southeast Asian languages also convey the image of insanity and associated with animals, possibly due to the influence of Traditional Chinese Medicine. In the case of Malay who are mainly Muslim, it is also religiously unclean (*gila babi*, mad pig disease), contributing to stigma of the epilepsy patients. The names of epilepsy have been replaced by a neutral terminology in Malay in Malaysia, and also for Chinese in Hong Kong, and Korean in South Korea, aiming to reduce the impact of naming on epilepsy stigma.

Examination of upbringing style in dialogue with traditional culture may be important in overcoming epilepsy stigma. In traditional Chinese culture, the sense of shame is the foundation of morality; "feeling shame" and "being shameless" are important moral concepts. The ideal person, a 'gentleman' 君子 has a sense of shame. However, the ability to resist feeling inappropriate shame 不耻 is also a trait of the gentleman. Thus, based on traditional Chinese philosophy, one should resist feeling ashamed for having epilepsy. Chinese culture emphasizes the importance of exerting vitality in the presence of adversity; people with epilepsy who do not feel ashamed of their deficiency is manifesting such a vitality. Traditional Chinese culture takes a positive attitude towards hardship and adversity, that it is essential for developing character and skills. Overcoming adversity requires responsibilities, the pre-requisite is personal freedom. Thus, allowing freedom and nurturing independence is consistent with traditional Chinese attitude to upbringing.[115] Dialogue with other traditional SE Asian culture should thus be encouraged.

PSYCHIATRIC COMORBIDITIES

In Malaysia, PWE reported higher depression score and 9.68 times more likely to have suicidal ideation as compared to the controls.[116] In Thailand, the prevalence of psychiatric disorders among Thai PWE was significantly higher than the general population, with depressive disorders in 17.1%, followed by psychotic disorders (8.2%), bipolar disorder (7.1%), anxiety disorders (5.3%), and obsessive-compulsive disorder (2.9%) respectively.[117] People with epilepsy (PWE) are at risk of domestic violence with 51.4% having violence towards others and 40.0% being the victim of violence in Thailand.[118] Among children with epilepsy, attention deficit hyperactivity disorder (ADHD) was reported to be a common comorbid in Thailand (8%-77%).[119]

A survey among PWE in Malaysia showed that psychological interventions delivered in short-group session were highly preferred.[120] A systematic review reported that depression is highly prevalent (about 25%) in PWE in Asia; however, high quality data is scarce and validated screening tools are still lacking in many languages in Asia limiting the research on psychiatric comorbidities in this region.[121]

EPILEPSY SERVICE AND EPILEPSY SURGERY

Epilepsy care in SEA is mainly provided by general physicians, paediatricians or psychiatrists, and in larger centres by neurologists or neuro-paediatricians. Epilepsy center is not available in all SEA countries, including Brunei, Cambodia and East Timor.[122] In East Timor, there is one

neurologist, but no MRI brain, EEG or epilepsy surgery services. In order to promote epilepsy care in this region, Asian Epilepsy Academy was formed under ILAE (International League Against Epilepsy)-Asian Oceanian Commission to organise teaching courses, EEG certification examination and fund epilepsy fellowship. There was a total of 62 neurologists who have undergone 6-month epilepsy/EEG fellowship in ASEAN.

Epilepsy surgery has been underutilized in Southeast Asia despite a clear evidence supports the benefits of surgery over medical therapy for patients with refractory focal epilepsy. Singapore reported the highest rate of utilization of epilepsy surgery at 4%.[123] However, a recent regional study reported that only 5 countries in this region (Indonesia, Malaysia, Philippines, Singapore, and Thailand) has at least one level 4 epilepsy centre.[122] (Table 3) Neurologists specialised in epilepsy and pre-surgical evaluation are limited, with one neurologist serving 0.13 to 25.83 million people. In Brunei and Cambodia, there was no neurosurgeon or paediatric neurologist involved in epilepsy surgery, thus only initial epilepsy presurgical evaluation is provided but not epilepsy surgery. Provision of level-3 and level-4 epilepsy surgical care with intracranial EEG monitoring (IEEG) is possible with joint multidisciplinary effort in this region, as reported in Malaysia with a 65% success rate with epilepsy surgery comparable to the literatures. The main limiting factors are cost, cultural perception and lack of facilities.[124]

CONCLUSION AND FUTURE DIRECTION

There have been significant advances in the epidemiological understanding of epilepsy in Southeast Asia over the past 23 years. The number of affected patients in this region is large and much remains poorly documented. The treatment gap in most countries remains substantial and could be affected by various factors like public attitudes, psychosocial, cultural, economic and political factors. More studies in these areas are needed and governments must provide more emphasis and higher priority in the effort of fighting against epilepsy. Most Southeast Asia countries have progressed positively in terms of organizational and financial stability and are no longer poor, now able to provide free and subsidized anti-epileptic drugs to the general public to further reduce the treatment gap. More resources should also be channelled in training adequate number of epileptologists who can spearhead epilepsy care around the region. Medical treatment gap can also be improved by training primary care physicians, paediatricians, and general physicians in the principles of optimizing AEDs, diagnosing drug resistant epilepsy and early referral for epilepsy surgery. Streamlining the referral process of patients with suspected surgically remediable syndrome allowing quicker and hassle-free access to dedicated epilepsy program can narrow surgical treatment gap. Attitudes towards epilepsy is greatly affected by the socio-cultural factors and individual perception, and thus more research efforts to understand these underlying factors may help to mitigate the negative perception and stigma, and perhaps on the positive cultural values that strengthen the individuals.

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Table 3: Number of epilepsy centres and clinicians involved in epilepsy surgery in each country

Country	GDP per capita, USD (2019)	No of epilepsy center	Neurologist	Neurosurgeon	Paediatric neurologist	Population (million)	Population per neurologist (million)	No. of centres per pop. (10 million)	No. of neurologist undergone epilepsy/EEG fellowship
Brunei	27,871	0	3	0	0	0.4	0.13	0	0
Cambodia	1,620	0	11	20	0	16.0	1.45	0	2
East Timor	2,035	0	0	0	0	1.26	1.26	0	0
Indonesia	4,163	5	15	15	10	261.1	17.41	0.2	10
Laos	2,670	1	3	3	1	6.8	2.27	1.5	0
Malaysia	11,136	4	7	10	6	31.2	0.22	1.3	10
Myanmar	1,244	8	25	18	7	52.9	2.12	1.5	0
Philippines	3,294	4	4	1	4	103.3	25.83	0.4	10
Singapore	63,987	4	4	2	2	5.6	1.4	7.1	10
Thailand	7,791	7	15	7	15	68.9	4.59	1.0	10
Vietnam	2,739	9	20	30	5	92.7	4.64	0.9	10
Total	**4,601**	**42**	**107**	**106**	**50**	**640.2**	**6.00**	**0.66**	**62**

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