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Review Article

Epilepsy and Seizure Disorder in Nepal: A Scoping Review

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Abstract

Seizure disorder and epilepsy (SE) is a common neurological disorder with various implications; i.e., physical, psychological, emotional, social, career, economical and many others. Seizure-epilepsy is a public health concern in Nepal, with various manifestations and complications. Despite positive changes, like- increasing public awareness, inclusion of anti-epileptics in essential drug list and 'mental, neurological and substance use (MNS) disorders' for the training of health professionals and some researches; we still have some gruesome realities; e.g., stigma, under-recognition, under-diagnosis, wide treatment gap, lack of anti-epileptics in practical reality, scarce community-based and intensive studies. Though some reports are available from Nepal in some aspects of SE; its prevalence, magnitude, burden and effects are under studied. The purpose of this review is to explore existing literature regarding various aspects of seizure disorders and epilepsies in Nepalese contexts. Search for the articles for this review was performed in Nepjol (Nepalese medical/ health Journals), PubMed, and Google Scholar, online. The collated body of literature shows preponderance of studies carried out in clinical setting and of descriptive type. Hence, we need more comprehensive, in-depth, community based and multicentre studies. Various facets of this problem should be investigated further for needful attention and prevention/intervention of all levels. Overarching objective would be to develop its comprehensive database.

Keywords: epilepsy; seizure disorder; nepal; co-morbidity

Introduction

*Seizure (*derived from Latin *sacire* meaning 'to take possession of') is defined as a paroxysmal event due to abnormal excessive synchronous electrical discharges from brain. It may be motor, sensory, autonomic or psychic in nature. Seizure is currently classified according to: i) origin of onset, as: focal, generalized or unknown; ii) level of awareness, as: intact or impaired; and iii) manifestation, as: motor or non-motor. This newer classification has made diagnosis based on semiology, lateralization and localization of epileptic foci, possibly aiding epilepsy surgery [1].

Epilepsy is a brain disease defined by: at least two unprovoked (or reflex) seizures occurring >24 h apart; and tendency to further seizures (at least 60%) after two unprovoked seizures, occurring in 10 years' period [2]. *Convulsions* are uncontrolled rapid and repeated muscle contractions. Motoric manifestation of seizure, non-epileptic event or other types of dyskinesias can all be convulsions.

Seizure disorders and epilepsies (SE) result from a shift in the balance of excitation and inhibition within the CNS which may be due to numerous causes perturbing this normal balance and decreasing individual's seizure threshold. Seizure causes differ with age of onset, threshold and maturation status of brain. SE could be due to hypoxic-ischemic injury, CNS infections, intracranial hemorrhage, trauma, high grade fever, metabolic disturbances, genetic factors, drug withdrawal, developmental disorders and idiopathic among children; and in adult, can be precipitated by drug abuse, alcohol use, cerebrovascular events, brain tumors and degenerative neurological conditions.

Global Scenario:

SE is one of the most common neurologic conditions. Around 50 million people suffer from epilepsy worldwide [3], nearly 80% in low- and middle-income countries (LIMICs) [4], 50-75%, up to 90% in developing countries of which do not receive adequate treatment [5]. Disability-adjusted life years (DALYs) attributable to epilepsy are estimated at 13 million/year [3]. SEs are associated with various neuropsychiatric disorders [6], and can have a variety of manifestations as evident in its history being referred as Sacred disease of God [7]. SEs related deaths are declining possibly due to availability of treatment modalities and awareness mostly in developed and resourceful settings. Since early 19th century, varieties of anti-epileptics

focusing on seizure types have developed, along with seizure-surgeries; however, it is still under-utilized in most LIMICs [8].

