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SEIZURE PATTERNS AND THERAPEUTIC PROGNOSIS IN ACTIVE EPILEPTIC PATIENTS FROM DIFFERENT ETHNIC GROUPS

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ABSTRACT

This paper aims to discuss epilepsy, which is a chronic neurological disease defined as recurring seizures leading to changes in the patients' thinking, awareness, behaviour, social interactions as well as social and economic functioning. The cross-sectional study was conducted in Pakistan and sought to comprehend seizure characteristics, sociodemographic variables and treatment response within different ethnicities, 132 patients experiencing epilepsy from both urban and rural settings. Conclusions show that the generalized ones exist more frequently than the partial ones, with the involvement of male patients and those who are younger. Valproate is recognized as the most used AED for both the generalized and the partial epilepsy. It is established that polytherapy has better efficacy in the treatment for partial seizures while monotherapy and polytherapy have similar effects in treating generalized seizures. Head injuries and parental consanguinity are such important factors, which predict genetic factors. Also, the study focuses on the psychosocial problems related to the epileptic patients including stigma and discrimination resulting to the poor quality of life. The study emphasizes the significance of timely intervention, proper use of AED as well as correct perception dissemination; the overall target of which is better epilepsy care and enhanced patient outcomes in Pakistan.

Keywords: *Epilepsy, Seizures, Antiepileptic Drugs (AEDs), Sodium Valproate, Polytherapy, Monotherapy, Genetic Risk Factors, Parental Consanguinity, Neurological Disorder, Stigmatization, Pakistan.*

INTRODUCTION

Epilepsy is a Greek word ''epilembanein'' which means ''to seize or attack'' (Shafiq et al., 2007). Epilepsy is a long term brain ailment that is due to the generation of seizures and it resulting into changes in the thinking, psychological, anatomy and physiology of the brain as well as changes take place in physical, economic and social consequences (Mac et al., 2007). Epilepsy is stimulated by repeated and disturbed neurological activity known as epileptic seizures. Seizure is a Greek word meaning to take hold (Fisher et al., 2005). These are the uncertain patterns and brief deterioration of the central nervous system due to abnormal neuronal activities in the cortical areas of brain (El-Menshawy et al., 2015).

Seizures, the core symptom of epilepsy and brain insult (Fisher et al., 2005). The major patterns of seizures are generalized and partial seizures. In generalized seizures whole brain is affected includes cortical and subcortical structures and this type is further classified into absence, myoclonic, atonic, tonic and clonic seizures whereas in partial seizures only specific part of the brain is affected commonly limited to one hemisphere and it is subdivided into simple and complex partial seizures (Banerjee et al., 2009). Epileptic seizures are not only generated in the cerebral hemispheres but can also generate in the brain stem (Fisher et al., 2005). Sudden unexpected death in epilepsy (SUDEP) is an important unsolved problem.

Studies shows that to prevent SUDEP, special treatments should be used to frequent generalized seizures with nocturnal patterns (Rektor et al., 2015). The seizures are precipitated by various factors mental depression and physical stress, consumption of alcohol, menstrual cycles, photosensitivity and the most important is sleep deprivation (Ramachandraiah et al., 2012).

Epilepsy is categories on the basis of its primary causes although many defects cannot fit straightforwardly to only one given category (Jabbari and Nurnberg 2016). Epilepsy may have predisposing or exciting causes that include physiologic, psychical or pathologic causes (Shorvon, 2011). It is classified on the basis of etiology including idiopathic epilepsy usually childhood onset which have genetic basis and can be inherited while symptomatic epilepsy including pathological causes that follow the identified brain insult and the type of epilepsy in which causes has not been identified or with unknown causes is known as cryptogenic epilepsy (Banerjee et al., 2009). The comorbidities faced by the epileptic patient mainly depression, anxiety, psychoses, attention deficit, learning disabilities, unconsciousness, disorientation and memory distortion (Boer et al., 2008).

Epilepsy is an inherited disorder. Studies on human genetics explained the defects occur in cellular and molecular mechanisms that maintains the normal development of neural homeostasis and nervous system lead epileptogenetic processes. Many epileptogenic mutations have been discovered in genes such as ARX, ALG13, TBC1D24, PCDH19, LG11, STXBP1, SYNGAP1, EFHC1 and CHD2 that contributes in cellular processes like structure of neurons, synapse development, transcriptional command and intercellular signaling transmission in nervous system (Cunliffe et al., 2015).

Electroencephalography (EEG) is an important diagnostic tool for studying activity of human brain and epileptic discharges. For the initiation of therapeutic methods, the EEG gives very important information about the epileptogenic zone and changes of electrical activity in term of frequency, time and space (Faust et al., 2015). The diagnosis of epileptogenic zone is also commonly held with video electroencephalography (V-EEG) using scalp electrodes, or intracranial electrodes. Other brain functional imaging techniques includes computerized tomography (CT) scan, magnetic resonance imaging (MRI), positron emission tomography (PET), single-photon emission computer tomography (SPECT), and magneto encephalography (MEG) (Pataraia et al., 2004).

To control seizures is the main target in the treatment of epilepsy and the best way of controlling epilepsy is to use antiepileptic drugs (Mac et al., 2007). Antiepileptic drugs (AEDs) are called as an unreplaceable resource for the treatment of epilepsy but incorrect use of antiepileptic drugs can lead to number of complications (Beghi, 2016). Various antiepileptic drugs are used to treat different seizure types including Valproic acid, Felbamate, Phenobarbital, Zonisamide, Carbamazepine, Benzodiazepines, Rufinamide, Phenytoin, Oxcarbazepine, Topiramate, Primidone Eslicarbazepine, acetate, Lamotrigine, Tiagabine, Levetiracetam and Ethosuximide (Moshe et al., 2015). Clobazam, Oxcarbazepine, and Levetiracetam are available in large Asian countries, such as India, but are prohibitively expensive. In epileptic patient the seizures reoccurred within five years after the first unprovoked seizure (Mac et al., 2007). More than 30 percent epileptic patients do not become seizures free despite of using anticonvulsant drugs (Jin et al., 2016). Some of these patients can be recuperate by epileptic surgery whereas many other brain stimulation therapies are also available to treat epilepsy like invasive vagus nerve stimulation (iVNS) is commonly used. For this purpose surgical implantation of stimulator and an electrode is connected with left vagal nerve are required. Transcutaneous vagus nerve stimulation (tVNS) is relatively recent method which is used to overcome the drawback of surgical implantation devices. It is non-invasive technique to innervate the left auricular branch of the vagus nerve at the ear conch (Bauer et al., 2016). Studies reveal that about 35 million people with epilepsy do not receive treatment. In Pakistan only 27.5 percent of urban and 1.9 percent of rural areas of epileptics receive AEDs (Shafiq et al., 2007).

