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Clinical Investigation in Selected Patients of Epilepsy in Hazara Division Kpk Pakistan

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Abstract

Epilepsy is a neurological disorder characterized by recurrent seizures. Seizures occur due to sudden abnormal electrical activity in the brain. Usually, the exact causes of epilepsy are may not be known but there are several known factors and potential causes (genetic factors, brain injuries, brain tumors, stroke, brain infection, developmental disorders, metabolic disorders, perinatal injuries, vascular abnormalities, Alzheimer's disease and Dementia) can contribute in the development of epilepsy. The worldwide prevalence of epilepsy is estimated is 7.60 per 1000 people, it may varies between countries and regions. Low and middle-income countries tend to have high prevalence comparatively to high-income countries, due to limited access to healthcare and higher rates of risk factors such as head injuries and infections. The reported prevalence of epilepsy in Pakistan is 9.96 per 1000 people. The treatment of epilepsy is generally a combination of medications, adjustments in lifestyle, and in certain instances, surgical procedures. The treatment objective is to decrease the occurrence and intensity of seizures while mitigating adverse effects and enhancing overall quality of life. We collected 11 effected samples from the Hazara division. The clinical characteristics and medical history of each patient were recorded and the samples were sent to UCL UK for genetic analysis, to understand the cause of the disorder. We used whole exome sequencing for the identification of mutation in DNA and later on used CRISPR technology to see whether the changes are reversible or not. For this purpose, animal models are being used like Mouse and Drosophila models in Germany and Italy in collaborating groups. We are waiting for the genetic analysis. A survey among 110 students was also conducted to know public perspective about Epilepsy in studied group.

Introduction

A **"seizure"** is a paroxysmal alteration of neurologic function caused by the excessive, hypersynchronous discharge of neurons in the brain. "Epileptic seizure" is used to distinguish a seizure caused by abnormal neuronal firing from a nonepileptic event, such as a psychogenic seizure. "Epilepsy" is the condition of recurrent, unprovoked seizures. Epilepsy has numerous causes, each reflecting underlying brain dysfunction[1]. A seizure provoked by a reversible insult (e.g., fever, hypoglycemia) does not fall under the definition of epilepsy because it is a short-lived secondary condition, not a chronic state. "Epilepsy syndrome" refers to a group of clinical characteristics that consistently occur together, with similar seizure type(s), age of onset, EEG findings, triggering factors, genetics, natural history, prognosis, and response to antiepileptic drugs (AEDs). The nonspecific term "seizure disorder" should be avoided.

Epilepsy is one of the most common neurologic conditions, with an incidence of approximately 50 new cases per year per 100,000 population [2]. About 1% of the population suffers from epilepsy, and about one-third of patients have refractory epilepsy (i.e., seizures not controlled by two or more appropriately chosen antiepileptic medications or other therapies).

Approximately 75% of epilepsy begins during childhood, reflecting the heightened susceptibility of the developing brain to seizures[3]. Epilepsy is not a singular disease entity but a variety of disorders reflecting underlying brain dysfunction that may result from many different causes. Little common agreement exists on the definition of the terms seizure and epilepsy. Such definitions are important for communication among medical professionals and also for communication others involved in legislation, disability pensions, driving regulations, workplace safety, education, and for many other purposes. The definition in this thesis are directed to a diverse group of physicians, educators, researchers, public officials, and people with epilepsy and their families. Regarding epileptic seizures, a statement concerning the electrical activity of the brain during the episode appears to be necessary in the definition, but difficult to apply in clinical practice. A definition ideally would include assertions about pathophysiology and the metabolic consequences of the seizure, but the understanding of pathophysiology changes with each research advance. As a word, seizure derives from the Greek meaning **to take hold.** Modern popular terminology uses the word seizure for any sudden and severe event (for example, "he had a heart seizure"). Many physical or psychological sudden events, some of them not even pathological, all resemble epileptic seizures in some ways. To emphasize this usage, typically, we will refer to an epileptic seizure [5][6].

Classification

There are several types of seizures, and they're split into two categories: generalized and focal.

Generalized seizures: Generalized seizure originated in neuronal network of both left and right hemisphere.