SE data are scarce many where, and inconsistent because of differences in sampling frames, case definitions, measurements (e.g., point vs. period or lifetime prevalence), screening tools, diagnostic accuracy and different methodological approaches. The prevalence varies substantially between developed and developing countries: estimated as 4–7/1,000 persons in developed and 5–74/1,000 persons in developing countries [9]. It appears higher in rural than urban areas of developing countries. Rural areas have a large burden of untreated epilepsy possibly due to illiteracy, ignorance, stigma, beliefs and attitudes about causes and consequences of epilepsy and limited access to health services, and underestimation of its prevalence [10]. SE accounts for 0.75% of the global burden of disease [11]. An estimated 2.4 million people are diagnosed with epilepsy annually. In 2012, approximately 20.6 million disability-adjusted life years were lost to epilepsy [11]. These numbers represent epilepsy as a public health concern and reduction of prevalence and incidence can be done with appropriate diagnosis and treatment.

The purpose of this review is to explore existing literature regarding various aspects of seizure disorders and epilepsies in Nepalese contexts. Search for articles for this review was performed online in Nepjol (Nepalese medical/ health Journals), PubMed, and Google Scholar.

Nepal at a glance:

Nepal is a landlocked country situated between China to north and India to east, west and south with a total area of 1,47,516 square km. There is high degree of geographical diversity in its three regions, i.e., Terai, Hilly and Himalayan regions with 17, 68 and 15% area respectively. The total population of Nepal as per census of 2021 AD is 29,164,578 majority of which (78.55%) reside in rural areas. There is provision of 1 central, 7 provincial and 753 local governments out of which 460 are rural municipalities. The health system is also organized accordingly from primary to tertiary levels. This is one of the poorest countries with gross domestic product of about 1300 USD per year. The doctor patient ratio here is 0.85/1,000 population who mostly are urban based, rural ratio is 1 in 150000. There is wide diversity of religion, mostly comprising Hinduism, Buddhism, Islam, Kirat, Christianity, and others. Diverse ethnic communities consist of Brahmin, Kshetri, Vaishya, Shudra, Tharu, Tamang, Newar and many more indigenous ethnic groups with individual beliefs and traditions. Nepali is the most common spoken language and there are 121 recognized national languages of different ethnicities.

Seizure/ epilepsy in community:

Charaka and Susruta, the ancient Ayurvedic Hindu physicians of 3000 B.C. described ‘Apasmara’ as Sanskrit synonym for epilepsy where ‘Apa’ means loss and ‘Smara’ means memory or cognition. Various Nepalese ethnic groups also use different terms, e.g., Chhare, Murchhe, Mirgi Rog, Chariphai, Bakhre rog for epilepsy [12,13]. Many ethnic groups believe epilepsy occurs due to sin, it as a communicable disease and follow traditional rituals to heal this disease. KAP studies conducted among public [14], students [15,16], teachers [17], patients [18] in Nepal largely report inadequate patchy knowledge, inappropriate practices and stigma with the need of some strategies to address them. Mothers have inadequate information about febrile seizures [19]. Many people here believe that it’s due to supernatural causes or ancestor sins [18].

Studies show high prevalence of epilepsy in Asian countries: 7.3/1000 in Nepal [12,20], 4.6-7/1,000 in China, 10.0/1,000 in Pakistan and 3-11.9/1,000 in India [21]. The lower prevalence in Nepal may be due to under-reporting, lack of adequate human resources for diagnosis, lack of awareness, geographical adversity and stigma. A study of Morang district (in eastern Nepal) based on house-to house survey of 823 households covering 4,636 people showed a prevalence of epilepsy of 7.3/1,000 populations, 6.8 for males, and 7.9 for females [22]. This study also highlighted that most of the patients with epilepsy were treated by traditional healers and few had attended health care facility with high dropout rate. Lack of adequate manpower, inconsistency with the diagnosis and rampant use of available anti-epileptic medications are challenges to treat epilepsy at community level. A study at village health post in Kaski district reported that it was more convenient to visit a traditional healer (Jhankri) than to come to the village health post. The traditional healers often made ‘house calls. Largely rural population and low number of doctors probably contributed to the frequent use of traditional healers’ services [23]. A community-based survey showed 1.9% (18/911 people of 3 districts Sankhuwasabha, Dhankutta and Sunsari of eastern Nepal, one each from 3 geographical regions) with SE [24]. SE was a common presentation (3.13%; 5/160) among the people attending a multi-specialty health camp who were seen by a psychiatry team [25] as in a relatively recent report (4/100) [26].