Beside medical problem epilepsy is a social tag because people having epilepsy are facing psychosocial problems. This stigmatization causes unemployment, frustrations, social stigma, less likely to marry and problems in getting education. Hence these stigmatization causes discrimination

which greatly influences on the quality of life (QOL). So appropriate treatment with the observation of its side effects and monitoring of QOL as an outcome measurements are essential in the management of epilepsy to get seizure control (George et al., 2015). The present study was designed to evaluate the patterns of seizures and therapeutic prognosis including the use of AEDs as monotherapy or polytherapy to examine their impact or different demographic factors affecting on the patterns of seizures of active epileptic patients.

Sixty five million people are affected due to epilepsy throughout the world (Hawley et al., 2015). The prevalence of epilepsy in developed nations is 4-7 per 1000 population whereas it is 5-74 per 1000 population in developing nations (Ablah et al., 2014). Whereas the rate of incidence of epilepsy is 24-53 per 100,000 person per year in developed countries while in developing countries it is high as 190 per 100,000 person per year (Mac et al., 2007). Prevalence and incidence may be affected or underestimated due to stigmatization, cultural beliefs about the existence of epilepsy and negative attitudes towards its diagnosis and treatment (Banerjee et al., 2009).

In Asia there are more than half of the 50 million people are affected due to epilepsy. In Pakistan the rate of prevalence is varying from 10 per 1000 population (Mac et al., 2007). Worldwide it is very common neurological disorder and it is making 1 percent of the Pakistani population with number of epileptics under the age of 19 years (Shafiq et al., 2007). Epileptic burden in low developed areas of Pakistan is twice than the urban areas. Generalized seizures are more common in Pakistan than partial seizures. In Pakistan epilepsy is more common in males than females and mostly it is prevalent in younger population usually begin at the age of 13.3 years (Khatria, 2003). Keeping in view the above mentioned scenario the study was designed under the following objectives,

- To calculate the frequency of epilepsy in term of age, gender, location and seizure patterns.
- Identification of ethnic specific seizures patterns.
- To check therapeutic prognosis in active epileptic patients to develop medical information and the treatment of epilepsy.

REVIEW OF LITERATURE

2.1 EPIDEMOLOGY AND ETIOLOGY

Mac et al. (2007) were studied prevalence, causes and treatments of epilepsy in Asia. They studied that more than half of the 50 million epileptic patients are present in Asia. In low income countries the prevalence rate is greater than high income countries. The causes of epilepsy included stroke, birth trauma, consanguineous marriage, head injuries and infection of the central nervous system. They also studied temporal-lobe epileptic surgery which shown good result in Indonesia and India.

The prevalence of epilepsy was estimated in mainland China in term of gender, seizure type, location, age and prevalence of date. Thirty eight studies were included that comprised total 13,224 epileptic cases. The total prevalence was 2.89 percent. In case of gender, the prevalence of male was 3.83 percent while female prevalence was 3.45 percent. In case of seizure types, the prevalence of generalized, partial and unclassified seizure was 3.12 percent, 0.57 percent and 0.23 percent. As far as location based prevalence was 2.34 percent in urban areas while in rural areas it was 3.17 percent. Prevalence by age groups were 2.21 percent, 3.23 percent, 3.14 percent, 2.83 percent, 2.96 percent, 2.61 percent, 2.76 percent and 2.22 percent in different age groups 0-9, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69 and 70 or above. In subgroup analysis prevalence by date ranged from 1.19 percent to 6.70 percent (Gu et al., 2013).

In rural Kansas the prevalence of epilepsy is calculated on the bases of medical record and interview. The study included 404 individuals with active epilepsy. The prevalence of active epilepsy was 7.2 per 1000. The type of seizures in 71.3 percent cases was unknown whereas among 76 patients the seizure type was known including 55.3 percent had focal with secondary generalized seizure. In 222 cases the Etiology of seizures was classified that include 53.1 percent were idiopathic /cryptogenic (Ablah et al., 2014).

2.2 MISCONCEPTIONS ABOUT EPILEPSY

A Study was conducted in Nigerian rural areas on the misunderstanding and misconception of epilepsy. The method included the Interviews of 365 persons which were not affected of epilepsy.

Among them 12 percent called epilepsy as a neurological dysfunction, due to fortune 49.8 percent, 81.4 percent called it witchcraft, 27.8 percent heredity and evil believe 26.8 percent. The views about therapy were herbal preparation 68 percent, specific diet 29.3 percent, spiritual exorcism 33.7 percent, magic 26.2 percent and sacrificial offering 24.1 percent. The beliefs about spreading epilepsy through saliva 28.8 percent, making laughter of epilepsy 12.1 percent and sharing utensils 19.5 percent. These types of misconception and traditional perspectives for epilepsy lead to treatment gap in low income countries (Osungbade and Siyanbade, 2011).

2.3 SOCIAL STIGMA

It was reported that people with temporal lobe epilepsy display more aggression, reprisal attitudes, anger, and behavioral antagonism as compared with control (Gul and Ahmed, 2014). Epilepsy not only produces its impact on patient but also affects family and then whole community. Epileptic patients face negative attitudes from others and social stigma including children banned from schools, adults from marriages and unemployment which increases pessimism, eagerness and poor self-confidence as compared to controls (Boer et al., 2008).