Absence seizures Also called petit mal, these may cause you may to lose focus, blink rapidly, or stare out into space for a few seconds [7].

Tonic-clonic seizures Also called grand mal, these may cause you to cry out, fall to the ground, or experience strong muscle jerking or contractions [8].

Focal seizures Focal seizure is limited to part of one cerebral hemisphere.

- **Simple focal seizures** These affect just a small part of the brain and can have minimal symptoms, like a small twitch or a strange taste in your mouth.
- **Complex focal seizures** These involve multiple areas of the brain and can cause confusion. You may become disoriented or unable to respond from a few seconds to a few minutes.
- **Secondary generalized seizures** These seizures begin as a focal seizure in one part of the brain and progress to a generalized seizure [9].

Seizure descriptions

Seizures can take on many forms. Here are a few of the most common ways:

- **Tonic** muscles stiffen.
- **Atonic** muscles go limp.
- **Myoclonic** there are quick, jerking movements.
- **Clonic** there are repeated periods of shaking or jerking movements [9].

Epilepsy in Adults There are several kinds of epilepsy in adults: [10].

Progressive myoclonic epilepsy This includes several rare, generally hereditary conditions that stem from metabolic disorders. This disorder usually begins late in childhood or in the teen years and appears with seizure activity, myoclonus, and weakness that become progressively worse over time [11].

- **Refractory epilepsy** Your epilepsy may be called refractory if the seizures continue despite medication.
- **Reflex epilepsy** These types of epilepsy involve seizures are triggered by external or internal stimuli like emotions, temperature changes, or lights.

- **Photosensitive epilepsy** This is the most common type of reflex epilepsy and is triggered by flashing or strobing lights. This type of epilepsy usually begins during childhood and may lessen or disappear in the adult years [11].

Epilepsy in Children

There are also a few types of epilepsy that are specific to childhood, including:

Myoclonic astatic epilepsy childhood (Doose syndrome) of these seizures are characterized by a sudden loss of muscle control with no known cause.

Benign rolandic epilepsy (BRE) These seizures involve twitching, numbness, or tingling of the face or tongue and can cause speech problems or drooling. This condition usually ends in adolescence.

Rasmussen syndrome This rare autoimmune syndrome is characterized by focal seizures which are usually the first symptom. Surgery is typically the best treatment for this condition, as seizures can be difficult to manage with medications.

Lennox-Gastaut syndrome This rare condition involves multiple types of seizures and is often seen in children with developmental delays. The cause for this condition is unknown.

Electrical status epilepticus of sleep (ESES) This disorder is characterized by seizures during sleep and abnormal EEG findings during sleep. It usually occurs in school-aged children, mainly while they sleep. It can involve learning or language delays as well [12].

Sturge-Weber syndrome. Children with this condition usually have nevus flammeus — also called a port-wine stain — on their scalp, forehead, or around the eye. They can have seizures, weakness, developmental delays, and vision difficulties. Surgery is sometimes required when medications can’t manage the condition [13].

Juvenile myoclonic epilepsy. This condition starts around puberty and mostly appears as small, rapid jerking movements called myoclonic seizures [14]. Absence seizures may also occur. This condition can usually be managed with medication. [15].

Definitions and Terminology

While all people with epilepsy experience seizures, not all individuals with seizures have epilepsy. Epileptic seizures may also occur after an acute central nervous system (CNS) insult (structural, systemic, toxic, or metabolic). These events (acute symptomatic or provoked seizures) are intended as acute manifestations of the insult [16] and may not recur when the underlying cause has been removed or the acute phase has elapsed [17]. According to the International League Against Epilepsy (ILAE), epilepsy is defined by any of the following conditions

1: at least 2 unprovoked (or reflex) seizures occurring >24 h apart.

2: one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after 2 unprovoked seizures, occurring over the next 10 years;

3: diagnosis of an epilepsy syndrome [18]. However, for the purpose of conducting population-based studies, the ILAE Epidemiology Commission advises that epilepsy be defined as 2 or more unprovoked seizures occurring at least 24 h apart [19].