Seizure/ epilepsy in clinical settings:

SE is a common presentation among adult [27,28] and child [29,30,31] patients in clinical settings in Nepal. A report from a teaching hospital in Pokhara shows statistically significant decline of year-wise incidence of NCC cases, a common cause of seizure from 2003 to 2015 [32]. Seizure is reported as the most common presentation among admitted cases for NCC [33]. QOL was statistically different in education, marital status and frequency of seizures within the last 6 months. Seizure duration had negative effects on the QOL [34].

Seizure/ epilepsy in psychiatry setting:

Patients with SE frequently present to psychiatry out-patient service as a major MNS condition, usually with co-morbid psychiatric illness and mostly referred for behavioral and mood disorders. A remarkable proportion of referred psychiatry out-patients (14%) had neurological symptoms including seizure and epilepsy [35]. SE was reported in 15% of child and adolescent [36] and around 4% in old age psychiatry out-patients [37].

Causes and etiology:

In Nepal, studies show that CNS infection with neurocysticercosis (NCC), toxoplasma, brain tumors, metabolic, trauma, substance use were common causes of seizures [38]. Nepalese studies replicate the notion that cause of SE are different in different age groups. In neonates [39-41] and children [42,43]; perinatal hypoxia and ischemia, intracranial hemorrhage and trauma, developmental disorders, CNS infections, metabolic causes, genetic disorders, febrile seizure, idiopathic and drug withdrawal are reported. In adults and older patients; substance use [44-46], brain tumors, cerebrovascular disease, degenerative diseases and abnormal electrical discharges cause seizure [47,48].

In Nepalese context, NCC is a remarkable, rather reported as the commonest cause of seizure; hence, has widely been reported on its various prospects, including prevalence and management [33,49-54]. Reports of seizure from Nepal in relation to long haul flight in known seizure cases [55], status epilepticus with Olanzapine use [56], Sildenafil induced seizure [57], primary hypoparathyroidism [58], anemia in febrile seizure [59] give a wide picture of underlying etiology of seizure. Abnormal EEG finding [60], NCC are reported as risk of recurrence [61], and seizure onset in infancy, abnormal neuroimaging findings and frequent seizure as the predictors of uncontrolled seizure in children [62]. SE studies among children; more so on febrile convulsions make a remarkable presence in Nepalese literature. Febrile convulsion has been reviewed [63], and studied on various aspects like: features [64-66], evaluation [67], investigations [68], management, outcome, recurrence risk factors [69].

Family history of SE is also found relevant in most of the subjects; 9-15% of psychiatric out-patients with seizure have family history of seizure [6,70]. Psychosocial and others stressors, plus sleep deprivation have also been reported among the seizure cases [6,70,71]. Many of the SE patients (46%) reported some stressors preceding the seizure attacks; relational and health related stressors being the common ones [6,70,71]. Caution about relapse/ trigger factors is important. A situation of SE in pilots has been discussed in a paper from Nepal [72].

Clinical features:

The clinical feature of SE can be divided into three phases: pre ictus, ictus and post ictus. Pre ictus phase is characterized by wide range of epileptic auras, ictus phase by stereotypy, up rolling of eyes, clenching of teeth, tongue bite, bladder and bowel incontinence, night time episode, rigid posture and frothing from mouth. Careful history and physical examination aid in diagnosis of SE (70). At times, unusual presentations are often accompanied by psychiatry co-morbidities [6,7].