2.4 SEIZURE RECURRENCE

Irregularity in taking medicine and stop continuing treatment due to social as well as low economic status of patients are the main problems of epilepsy in developing countries. In India the rate of prevalence is between 4.15 and 7.03 per 1000 population and it was observed that in India among 1450 patients 620 patients stopped continue their antiepileptic therapy due to low socio-economic factors. These various socio-economic factors were income verses expenditure, negative behavior toward treatment, unavailability of antiepileptic drugs, unemployment status and other psychological diseases. It results in the recurrence of seizure among 42.75 percent patients (Das et al., 2007).

2.5 RISK FACTORS

Cansu et al. (2007) studied the risk factors in children with epilepsy in Turkey. The total cases were 805 of aged 1-16 years with epilepsy were matched with 846 normal children of the same age. The various factors responsible for epilepsy under study were gender, convulsion such as febrile, head injuries, infections of central nervous system, consanguineous marriages of parents, epilepsy in family, brain disorders, complications before or during birth and newborn jaundice. The various resources of the study were questionnaire, personal interview, by medical record and analysis. The result of this study was CNS infection (4.76-fold) history of atypical febrile seizure (21.97-fold), head injury (27.76- and 7.09-fold), family history of epilepsy in first , second or third-degree relatives (6.42-, 3.09- and 2.66-fold, respectively) and presence of maternal hypertension (4.31-fold).

Light is another risk factor involving in epilepsy. Various studies have been reported on abnormal EEG response to light. The total prevalence of light stimulated seizure was one per 10,000 or 1 per 4000 individual of age 5-24 years. 2-14 percent seizures have been measured in epileptic patients that were precipitated by light. Other factors included light –dark borders and red color (Fisher et al., 2005).

2.6 EPILEPSY IN PAKISTAN

Khatria et al. (2003) explained that in Pakistan the prevalence of epilepsy is 9.99 in 1,000 populations. Epilepsy is less common in urban areas than rural areas of Pakistan. In urban areas its prevalence is 7.4 per 1000 population whereas in rural areas it is 14.8 per 1000 population. The study also included childhood epilepsy which varied from 15.5 to 23 per 1000 children. It was observed that the younger population below 30 years of age is more prevalent whereas less prevalence is observed between the age of 40 and 59. Generalized seizures are more common in epileptic patients. In urban areas 27.5 percent while only 1.9 percent epileptic patients are treated with antiepileptic drugs AEDS. The burden of epilepsy is not fully figure out.

These Studies also conducted on seizures patterns in Pakistan and it was observed that generalized seizures are more common than partial seizures. The outcome of study was that 52 to 70 percent epileptic patients had Primary generalized seizures whereas secondarily generalized seizures were present in 15 to 25 percent cases. Other types of seizures included simple partial seizures which

were reported in 5 to 9 percent cases and 5 to 12 percent patients had Complex partial seizures.

2.7 CIRCADIAN PATTERNS OF EPILEPTIC SEIZURES

Epilepsy is a chronic brain disorder. Diurnal patterns of epileptic seizures have been investigated in studies. Study on 170 epileptic patients was carried out whose EEG monitoring occurring since the last 5 years. The seizures were classified on the bases of symptoms and the origin of seizures was also defined on the bases of wavelet form on EEG. Seizures were monitored in term of occurrence either during the day or night, in sleep or wakefulness, within a 3-hour interval throughout the whole day. The findings included 909 seizures in which Auras, hypomotor, dialeptic, atonic, myoclonic and epileptic spasms occurred in wakefulness; hypomotor , tonic and clonic seizures were recorded in sleep; dialeptic, epileptic spasms, auras and atonic seizures were observed during daytime; hypomotor seizures were observed more frequently during night.

Generalized seizures occurred in wakefulness (between 12:00 and 18:00 h); frontal lobe seizures were observed in sleep and at night (between 24:00 and 3:00 h), temporal lobe having seizures were observed in wakefulness (between 6:00 and 9:00 h and between 12:00 and 15:00 h), occipital seizures were observed during wakefulness and day time (between 9:00 and 12:00 :00 h and between 15:00 and 18:00 h) and partial seizures were observed frequently during day time. It was concluded in this findings that circadian patterns and sleep/wake distributions depend on seizure onset origin and semiology of seizures (Gurkas et al., 2016).

2.8 STATUS EPILEPTICS

Causes of status epileptics explained in one of the systematic review. 181 causes were reported and these were grouped into 5 main etiological categories. These were immunological disorders, genetic disorders, mitochondrial disorders, drug/toxin and infectious diseases. Immunological disorder included paraneoplastic encephalitis, Hashimoto encephalopathy and Anti-NMDA receptor encephalitis. Genetic disorders included ring chromosome 20, angelman syndrome, and porphyria. Mitochondrial disorders included POLG1 mutation, MELAS (mitochondrial, myopathy, encephalopathy, lactic acidosis, stroke like episode). Drugs included some antiepileptic drugs, antimicrobials, and chemotherapeutic drugs while toxin like domoic acid also reported. Infectious diseases may be due to cat scratch disease encephalopathy, creutzfeldt-jakob disease and HIV related diorders. All these categories included the patients of status epileptics (Tan et al., 2010).

Another study analyzed the electro clinical characteristics, causes, treatments and prognosis in patients with epileptic encephalopathy with status epilepticus during sleep (ESES) based on EEG features. Different patterns of EEG were observed in 17 patients with ESES syndrome. On EEG discharge they show focal and generalized seizures. Cognitive impairment and behavioral problems also related to ESES. Bilateral synchronous and asynchronous ESES with similar or different morphology, progressive or sub progressive or some time multifocal paroxysms with or without slow wave activity during slow sleep were observed in EEG. Mean age of onset was 7.5 years. An idiopathic cause was observed in seven patients, structural cause was found in eight cases and unknown causes in two patients. Negative myoclonus seizure type found in seven cases, absences in nine and positive myoclonus in five patients. Motor defects found in six patients, two had auditory problems and two had motor speech defects. Attention defects, aggressiveness and memory problems existed (Caraballo et al., 2015).