An unprovoked seizure is a seizure occurring in the absence of precipitating factors. Unprovoked seizures include events occurring in the absence of recognized etiological or risk factors (idiopathic and cryptogenic seizures), in patients with antecedent stable (non-progressing) CNS insults (remote symptomatic seizures), or in those with progressive CNS abnormalities, like brain tumors or degenerative conditions (progressive symptomatic seizures). Seizure onset can be focal (seizures arising in one hemisphere of the brain), generalized (seizures originating in both hemispheres simultaneously), and unknown [20]. Focal seizures are classified according to whether awareness (a marker for consciousness) is intact or impaired. Focal and generalized seizures are also divided into motor and nonmotor. Active epilepsy is defined by regular treatment with antiepileptic medications or when the most recent seizure has occurred within the last 5 years [19]. Status epilepticus (SE) is an epileptic seizure that is sufficiently prolonged or repeated at sufficiently brief intervals so as to produce an enduring epileptic condition. SE can have long- term consequences including neuronal injury or death and alteration of neuronal networks, depending on the type and duration of seizures. A new diagnostic classification of SE has been recently proposed [21]. Sudden unexpected death in epilepsy (SUDEP) is the sudden, unexpected, witnessed or unwitnessed, nontraumatic, and non-drowning death in patients with epilepsy, with or without evidence for a seizure and excluding documented SE, in which postmortem examination does not reveal a toxicologic or anatomic cause of death [22]. In most cases, SUDEP is triggered by a seizure, and seizure induced cardiorespiratory alterations are a plausible hypothesis.

Incidence of Acute Symptomatic Seizures

The median incidence of acute symptomatic seizures is 29–39 per 100,000 per year [23]. Acute symptomatic seizures predominate in the youngest age class (under 1 year of age) and in the elderly. Fever, traumatic brain injury (TBI), cerebrovascular disease, drug withdrawal, infection, and metabolic insults are the commonest precipitating factors.

Incidence of Epilepsy

In a systematic review and meta-analysis of incidence studies, the pooled incidence rate of epilepsy was 61.4 per 100,000 person-years (95% CI 50.7–74.4) [24]. The incidence was higher in low/middle-income countries (LMIC) than in high-income countries (HIC), 139.0 (95% CI 69.4–278.2) vs. 48.9 (95% CI 39.0–61.1). This can be explained by the different structure of populations at risk and a greater exposure to perinatal risk factors, higher rates of CNS infections, and TBI in LMIC. The incidence of epilepsy is also higher in the lowest socioeconomic classes in HIC and, within the same population, people of differing ethnic origin [25]. Differences can be also explained by methodological issues, such as more stringent case verification and the exclusion of isolated and acute symptomatic seizures in some studies.

Prevalence of Epilepsy

The prevalence of epilepsy differs significantly among countries depending on the local distribution of risk and etiologic factors, the number of seizures at diagnosis and if considering only active epilepsy (active prevalence) or including also cases in remission (lifetime prevalence). In the Fiest et al. [24], the overall lifetime prevalence of epilepsy was 7.60 per 1,000 population (95% CI 6.17–9.38) and was higher in LMIC (8.75 per 1,000; 95% CI 7.23–10.59) than in HIC (5.18 per 1,000; 95% CI 3.75–7.15). The point prevalence of active epilepsy was 6.38 per 1,000 (95% CI 5.57–7.30). The median point prevalence of active epilepsy in LMIC was 6.68 (95% CI 5.45–8.10) and in HIC was 5.49 (4.16–7.26). In selected populations, prevalence estimates also vary and tend to be higher in individuals of certain ethnicities [26], people in poor health, and socially deprived subjects [27]. Along with issues in the study design, the demographic structure of the study population, the prevalence of environmental risk factors, and the quality of health management can be implicated.

Incidence and Prevalence of Epilepsy by Sex and Age

Incidence and prevalence of epilepsy are slightly higher in men than in women. The difference might be explained by the different prevalence of the most common risk factors and the concealment of the condition in women for sociocultural reasons in certain regions [28].The incidence of epilepsy is higher in the youngest and oldest age-groups [24], with estimates of 86 per 100,000 per year in a well-defined population in the first year of age, a trend to decrease to about 23–31 per 100,000 in people aged 30–59 years, and a subsequent increase up to 180 per 100,000 in the over 85 age-group [29]. In children, the incidence of epilepsy is highest in the first year of life and declines to adult levels by the end of 10 years of age [30]. In LMIC, epilepsy peaks in children; this may be a result of under-ascertainment of the condition in older individuals as well as the demographic structure of the country.