More child seizure patients have generalized tonic clonic seizures (GTCS) [73-75] whereas more adult seizure patients have complex partial seizures (CPS) than GTCS [6]. Among 70 partial seizure patients, a study shows 20 each with simple and complex partial seizure and 30 with partial with secondary generalization [76]. All psychiatric out-patients with seizure had some significant BPRS (Brief Psychiatric Rating Scale) symptom item. Seizure related symptoms: loss of consciousness, abnormal body movements, and stereotypy/mannerism were the most common BPRS symptom items. Others were somatic concerns, hallucinatory behavior, anxiety, depression and hostility [6].

Seizure is among common symptoms in admitted children with acute bacterial meningitis; and malnutrition, longer duration of fever, and abnormal neurological and laboratory findings are usually associated with higher rates of complications [64]. A hospital-based survey reports common epilepsy syndromes (ESs) as: West syndrome (WS)- 26.7%, generalized tonic-clonic seizures alone (GTCSA)- 21.7%, self-limited childhood epilepsy with centrotemporal spikes (SLCECTS)- 12.5%, childhood absence epilepsy (CAE)- 10.0%, Lennox-Gastaut syndrome (LGS)-10.0%, other developmental and epileptic encephalopathies (DEE)- 5.8%, self-limited familial infantile epilepsy (SLFIE)- 4.2%, and juvenile myoclonic epilepsy (JME)- 3.3% [77]. This study concluded that SE can be diagnosed also in resource constrained settings and it aids in individual treatment plan and psychoeducation [77].

There are reports of seizure cases with laughter or smiling as its manifestation [78,79]. The case reports of rare and interesting syndromes associated with SE have been made from Nepal, like: Dyke-Davidoff-Masson Syndrome (seizures, facial asymmetry, contralateral hemiplegia and mental retardation) [80], Lennox Gastaut Syndrome (generalized multiple type seizures, slowness of intellectual growth, and a specific EEG disturbance) [81], Opercular Syndrome (seizure, cortical pseudobulbar palsy, dissociation of automatic voluntary movements in the affected muscles) [82], chromosomal deletion syndrome (seizure, facial dysmorphism, congenital umbilical hernia and undescended testes) [83], Bruns Syndrome (Intraventricular Neurocysticercosis and headache and seizure with head position changes) [84], Intracranial Calcification and Seizure with Down Syndrome [85], Hemiconvulsion-Hemiplegia-Epilepsy Syndrome [86], Guillain Barré Syndrome [87], West Syndrome [88]. Febrile seizure in terms of its type has been studied, simple being more common [89]. GTCS was the most common seizure type in 79% of febrile seizure cases [89,90].

Most of the cases of SE are seen by primary care attainder in different settings; majority of them from rural parts have been underreported due to cultural stigma, lack of awareness and financial constraints, diversity in belief, lack of adequate settings and trained health workers, treatment cost and lack of proper diagnosis in Nepal. Most patients of SE cases present with other comorbidities. Studies have shown strong traditional belief, low economic status, male gender, low socio-economic condition, unemployment in patients with epilepsy [38].

Other Physical & Neurological Diseases in Seizure-Epilepsy:

Physical signs and symptoms depend on the underlying etiology. Infectious causes like meningitis have fever [61]; and electrolyte imbalance may present with features of weakness and delirium. Seizure was one of the neurological manifestations of COVID-19 (SARS-CoV-2) as described in a review from Nepal [91]. Bullous lesion, Lupus Nephritis and seizure have been reported from Nepal as presentation of Systemic Lupus Erythematosus [92]. Substance use disorder may present with features of either drug overdose or withdrawal, along with seizures [44-46]. A comorbidity study in alcohol dependence syndrome reported about 7% female subjects with the feature of seizure alone [93]. There is a recent case report of the development of seizures with the use of increasing dose of tramadol [94]. Understanding the diverse manifestations of SE is crucial for accurate diagnosis, effective treatment and improved quality of life for individuals affected by this condition.