2.9 GENETICS OF EPILEPSY

A study shows the patterns of inheritance of epilepsy in many generation Algerian families. The affected members with familial epilepsy were assessed and data on the basis of medical records, EEG, brain imaging and neuronal examination was analyzed. Epilepsy was classified according to International League Against Epilepsy (ILAE) and mode of inheritance pattern with the help of pedigree was observed. The outcome shows out of total 40 patients 23 (57.5 percent) were male and female were 17(42.5 percent). According to type of seizures 40 percent had focal seizures, 50 percent had generalized seizures, and 25.7 percent had early febrile seizures. The mean age of seizures onset was 9±6 years. 12 patients got psychiatric

issues and four families had pathological cause of epilepsy. The consanguinity rate was 50 percent. Pedigree analyzed autosomal dominant (AD) inheritance in 18 families, autosomal recessive (AR) inheritance in 14 families while X-linked recessive inheritance was observed in one family (Chentouf et al.,
2015). Some other genetically based studies of epilepsy including:

2.9.1 Familial Based Generalized Epilepsy

Fjaer et al., (2015) reported two sisters having primary familial brain calcification due to the variant in SLC20A2 gene and also tonic clonic generalized seizures. The blood samples of whole family were taken and the whole exome sequence of both sisters was done. Sanger sequencing used for the whole family. They concluded that SLC20A2 variants inherited from father that causes epilepsy as a phenotypic trait beside brain calcification. The findings also included CHRNB2 variants inherited from mother also responsible for additional genetic influences.

2.9.2 Stx1b Gene Associated With Myoclonic Astatic Epilepsy

Deletion on chromosome 16p11.2 results in haploinsufficiency of STX1B and other genes. In 18 year old male patients it was observed that STX1B is not only involved in fever base epilepsy but also in non-fever related epilepsy such as myoclonic astatic epilepsy. STX1B encodes for syntaxin-1B which is required to interact with protein encoded by STXBP1 gene necessary for synaptic transmission of neurotransmitters. The patient developed the severe intellectual disability, behavioral problems and severe dysmorphisms. Currently his epilepsy is well controlled by valproic acid as a monotherapy (Vlaskamp et al., 2016).

2.9.3 Role of microRNA-146a gene in epilepsy

MicroRNA is the family of noncoding RNAs that post-transcriptionally control the expression of their target gene through RNA interference. One of the types of microRNA called miRNA-146a is known to function in the regulation of TLR signaling pathway and proinflammatory cytokines like IL-1β and TNR-α. Recently evident that miRNA-146a is reported as important regulator involved in pathogenesis of epilepsy. Two SNPs in this gene are rs2910164 and rs57095329 may change the expressional level of mature miR-146a gene. 249 healthy control and 249 epileptic cases were included in the study and blood was taken for DNA extraction and genotyping. It was concluded that only rs57095329 associated with the susceptibility of drug resistant epilepsy which is located in the promoter region of miR-146a gene and rs2910164 has less capacity to change the susceptibility to epilepsy because it can only alter the expression of miR-146a by only affecting its stem structure (Cui et al., 2015).

2.10 CLINICAL MANAGEMENTS

In India 6 to 10 million people are suffering from epilepsy. A study was conducted to evaluate the pattern of using antiepileptic drugs (AEDs) and their impacts on the health of epileptic patients. The outcome of this cross sectional study included 200 epileptic patients. Males were more affected and 60 percent patients were younger than 30 years. Partial seizures were more common with idiopathic origin. The ratio of using monotherapy and polytherapy was equal. Most frequently as one AED used was clobazam 37 percent, phenytoin 25.5 percent and oxycarbazepine in 20 percent of the patients while in polytherapy also clobazam was most frequently used as 63 percent patients. Carbamazepine was most frequently used against partial seizures while the use of sodium valproate and lamotrigine was observed more again generalized seizures. The epileptic patients who were on polytherapy experienced significant number of high seizures frequency and adverse drug reactions (Georage et al., 2015).

It have been reported that AEDs used to treat seizures in children, adults and pregnant women that are responsible in causing cognitive deficit, microcephlay and biochemical abnormalities at birth. Some revealing AEDs includes phenytoin, clonazepam, phenobarbital, vigabatrin, diazepam and valproate cause apoptotic neurodegeneration in developing rat brain that are also relevant to human for seizure control. Less concentration of survival promoting proteins and less expression of neurotrophins in brain are associated with neuronal death. Postnatal and prenatal act of human to AEDs is associated with reduced brain mass (Bittigau et al., 2002).

Some elder patients of epilepsy with key features of disease like lateralization and focal epilepsies, some curative process including lobectomy and lesionectomy are the treatments for seizure freedom. But this procedure is not applicable for every patient, so palliative methods including vagus nerve stimulation (VNS) or deep brain stimulation are good options (Gallo, 2006).

In non leisonal refractory mesial temporal lobe epilepsy the deep brain stimulation (DBS) was done. Three patients were treated with DBS. Chronic continuous high frequency hippocampal stimulation was applied during treatment. Two patients got the unilateral activation of electrodes and showing 95 percent and 92 percent reduction in seizures frequency while third received the bilateral electrode stimulation getting 91 percent reduction in seizures. It was observed that generalized tonic-clonic seizures resolved completely after DBS with no side effects and psychological deterioration (Jin et al., 2016).