Temporal Trends of Epilepsy

In the last decades, the age-specific incidence of epilepsy has decreased with time in the youngest age-groups, probably due to improvements in perinatal care, better sanitation, and increased control of infectious diseases [31]. In contrast, the incidence has increased in the elderly, likely due to improved life expectancy (with parallel increase of aging-related epileptogenic conditions, such as stroke, tumors, and neurodegenerative disorders) and increased ascertainment of the disease in this age-group.

Incidence and Prevalence by Seizure Type

Focal seizures are the predominant seizure type both in children and in adults [29, 32]. The most common type of focal seizure is a focal impaired awareness seizure (accounting for approximately 36% of all people with seizures) [29]. In most LMIC, however, the predominant types reported are generalized tonic-clonic seizures [33], a reflection of under ascertainment of the other seizure types, likely due to a lack of recognition and diagnostic tools. The incidence of SE has been found to vary from 6.8 to 41 per 100,000 per year [34] with a bimodal distribution (peaks in children <1 year and the elderly). The wide range can be explained by the population at risk, the accuracy of the diagnosis, the differing distribution of the underlying causes, and the inclusion or exclusion of acute symptomatic seizures.

Incidence and prevalence by epilepsy type

In a population-based study done 20 years ago in a US population [35], focal epilepsies of unknown etiology were the most common group in people newly diagnosed with epilepsy (17.5 cases per 100,000 per year), followed by symptomatic partial epilepsies (focal epilepsies of structural or metabolic etiology according to the new ILAE classification) [36] (17.2), unknown epilepsies (epilepsies of unknown etiology; 9.7), symptomatic/cryptogenic epilepsies (epilepsies of structural or metabolic etiology/unknown etiology; 4.0), idiopathic generalized epilepsies (3.7), and idiopathic partial epilepsies (i.e., generalized and focal epilepsies of presumed genetic origin; 0.2). The proportion of epilepsies with unknown etiology has remained substantially unchanged in more recent years, at least in HIC [37]. In children, age at onset was significantly correlated with etiology. Approximately half had a documentable etiology. Of them, 28% were structural/metabolic, which predominated when seizures started before 12 months of age, and 22% were presumedly genetic, most likely associated with older age at onset. A specific epilepsy syndrome could be detected in 28% of cases at first diagnosis.

Prognosis of Epilepsy

Epilepsy is a treatable condition, with up to 80% entering prolonged periods of seizure remission and up to 50% continuing to be seizure-free after treatment discontinuation [38,39]. However, reports from several LMIC (where treatment gap is high) give prevalence and remission rates overlapping to HIC [40]. As in most LMIC, the incidence of epilepsy is higher than in HIC and increased mortality can explain only in part the difference between incidence and prevalence, misdiagnosis and acute symptomatic seizures must be also considered. Studies in newly diagnosed patients have consistently shown that 55–68% of cases tend to achieve prolonged seizure remission (40). However, in a long-term population-based study done in patients with childhood-onset epilepsy, differing remission patterns were seen. Half of the patients entered terminal remission, without relapse, and one-fifth after relapse. About one-third had a poor outcome in terms of absolute absence of remission or relapsing seizures after periods of remission [39]. These patterns have been confirmed in part by others [41-42]. The prognosis of untreated epilepsy can be assessed only in LMIC where epilepsy is largely untreated (treatment gap ranging from 70 to 94%) [44]. In a population based study done in Ecuador, the cumulative annual incidence rate was 190 per 100,000 and the prevalence rate of active epilepsy was 7 per 1,000, which implies a remission rate of at least 50% [45]. Similar prevalence rates of active epilepsy were found in other countries [43, 46 and 47]. As proposed by Sander [48], epilepsy patients can be classified into 4 different prognostic groups: **(1) Excellent prognosis** (about 20–30% of the total) with high probability of spontaneous remission; these include benign focal epilepsies, benign myoclonic epilepsy in infancy, and epilepsies provoked by specific modes of activation, that is, reflex epilepsies**;**