Psychiatric manifestation and comorbidity:

A Nepalese study conducted in a tertiary care center reported the prevalence of psychiatric disorders in 45% SE patients. As they were referred to psychiatry OPD, all had one or other BPRS symptom items, i.e., psychopathology. Mood (mainly depression) and anxiety disorders were the most common psychiatric co-morbidities. The most common BPRS items (besides seizure and related) were: somatic, mood, psychotic, hostility and anxiety symptoms. Hence, seizure may manifest with various psychopathology mainly: somatic, mood, psychotic, hostility and anxiety besides seizure-related symptoms (e.g., disorientation) [6].

Depression and seizure:

Depression is the most common psychiatric disorder [6]; comorbid in about 1/3rd of SE patients at the time of study [95]. A case report of seizure with depressive episode with hanging attempt presented to a health camp highlighted the unmet needs of these patients in Nepalese context. It also discusses the need of mood stabilizing anti-epileptic and seizure friendly antidepressant in management of such cases [96].

Bipolar in seizure:

Symptoms are similar to those of mania, with the atypical features of amnesia, loss of consciousness, derealization and depersonalization [97]. Transient features are more common than episodic disorders. A case report from Nepal discusses about diagnostic dilemma, management issues and drug interaction [97].

Psychosis in seizure:

Delusion, hallucination, disorganized behaviours may present in cases of seizure along with periods of confusion, disorientation, stereotypy; a case report has been made to discuss intricate interaction among bio-psycho-social factors for genesis of psychotic state [98]. Psychotic state akin to schizophrenia in epilepsy [99], acute psychosis in NCC [100], postictal aggression in CPS in eclamptia [101], intermittent outburst of anger [102], thyrotoxicosis, epilepsy and psychosis combination [103], delusion of love in temporal lobe epilepsy [104] and Capgrass syndrome in post-ictal delirium [105] have been presented in case reports from Nepal.

Pseudo-seizure and seizure:

Psychogenic non-epilpetic seizures (PNES) or pseudo-seizures co-occur in a remarkable proportion of SE patients. Intricate interactions among stigma, psychosocial stressors/ factors and biological underpinnings have been discussed in a case report to highlight the need to address the related factors for comprehensive management of both seizure and pseudoseizure [70]. Accurate diagnosis and differentiation between epileptic and non-epileptic seizures are crucial for appropriate management and treatment. Management includes the exploration of comorbid psychiatric disorders and their treatment. Identification of psychosocial and seizure-related stressors and addressing them, appropriate psychotherapy for resolving the underlying conflict and optimization of antiepileptic drugs all make important strategies while dealing with such patients.

Self-injurious behavior/ suicide in seizure:

Suicide and self-injurious behaviors are more common among people with SE, occur both consciously and unconsciously. Psychiatric comorbidity mainly depression is the most important factor for suicide [96]. They may be

unaware of such behaviors, as it may be part of seizure semiology. Mostly, such behavior is common in complex partial seizures or in the post-ictal psychosis phase [98]. If the act is part of a seizure, adequate optimization of anti-epileptic drugs is the primary goal. Anti-epileptic drugs with mood-stabilizing properties are chosen. Treatment of co-morbid psychiatric illness and psychotherapy, suicide precautions and 24-hour vigilance are important strategies.

Investigation related to seizure epilepsy:

EEG studies have been reported from Nepal regarding indication [106], utilization [107], findings [108], EEG evaluation [109] and atypical presentation of absence seizure [110] and profile [111]. EEG is a primary diagnostic tool in Nepal [108]; it aids/ supports the diagnosis of SE [106,107]; but not confirmatory.

In pediatric age group, a study from Nepal shows abnormal CT-SCAN findings in 32% of the seizure subjects [112]. Lesions that are better detected in MRI include hippocampal sclerosis and T2 hyperintensities and stroke making it the investigation of choice [113]. The yield of MRI with EEG combination is better than either MRI or EEG alone in the diagnosis of seizures [109].