Non-invasive technique called transcutaneous vagus nerve stimulation (tVNS) is used to treat epilepsy. In this method frequency of 25Hz is applied to 39 patients while frequency of 1Hz is applied to 37 control patients in reducing the frequency of seizures over 20 weeks. It was observed that mean reduction in seizure frequency at the end of treatment was -2.9 percent in 1Hz group while in 25 Hz group the significant reduction rate was 23.4 percent. Adverse effects usually mild including headache, fatigue, ear pain, nausea and 1 sudden unexpected death in epilepsy (SUDEP) were observed during this treatment (Bauer et al., 2016).

2.11 EFFECT OF EPILEPSY ON CHILD EDUCATION

Ali et al. (2014) studied the epileptic effect on the education of child in Sierra Leone. The study included child's regularity at school, involvement in the extracurricular activities and the behavior of his class fellows. Data was collected through questionnaire and interview. The cases included in the study were 50 patients and the result was 51 percent of the children were not regular in the school, 90 percent did not participate in the physical activities due to seizures fear, 36 percent epileptic children get negative attitude from their classmates.

2.12 ADHERENCE TO EPILEPSY

Paschal et al. (2008) explained the adherence to epileptic treatment of patient with the help of direct measures the level of antiepileptic drugs in the blood, Detection in human hair or Saliva concentration and by indirect measures including tablets counting, regular checkup, Medication refills or the frequency of seizures. This information helped in the improvement of antiepileptic medicine, consideration of cultural factors, patient awareness about treatment and precautionary measures.

2.13 EPILEPTIC DEMENTIA

Study was done on using antiepileptic drug during pregnancy and its effect on the cognitive function of 3 years child. It was observed that those mothers who were taking valproate as an antiepileptic drug having children associated with impaired cognitive function at 3years of age. The conclusion of this study was that the women of childbearing potentials should not use valproate for the treatment of epilepsy (Meador et al., 2009).

As Epilepsy is a neurological disorder and is associated with the cognitive impairment. Decline in specific functions like concentration, memory, word fluency has been associated with long term duration of disease. Secondary generalized tonic clonic and complex partial seizures contribute in the declining of cognitive functions. Some conditions like infantile epileptic disorders called Dravet's responsible for cognitive impairments that worsens with the persistence of seizures. Some coexisting diseases like vascular diseases, Alzheimer and traumatic brain injury produce significant effect on the cognitive outcomes. In several studies it has been stated that long term administration of various antiepileptic drugs are associated with cognitive impairments. Decrease in intelligence in young epileptic patients is due to long term using of Phenobarbital (PB), declining of visuomotor functions are observed due to the administration of Phenytoin (PHT) and Topiramate (TPM) is a new anti-epileptic drug showing a significant declining in verbal memory and verbal IQ. Onset of epilepsy in early age is a major factor in the driving of poor intelligence in children due to long term using of anti-epileptic drugs while in late onset epilepsies the epileptic dementia

observed due to poor neuronal adjustment and plasticity failure (Breuer et al., 2016).

2.14 SLEEP DISTURBANCE

Sleep and epilepsy are interrelated. Studies shows that epileptic patients have more sleep problems as compared to normal population. Sleep disorder was studied in temporal lobe epilepsy (TLE) and in extra temporal lobe epilepsy (ETLE). One hundred and eighty nine patients were observed for refractory epilepsy by video EEG and different sleep scales were used to measure the outcome. According to this report it was concluded that patients with TLE have high risk of obstructive sleep apnea (OSA) (Yildiz et al., 2015).

Weerd et al. (2004) investigated the effect of partial epilepsy on the sleep of epileptic patients through questionnaire method. They took two groups one was partial epileptic patients group and the other was normal. Responses from 492 19 normal and 486 epileptic patients were analyzed. The result of this study was that the prevalence of sleep disturbance is greater in partial epileptic patients as compared with normal population.

MATERIALS AND METHODS

3.1 STUDY AREA

Present study included the patients of epilepsy belonging to different areas of Pakistan representing different caste or clans. Most cases for data collection were taken from Neurology department of different hospitals in Rawalpindi and Islamabad while some other hospitals of the country were also included. Most cases were representing the areas of Punjab, Khyber Pakhtun Khawh while less representation were from Azad Kashmir and Pothohar Plateau.

3.2 DATA COLLECTION

Sporadic and familial cases of epilepsy were included in this study. Patients of any kind of epilepsy from any area of country were included. 132 patients of epilepsy were selected for questionnaire filling and interview with complete medical records and history of patients.

3.3 ETHNIC CONCERNS

Due to the involvement of Human subjects the study was approved by Ethnic committee of Pir Mehr Ali Shah University of Arid Agriculture Rawalpindi. Patients consent was also prescribed compulsory before data collection.

3.4 SELECTION CRITERIA FOR EPILEPTIC PATIENTS

This study included the patients of epilepsy diagnosed by the Neurologists on the bases of neuroimaging tests with the prescription of medicines and showing the history of seizures. Individuals belonging to different age groups, different areas and ethnicity were selected for questionnaire and interview. Only active epileptic patients (a person with epilepsy who had at least one epileptic seizure in the previous five years or an individual who had unprovoked epileptic seizures which were disabling to the person on at least two different days in the previous 12 months.) were included. For familial study, families having history of epilepsy have been asked for questionnaire and medical record of all family members.

3.5 PROCEDURE FOR QUESTIONNAIRE

Questionnaire for epilepsy had been filled after having their consent. Questionnaire was developed according to the requirements of the topic of research. It consists of different questions included the general information of patient, family history , seizures information, causes, symptoms and duration of seizures, diagnosis of seizures type and treatment with side effects. Questions were in English language while it has been translated into Urdu language for their convenience.

3.6 INTERVIEWS OF EPILEPTIC PATIENTS

Interviews of epileptic patients were conducted to gain detailed information about their seizures pattern, precipitation and conditions after the fits. Conversation 22 with their family members was also be made to explore about the family history, seizures patterns, behavior of patients during attack and the regularity of the treatment have been asked.

3.7 MEDICAL RECORD OF EPILEPTIC PATIENTS

Medical records of epileptic patients based on EEG, MRI, and CT scan were included and became helpful to study the frequency of seizures patterns and diagnosis of epileptic area in the brain. Most

patients had only their EEG report which was included in the study. These records were noted in questionnaire.