(2) **Good prognosis** (about 30–40%) with easy pharmacological control and possibility of spontaneous remission; these include childhood absence epilepsy and some focal epilepsies;

(3) **Uncertain prognosis** (about 10–20%), which may respond to drugs, but tend to relapse after treatment withdrawal; these include juvenile myoclonic epilepsy and most focal epilepsies (symptomatic or cryptogenic)**;**

(4) **Poor prognosis** (about 20%) in which seizures tend to recur despite intensive treatment; these include epilepsies associated with congenital neurological defects, progressive neurological disorders, and some symptomatic or cryptogenic partial epilepsies. This classification is still valid even after the advent of more sophisticated diagnostic techniques and after the introduction of several new antiepileptic drugs.

Mortality of Epilepsy

Epilepsy per se carries a low mortality risk, but significant differences in mortality rates are expected when comparing incidence and prevalence studies, children and adults, and persons with idiopathic and symptomatic seizures [49]. As with prevalence and incidence, epilepsy mortality reflects the quality of case ascertainment, the accuracy of the information on causes of death and the survey methods. People with epilepsy are at an increased risk of death than the general population. Among deaths attributable to epilepsy or seizures, important immediate causes include SUDEP, SE, unintentional injuries, and suicide. In HIC, standardized mortality ratio ranges from 1.6 to 3.0. In LMIC, the corresponding ratio is 19.8 (95% CI 9.7–45.1) [50]. Standardized mortality ratio is slightly higher in men than in women and in children and adolescents, in people with epilepsies due to documented etiology, and in those reporting less adherence to treatment. Indirect causes of death in LMIC include not only drowning and burns but also lack of access to health facilities and preventable causes. The incidence of SUDEP among people with epilepsy is 1.2 per 1,000 person-years (95% CI 0.9–1.5) and ranges from 1.1 (95% CI 0.5–2.3) in children under age 16 years to 1.3 (95% CI 0.9–1.8) in adults after the age of 50 years [51]. The major risk factors include generalized tonic-clonic seizures, nocturnal seizures, and persistence of seizures. Freedom from seizures, particularly generalized tonic-clonic, is associated with decreased risk and nocturnal supervision is protective [52].

Burden of Epilepsy

According to the Global Burden of Disease Collaborators (2016), epilepsy represents a relevant fraction of the worldwide disease burden, accounting for about 46 million people. Nearly 80% of people with epilepsy reside in LMIC, where rates of epilepsy prevalence and incidence are higher than in HIC [53]. The differences are likely due to differing causes, a higher incidence of injuries, and lack of access to health care. In 2016, epilepsy accounted for >13 million DALYs and was responsible for 0.5% of the total disease burden. In terms of age-standardized DALY rates for all neurological disorders by Global Burden of Disease region in 2016, epilepsy ranked second to eighth depending on the geographic region. The burden of idiopathic epilepsy (i.e., due to a genetic cause or when diagnostic assessment did not reveal a causative factor) was highest in eastern, western, and southern sub-Saharan Africa, central Asia, central and Andean Latin America, and southeast Asia. Age-standardized DALYs were 182.6 per 100,000 population, 163.6 per 100,000 population for women, and 201.2 per 100,000 population for men. The higher DALY rates in men than in women were due to higher years of life lost rates.

Between 1990 and 2016, there was a nonsignificant 6.0% increase in the age-standardized prevalence of idiopathic epilepsy, but a significant decrease in age standardized mortality rates (–24.5%) and age-standardized DALY rates (–19.4%). Between 1990 and 2016, a significant reduction was observed in the mortality rate in people with idiopathic epilepsy and, to a lesser extent, a reduction was found in DALY rates. This finding probably reflects improvements in access to health facilities and treatment, which in turn may lead to a lesser severity of the disease and lower risk of death.