A laboratory examination, including electrolytes, blood glucose and calcium levels, should be sent to determine the provoking factors of seizures. Blood and urine biochemistry is sent to exclude causes like inborn errors of metabolism [81,82]. Lumbar puncture should be considered in the case of any infection of the central nervous system [114-116]. Serum prolactin levels are helpful in differentiating seizure activity from other transient events mimicking seizures [117]. Prolactin level rises immediately after seizure activity. Seropositivity has been reported to be associated with neuroimaging studies consistent with NCC [118].

Management/ treatment:

SE is a great health issue in our country; incorporation of its management in health system has been an issue of thesis from Nepal [119]. While talking about SE in Nepal, NCC is a great cause and its management is a big study topic here. Albendazole either alone or combined with Praziquantel has been reported as effective for treating neurocysticercosis [120,121]. Antioxidant deficiency and subsequent development of oxidative stresses can be linked with the decrease in the glutathione peroxidase activity and haptoglobin, transferrin and ceruloplasmin functions. Use of anti-oxidants has been discussed in degrading conditions of SE cases [122]. Validation study of a phone app [123] and study on smart-phone application and telephone telemedicine for SE [124] indicate current tendency to follow the worldwide trend of taking the technology to door step of needy people. Number of seizure attack before the start of medication had direct correlation with seizure control [125] and these novel strategies would complement the outcome by early identification and diagnosis. Therapeutic drug monitoring of commonly used anti-epileptic agents (AEs); i.e., monitoring the therapeutic, sub-therapeutic and toxic levels of Phenytoin, Carbamazepine and Valproic acid has been studied and reported as useful [126]. Mild to moderate rise in liver enzymes has been seen and hence, routine LFT recommended while using AEs, like: Carbamazepine and Sodium valproate. Leveteracetam has no change in liver enzymes [127]. Case reports on leveteracetam induced hallucination [128], Lamotrigine induced severe cutaneous reaction [129], fetal Hydantoin syndrome in infant of a lady using phenytoin [130], all indicate the need to exercise caution regarding adverse drug events while treating SE cases. SE surgery is also taking step in Nepal, as evident in Nepalese literature [131,132]. Epilepsy surgery is expected to be an acceptable and cost-effective treatment for intractable seizure [132].

As reported long ago and still the situation has not changed much regarding treatment seeking behavior and treatment gap; many people visit faith healers, follow other ineffective measures and treatment gap is huge [133,134]. In Nepal, out of the pocket expenditure still exists; economic factor is also a major cause of treatment gap. Other challenges in epilepsy treatment include lack of: prioritization of resources and funding, access to health care facilities, underlying etiology of epilepsy, expertise and diagnostic capacity of health care personnel, treatment options, socio-cultural attitudes toward epilepsy, stigmatization, misconceptions, discrimination and treatment-seeking behavior. These various challenges need to be addressed to overcome the treatment gap. Sustained and coordinated action prioritizing epilepsy from the rural setting to the advance setting has been emphasized for tackling these challenges [135]. Awareness at various levels from general public to policy levels is vital towards this goal [136]. SE makes a chapter or an issue in the books authored by many of the Nepalese psychiatrist writers [137]. Various government projects including collaboration with NGO's and INGO's have been working in awareness program and identification of cases of epilepsy. Currently, Nepal government in collaboration with WHO has run mhGAP training to health workers at all local government level to identify and treat epilepsy (as MNS disorder) [11,138]. Sodium valproate, Carbamazepine and Phenytoin are distributed free of cost to patients from all government health services [139]. Regular supply and availability is still a challenge in Nepal [135].

Conclusion:

Something has definitely been achieved in SE management and control in Nepal and many things are yet to be achieved as outlined for this region, including Nepal [140]. The collated body of literature shows preponderance of studies carried out in clinical setting and of descriptive type. Hence, we need more comprehensive, in-depth, community based and multicenter studies. Various facets of this problem should be investigated further for needful attention and prevention and intervention of all levels.

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