3.8 PROGNOSIS

Therapeutic prognosis was checked on the basis of patients having seizures before taking treatment and response of seizures frequency and intensity after the treatment. Duration of the treatment and patient response was also included in the study. Only antiepileptic drugs were used as a treatment of epilepsy. No patient had been found who had surgery or any kind of brain stimulation treatment during study.

3.9 DATA SHEET

All the data was recorded in Excel sheet under the headings of age, sex, geographic distribution, ethnic group, family history, seizure types, causes, medicines, duration of treatments, number of seizures and EEG report. 23 3.10 STATISTICAL ANALYSIS Data of the collected samples was further arranged into groups and subgroups of age, sex and region. Descriptive statistical analysis and frequency estimation analysis was performed. Data analyzed was further represented in the form of tables, graphs and interpreted accordingly. All the statistical analysis were performed by using SPSS software version 21.0 (IBM).

RESULTS AND DISCUSSIONS

4.1 DEMOGRAPHIC FEATURES OF PATIENTS

A total of 132 samples of epilepsy were identified in this study. The Demographic data of collected samples was divided into sub groups of sex, age and location.

4.1.1 Sex based frequency

Among 132 identified epileptic patients, 59.1% (N= 78) were males and 40.9% (N= 54) were females (Table 4.1) which is showing that males are more affected than females. Our study is in accordance with one of review on the epidemiology of epilepsy in Pakistan included the higher ratio of epilepsy in males than females in Pakistan (Khatria et al., 2003). Prevalence of epilepsy in the People's Republic of China also indicated that men were 1.17 times more likely to have epilepsy than women (Gu et al., 2013). So it is concluded from this study that the frequency of epilepsy in males is higher. A possible explanation for this might be that males are more likely exposed to risk factors that cause epilepsy including head injuries, stroke, CNS infections or other cerebrovascular diseases. While females are more likely to conceal health issues may also be the reason.

4.1.2 Age based frequency

Epileptic patients under study were divided into two groups on the basis of age. Among 132 patients 96 were belonging to the group of age less than 25years 25 and 36 patients were aged greater than 25 years comprises 72.7% and 27.3% of the total studied population respectively (Table 4.1). It means that epilepsy is more common in younger population than older. Our results are in accordance to some previous studies on the population of China and South India showed that epilepsy was more frequent in younger age as compared to older population (Gu et al., 2013; Radhakrishnan et al., 2000). Our results are contrasting with a study showing that epilepsy was seemed to increase with age (Ablah et al., 2014) but this increase has not been found in this study. This inconsistency may be due to different diagnostic criteria or consideration of seizures in old age due to existed comorbidities.

4.1.3 Location based frequency

Analysis of studied subjects showed that the frequency of epilepsy is greater in people belonging to urban areas as compared to rural areas. Among 132 patients 61.3% were belonging to urban areas while 38.6% were from rural areas (Table 4.1). Our findings are consistent with previous study. A study in Pakistan indicated that the prevalence of epilepsy was lower in rural areas (7.4%) as compared to urban areas (14.8%) (Aziz et al., 1997) but these findings are also opposite to another study conducted in Pakistan included that higher prevalence of epilepsy was observed in rural population (Khatria et al., 2003) and also in China the rural areas were 1.37 times more affected to epilepsy than those of urban areas (Gu et al., 2013). The reason of this difference may be the misconceptions about epilepsy or lack of education in rural areas and the shortage of health facilities or the unavailability of diagnostic tools in rural areas

while the reason in the support 26 of present study outcomes are the more exposures of urban population to the accidents, depressions or other infectious diseases.

4.2 SEIZURES PATTERNS AMONG THE SUBJECTS

There are many patterns of seizures existed in epileptic patients but in our studied population only two patterns has been found. Among 132 patients 92 were suffering from generalized seizures while 40 were suffering from partial seizures calculated 69.7% and 30.3% of the total population under study (Table 4.2). Our findings are in accordance with a previous study conducted on population of Pakistan and Turkey indicated that generalized seizures were accounted for 80.5% and 65.4% respectively (Aziz et al., 1997) and generalized seizures were more common than partial seizures in Pakistan (Khatria et al., 2003). This result is also consistent with the findings of prevalence of epilepsy in the people of Republic of China accounted for 3.12% generalized seizures as compared to 0.57% partial seizures (Gu et al., 2013). The reasons for this high frequency are unknown. Although generalized seizures are more common in this study but there is need for more precise diagnostic tool to measure and classify the type of generalized seizures existed in patients.

4.2.1 Sex based seizures patterns

Out of 54 females 74.1% had generalized seizures and 25.9% had partial seizures while in 78 males 66.7% had generalized and 33.3% had partial seizures respectively (Table 4.2.1). These findings are showing that generalized seizures are more common in both genders. Furthermore the seizures are not the sex specific.

4.2.2 Age based seizures patterns

(Table 4.2.2) showing that those patients age less than 25 years had higher frequency of generalized seizures 71.9% than partial seizures 28.1% while in age greater than 25 years the same results has been found 63.9% generalized and 36.1% partial seizures. The study showing the higher frequency of generalized seizures regardless of patient of any age. So it is concluded that seizure patterns are not age specific and the patterns of seizures onset were observed from partial to generalized equally in all age groups.

4.2.3 Ethnic specific seizures patterns

The study included 61 subjects from Punjab showing the patterns of 65.6% generalized and 34.4% partial seizures, 31 from KPK comprised 74.2% generalized and 25.8% partial seizures, 29 belongs to Pothohar Plateau had 72.4% generalized and 27.6% partial seizures and 11 from AJK comprised of 72.7% generalized and 27.2% had partial patterns of seizures respectively (Table 4.2.3). Our data showed that Punjabis are more affected with epilepsy as compared to the other studied ethnic groups. No data on epilepsy has been found from Pakistan on race or ethnic group. While a study conducted in UK examined the racial differences between South Asians and non-South Asians found that the prevalence of active epilepsy is higher in non-South Asians in comparison to South Asians (Banerjee et al., 2009).