The Change of the Population Health and Its Impact on the Epidemiology of Epilepsy

The data on the global burden of epilepsy have clearly demonstrated that, contrary to other clinical conditions, the disease presents a decreasing trend, mostly explained by a significant reduction of mortality. A significant decrease of communicable diseases as a reflection of better sanitation and the introduction of preventive measures leads to the reduction of many environmental risk factors and epileptogenic conditions. Better health care is also followed by increased survival and, in turn, by a longer life expectancy. The progressive aging of the worldwide population is accompanied by a shift of age-specific incidence and prevalence of epilepsy with a progressive decrease of the disease in the youngest age-groups and a corresponding increase in the elderly. A better control of preventable causes of epileptic seizures, which mostly include pre-/perinatal injuries, CNS infections and infestations, TBI, and stroke will be followed by a decrease of these clinical conditions but an increase in aging-related diseases (in particular, CNS tumors and Alzheimer disease and other dementias [54, 55].

Prevalence in Pakistan

Recent increase in number of children diagnosed with epilepsy raised the need to find out and report the demographic and clinical features of childhood idiopathic epilepsy at a tertiary care hospital. Overall prevalence of epilepsy in Pakistan is estimated to be 9.99 per 1000 population. Highest prevalence is seen in people younger than 30 years of age. A slight decrease in prevalence is noted between the ages of 40 and 59. Higher prevalence is observed in rural population. Etiology of epilepsy is more commonly identified in pediatric population. Epilepsy was considered idiopathic in 21 to 76% cases. Only 27.5% epileptic persons in urban areas and 1.9% in the rural areas were treated with AEDs. The burden of epilepsy is not fully evaluated and understood. Generalized seizures were the most common seizure type noted. Knowledge about epilepsy and its care is extremely low [91].

Etiology

Seizures result from a shift in the normal balance of excitation and inhibition within the CNS as well as from abnormal brain function [79]. Because various properties control neuronal excitability, it is not unusual that this normal balance can be disturbed in many different ways; thus, there are many causes of seizures and epilepsy [79]. In about 70% of patients, no cause can be found [80]. The normal brain is capable of experiencing a seizure under certain circumstances, and individuals vary in their susceptibility or threshold for seizures. Patients may have seizures intermittently, with periods of months to years between seizures. There are several possible causes of seizures in a given patient [79].

1. Seizures may be induced by a high fever in children who are otherwise healthy, who have a structural defect, or who have genetic risk factors.
2. A severe, penetrating head trauma or injury is associated with almost a 50% risk of subsequent epilepsy.
3. In older patients, Alzheimer's disease and stroke may precipitate epilepsy.
4. Viral and parasitic infection can also induce the risk of epilepsy.

The pivotal role of synapses in mediating communication among neurons in the mammalian brain suggests that defective synaptic function might lead to seizures. That is, a decrease of inhibitory synaptic activity or enhancement of excitatory synaptic activity might be expected to trigger seizures, as corroborated by pharmacological studies [81]. The neurotransmitters mediating the main part of synaptic transmission in mammalian brain are amino acids; gamma aminobutyric acid (GABA) and glutamate are the principal inhibitory and excitatory neurotransmitters, respectively. GABA is the major inhibitory amino acid neurotransmitter in the mammalian CNS [82]. Its receptors have been divided into two main types: $GABA_A$ (the more prominent subtype) is a ligand-gated Cl^- ion channel that is opened after the release of GABA from presynaptic neurons. The $GABA_A$ receptor protein has been well characterized by its high abundance and its role in almost every neuronal circuit. $GABA_B$, a member of the G-protein coupled receptor family, is linked both to biochemical pathways and to regulation of the ion channels [82].

Genetic factors in epilepsy

Most primary epilepsies have a genetic basis. As in many other idiopathic diseases such as diabetes, the mode of inheritance is complex [83]. Most cases of partial epilepsy appear to be acquired as a consequence of a focal lesion of the cortex, with a minority of cases identified by genetic determinants. In contrast to partial epilepsies, genetic determinants seem to underlie most cases of the most common generalized-onset epilepsy [81]. That a genetic factor is involved in primary generalized tonic–clonic seizures is suggested by a familial incidence in 5% to 10% of such patients and, in particular families, by the inheritance of a generalized seizure disorder through specific genes or chromosomal regions. [83] The most common form of generalized-onset epilepsy—juvenile myoclonic epilepsy—appears to be a polygenic disease. Expression of the phenotype requires the simultaneous inheritance of multiple genes [81].