4.2.4 Seizures patterns and extent of antiepileptic drugs

Among 40 patients of partial seizures 15 were on monotherapy and 25 were on polytherapy. A significantly higher number of patients with partial seizures (P= 0.03) received polytherapy than those of other seizure type. It means that polytherapy is more effective for the patients with partial seizures. On the other hand among 92 patients of generalized seizures 44 were on monotherapy and 48 on polytherapy showing no significant difference (P=0.55). It means polytherapy and monotherapy are equally affected against generalized seizures (Table 4.2.4). These results are opposite to previous study conducted in India. Accoding to which that the frequency of seizures and adverse drug reaction were observed significantly higher among patients on polytherapy than those of monotherapy against both type of seizures (George et al., 2015).

4.2.5 Presentation and prognosis of Antiepileptic drugs (AEDs) among studied subjects with respect to specific seizures types

Combination of new and old AEDs are being using in Pakistan against epilepsy. The various AEDs used against specific seizures patterns including Carbamazepine 27.5%, Sodium valproate 47.5%,

Phenobarbitone 2.5%, Leviteracetum 40.0%, Oxcarbamazepine 20.0%, Topiramate 7.5%, Lamotrigine 20.0% and clonazepam 20.0% in partial seizures while against the generalized seizures Carbamazepine 33.7%, Sodium valproate 64.1%, Phenobarbitone 2.2%, Leviteracetum 29.3%, Oxcarbamazepine 10.9%, Topiramate 5.4%, Lamotrigine 9.8% and clonazepam 6.5% respectively (Table 4.2.5). These results are showing more use of sodium valproate against both types of seizures as compared to other AEDs. While second most preferred AED against partial seizure was Leviteracetum and in generalized seizure the frequency of using Carbamazepine is also higher after sodium valproate. According to previous study in India the significantly higher number of patients of partial seizures received Carbamazepine 29 than those of generalized seizures (P= 0.003) while the use of sodium valproate and lamotrigine used in generalized seizures are (P=0.004) significantly high (George et al., 2015). The prescription of Phenobarbitone is less in both types of seizures. The reason of prescribing less Phenobarbitone may be due to its side effects. According to studies this medicine causes hyperactivity and cognitive adverse effect in epileptic patients (Boer et al., 2008; George et al., 2015). All these AEDs are used as montherapy and polytherapy against specific seizures as described earlier. During data collection it has been observed that treatment of epilepsy started with the combination of different AEDs and antidepressants and with the lowering of seizures frequency the volume of AEDs also prescribed less and the patient reached monotherapy. It's explained that the dozes of medicine depends on the seizure frequency. No major side effect has been observed other than memory due to using of these AEDs which is consistent with one of the previous study including that phenobarbital, clonazepam and valproate were involved in the cognative impairment in children, infants and pregnant women (Bittigau et al., 2002). During interviews 31.8% patients reveals of taking treatment against epilepsy in 1 year while 68.2% had not completed the treatment at least one year (Table 4.2.6). This is also showing the treatment gap that responsible of the high frequency of epilepsy. While after taking the above mentioned AEDs the following results has been observed. Seizure frequencies become less frequent were in 68.2% patients, more frequent in 0.8%, no attack in 4.5%, seizures reoccur 4.5% and unchanged in 22.0% patients respectively (Table 4.2.7). Less frequency in seizures attack after using the single therapy mentioned above or combination of these AEDs proving the efficacy and effectiveness of using AEDs against specific 30 seizure types. The results of EEG reports are given in table 4.2.8 of different patients after using these AEDs against partial and generalized seizures also providing the knowledge about the effectiveness of treatment. But EEG is not the appropriate diagnostic tool because the patients who had recurrent seizures may have the normal scalp EEG during inter-ictal or even during ictal states of seizures.

4.2.6 Gender and age based AEDS

Results presented in Tables 4.2.9 showed that the more use of sodium valproate and Carbamazepine in both sexes while there is no use of Phenobarbitone has been observed in male due to unknown reasons. On the basis of age sodium valproate and Levetricetum are frequently being used in age less than 25 years while the use of sodium valproate and Carbamazepine is more in the age above 25 years. A possible explanation of this difference may be the more effectiveness of carbamazepine in older age and levetricetum in younger age to control seizures while sodium valproatre is equally effective in both cases. 4.3 RISK FACTORS Epilepsy is most serious neurological condition mostly with unknown causes. Study included some possible risk factors against epilepsy were panic attacks 2.3%, head injury 12.9%, febrile seizures 9.1%, family history of epilepsy 2.3%, birth anorexia 2.3%, bone marrow transplant 0.8%, stroke 1.5%, paralyze 0.8% and parental consanguinity 30.3% respectively (Table 4.3). Overlapping risk factors had been observed for epilepsy in Turkey including head injuries 27.76 31 fold, febrile seizures 21.97 fold, history of epilepsy 6.42 fold and the high rate of consanguineous marriages (cansu et al., 2007). Another finding also included that higher rate of consanguinity reported in Algerian population that may contribute to the genetic factors (Chentouf et al., 2015). Head injuries and parental consanguinity are found to be the important risk factors in this study and mostly unknown causes of

epilepsy had been observed. Consanguinity and unknown causes may indicate the involvement of genetic factors in epilepsy.

4.4 EPILEPTIC DEMENTIA

Cognitive impairments has been observed included memory distortion 30%, speech 2.5% and hearing problems 5% in partial seizures while in generalized seizures 17.4 % memory distortion, problem in speech 5.4%, writing difficulties 2.2 %, vision problem 2.2% and hearing problems in 1.1% respectively (Table 4.4). The study showing more epileptic dementia in generalized seizures than partial seizures. Cognitive impairments can be a result of side effects of many AEDs such as phenobarbital is known to cause hyperactivity and memory problems in epileptic patients (Boer et al., 2008).