In practice, the etiologic mechanism is based on the patient’s age, which is one of the most important factors in determining both the incidence and the likely causes of seizures or epilepsy [81]. Patients often have a family history of febrile seizures or epilepsy. Childhood marks the age at which many of the well-defined epilepsy syndromes are manifested [81].

Head trauma is a common cause of epilepsy in adolescents and adults. The development of epilepsy is strongly correlated with the severity of the head injury. In adults older than 65 years of age, cerebrovascular disease causes about 50% of cases of epilepsy; trauma, CNS tumors, and degenerative diseases are also etiologic factors in this population. Metabolic disturbances such as electrolyte imbalances, hypoglycemia or hyperglycemia, endocrine disorders, hematological disorders, renal failure, and hepatic failure may cause seizures at any age[79]Conditions most likely to simulate a seizure are syncope and transient ischemic attacks; other possible conditions include unexplained falls (“drop attacks”), subarachnoid hemorrhage, sleep disorders (sleepwalking, rapid-eye-movement sleep behavior disorder), panic attacks, migraine, hypoglycemia, cataplexy, paroxysmal ataxia and choreoathetosis, recurrent transient global amnesia, and psychogenic pseudoseizures[83].

(a) Infectious Agents Causing Epilepsy

Any infection of the cortex can potentially result in seizures. This primarily relies upon the structural damage occurring during the infection, although secondary inflammatory processes may also provoke seizures. Certain conditions, including viral encephalitis and parasitic infections—such as “cerebral” malaria and neurocysticercosis—are inherently associated with seizures and the risk of developing epilepsy. Other conditions, such as bacterial meningitis, can cause seizures in the acute setting, although this is less frequent and they rarely result in long-term epilepsy. Here we will review the most common central nervous system (CNS) infectious disorders causing epilepsy, specifically focusing on viral encephalitis and parasitic infections.

Viral Encephalitis

Encephalitis encompasses a broad range of pathophysiological process that result in inflammation of brain parenchyma and therefore the diagnosis is fundamentally a histopathological one. In view of the impracticality of obtaining brain tissue, surrogate markers of brain inflammation are routinely used to make the diagnosis. These include elevated cerebrospinal fluid (CSF) leukocyte counts, raised protein, evidence of viral nucleic acid in the CSF by polymerase chain reaction (PCR), or intrathecal synthesis of antiviral antibody. Neuroimaging can also help [57] [58]. Encephalitis usually presents with an encephalopathy syndrome for which there is often a broad differential diagnosis [59]. Features raising suspicion for infective encephalitis include a history of fever or coryzal illness, recent travel, and inadequate vaccination [57]. A wide range of pathogens can cause encephalitis. Antibody-associated encephalitis, which may be paraneoplastic or de novo, is of increasingly recognized importance. Acute symptomatic seizures occur in 2 to 67% of patients with a diagnosis of encephalitis overall. Head trauma is a common cause of epilepsy in adolescents and adults. The development of epilepsy is strongly correlated with the severity of the head injury. The pathogen may be important in determining whether a person subsequently develops epilepsy in the long term. For example, encephalitis caused by La Crosse virus has a cumulative incidence of epilepsy of 10 to 12% while Nipah virus encephalitis has incidence of 2.2% [60].

Causes of Infectious Encephalitis

Acute infections causing encephalitis group broadly into those occurring either sporadically or epidemically. The most common sporadic cause is herpes simplex virus, usually type 1, although 10% are type 2[57]. Others include varicella zoster virus and enteroviruses. Epidemic encephalitis most commonly occurs in geographically restricted seasonal epidemics and is caused by arthropod-borne viruses (arboviruses), although clinicians need to be vigilant to the potential for advances in the geographical distribution of these pathogens. Globally, the most important epidemic cause is Japanese encephalitis virus, while others include West Nile virus, tick-borne encephalitis virus and Nipah virus [61].

(1): Herpes Simplex Virus Encephalitis

Herpes simplex virus (HSV) encephalitis has an annual incidence of 1 in 250,000 to 500,000, although this may be an underestimate [62]. Herpes simplex virus type 1 is an α herpes double-stranded DNA virus with which most people are infected by adulthood [62]. It is transmitted by droplet spread and crosses the mucous membranes of the naso-oral cavity and then travels by retrograde axonal transport to sensory ganglia, predominantly the trigeminal ganglion.