Table: 4.1 Frequency of epilepsy in term of sex, age, location and seizure patterns

Parameter	Categories	Frequency	Percentages
Sex	Male	78	59.1
	Female	54`	40.9
Age	<25	96	72.7
	>25	36	27.3
Location	Rural	51	38.6
	Urban	81	61.3

Table: 4.2 Seizures patterns among the subjects

Parameter	Categories	Frequency	Percentage
Seizures Patterns	Generalized	92	69.7
	Partial	40	30.3

Table: 4.2.1 Sex based seizure patterns

Sex	Seizures Patterns	Frequency	Percentage
Female	Generalized seizures	40	74.1
	Partial seizures	14	25.9
	Total	54	100.0
Male	Generalized seizures	52	66.7
	Partial seizures	26	33.3
	Total	78	100.0

Table: 4.2.2 Age based seizure patterns

Age	Seizures Patterns	Frequency	Percentage
<25	Generalized seizures	69	71.9
	Partial seizures	27	28.1
	Total	96	100.0
>25	Generalized seizures	23	63.9
	Partial seizures	13	36.1
	Total	36	100.0

Table: 4.2.3 Ethnic specific seizure patterns

Ethnic group	Partial seizures		Generalized seizures	
	Frequency	Percentage	Frequency	Percentage
Punjab	21	34.4	40	65.6
KPK	8	25.8	23	74.2
Pothohar Plateau	8	27.6	21	72.4
AJK	3	27.2	8	72.7

Table: 4.2.4 Seizures patterns and extent of antiepileptic drugs

Seizure Pattern	No of patients	Monotherapy	Polytherapy	Significance level
Partial seizures	40	15	25	0.03
Generalized seizures	92	44	48	0.55

Table: 4.2.5 Presentation and prognosis of Antiepileptic drugs (AEDs) among studied subjects with respect to specific seizures types

AEDs used	Partial seizures N= 40	Percentage	Generalized seizures N=92	Percentage
Carbamazepine	11	27.5	31	33.7
Sodiumvalproate	19	47.5	59	64.1
Phenobarbitone	1	2.5	2	2.2
Leviteracetum	16	40.0	27	29.3
Oxcarbamazepine	8	20.0	10	10.9
Topiramate	3	7.5	5	5.4
Lamotrigine	8	20.0	9	9.8
clonazepam	8	20.0	6	6.5

Table: 4.2.6 Effects of treatment on the basis of duration

Prognosis		Frequency	Percentage
1 year Treatment	Yes	42	31.8
	NO	90	68.2
Effects on seizures after using AEDs	Less frequent	90	68.2
	More frequent	1	0.8
	no attack	6	4.5
	Reoccur	6	4.5
	unchanged	29	22.0

Table: 4.2.7 EEG report after using AEDs.

EEG report	Partial seizures		Generalized seizures	
	Frequency	Percentage	Frequency	Percentage
Abnormal	18	45.0	28	30.4
Normal	22	55.0	64	69.6

Table: 4.2.8 Gender based AEDS

Gender	AEDs used							
	Carbamazepine	Sodium valproate	Phenobarbitone	Levetricetum	Oxycarbamazepine	Topiramate	Lamotrigine	Clonazepm
Male N=78	24	49	0	26	11	5	7	9
Female N=54	18	29	3	17	7	3	10	5

Table: 4.2.9 Age based AEDs

AEDs used	Age <25 N=96	Age >25 N=36
Carbamazepine	28	14
Sodium valproate	60	18
Phenobarbitone	1	2
Levetricetum	35	8
Oxycarbamazepine	12	6
Topiramate	5	3
Lamotrigine	8	9
Clonazepam	10	4

Table: 4.3 Risk factors of epilepsy

Risk Factors	Frequency	Percentage
Panic	3	2.3
Head injury	17	12.9
Febrile seizures	12	9.1
Family history of epilepsy	3	2.3
Birth anorexia	3	2.3
Bone marrow transplant	1	0.8
Stroke	2	1.5
Paralyze	1	0.8
Parental Consanguinity	40	30.3

Table: 4.4 Epileptic dementia

Seizure Pattern	Cognitive consequences				
	Memory	Speech	Writing	Vision	Hearing
Partial Seizures					
Frequency	12	1	0	0	2
Percentage	30.0	2.5	0	0	5.0
Generalized Seizures					
Frequency	16	5	2	2	1
Percentage	17.4	5.4	2.2	2.2	1.1

SUMMARY

Epilepsy is a long term brain ailment that is due to the generation of seizures and it resulting into changes in the thinking, psychological, anatomy and physiology of the brain as well as changes take place in physical, economic and social consequences. Seizures are the core symptom of epilepsy and brain insult. These are the uncertain patterns and brief deterioration of the central nervous system due to abnormal neuronal activities in the cortical areas of brain. Epilepsy may have predisposing or exciting causes that include physiologic, psychical or pathologic causes. Epilepsy is also an inherited disorder. Studies on human genetics explained the defects occur in cellular and molecular mechanisms that maintains the normal development of neural homeostasis and nervous system lead epileptogenetic processes. Electroencephalography (EEG) is an important diagnostic tool for studying activity of human brain and epileptic discharges. This study was designed to evaluate the patterns of seizures and therapeutic prognosis in different ethnic group shows that partial and generalized seizures are existed in population under study. Polytherapy is more effective for the patients with partial seizures while polytherapy and monotherapy are equally affected against generalized seizures. This study also shows more use of sodium valproate against both types of seizures as compared to other AEDs. While second most preferred AED against partial seizure was Leviteracetum and in generalized seizure the frequency of using Carbamazepine is also higher after sodium valproate. Head injuries and parental consanguinity are found to be the important risk factors in this study and mostly unknown causes of epilepsy had been observed. The data showed that Punjabis are more affected with epilepsy as compared to the other studied ethnic groups.

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