(2): Japanese Encephalitis Virus

An estimated 70,000 cases of encephalitis due to Japanese encephalitis virus (JEV) occur per year, causing 20,500 deaths [63]. Although responsible for seasonal epidemics mostly centered around South East Asia, some cases also occur in the Western Pacific and Eastern Mediterranean [64]. Japanese encephalitis virus is a flavivirus that has a zoonotic transmission with infection between a wide range of vertebrates by Culex mosquitoes, and the predominant cycle is between wading birds, such as egrets, and pigs.

Japanese encephalitis virus causes acute symptomatic seizures in up to 85% of children and in 10% of adults [65 and 66]. Generalized tonic–clonic seizures are more frequent than focal motor seizures; however, the clinical signs may be subtle and seizures can be easily missed, especially if there is limited access to electroencephalography (EEG).

(3): Role of Human Herpes Virus 6

The relatively recently identified lymphotropic β herpes DNA virus human herpes virus 6

(HHV6) is now realized to be the most common cause of roseola infantum in children aged under 2 years [67]. More broadly, HHV6 may account for 20% of emergency department admissions for all febrile illnesses in children aged 6 to 12 months, of whom approximately13% may develop acute seizures [68].

Parasitic Infections

Seizures can complicate parasitic infections of the CNS and may develop both as an acute phase response as well as long-term consequence, although establishing the causality of some organisms can be difficult (Table 2.1) [69]. Seizures develop through several mechanisms, including local pressure effects from parasitic growth in the brain parenchyma (e.g., hydatid disease), from inflammation after larval migration, or as part of a diffuse encephalopathy (e.g., African trypanosomiasis). Two major infections associated with a high frequency of seizures and epilepsy are cerebral malaria and neurocysticercosis [70].

Table 2.1: List of parasitic infections associated with seizure disorders[71]

Type of lesion	**Agent**
Focal granulomatous/cystic lesions	Protozoa: Toxoplasma, free living amoeba, Chagas disease Nematodes: Toxocariasis, gnathostoma Trematodes: Schistosomiasis, paragonimiasis Cestodes: Cysticercosis, hydatid disease, coenurosis, sparganosis
Abscess	Entamoeba histolytica, toxoplasmosis
Encephalitis	Chagas disease, free-living amoebas, “cerebral malaria”
Meningitis	Angiostrongylus, cysticercosis
Mass effect	Cysticercosis, hydatid disease, coenurosis

(1) Cerebral Malaria

There are an estimated 1 million deaths attributed to malaria per year—with half of these resulting from cerebral malaria—of whom 90% are children [72]. The World Health Organization has defined cerebral malaria as unexplained coma in patients with a parasitemia without any other explanation [73]. In addition, cerebral malaria may be suspected clinically by a malaria-specific retinopathy, which is 95% sensitive and 90% specific for children who are comatose secondary to cerebral malaria [74]. The epidemiology and clinical phenotype of the condition varies by age and geographical location. Cerebral disease most commonly develops with falciparum malaria and affects mostly African children below the age of 5 years with a rapid onset of coma and focal motor seizures. Adults normally develop cerebral dysfunction in conjunction with dysfunction of other organs.

(2) Neurocysticercosis

Neurocysticercosis is the infection of the CNS by the larval stage of the tapeworm Taenia solium, and is the most common helminthic infection of CNS globally [75]. Taenia solium is endemic in most developing countries and as such is a major public health problem. Millions of people living in the developing world are infected by the larval form of T. solium, and many of these will experience some degree of clinical consequence of the infection [76]. It is rare in northern Europe, Canada, Australia, Japan, New Zealand, and in many countries with a predominant Muslim population. However, immigration from endemic countries has increased the incidence in these countries more recently. The increasingly widespread use of cysticidal drugs, improved sanitation, and public health educational measures have been associated with a decreasing prevalence of clinical infection. However, neurocysticercosis remains an important cause of hospital admission and a major cause for acquired epilepsy in many areas

[77, 78].

Pathology

Symptomatic epilepsy is associated with definable brain lesions [83]. These lesions include zones of neuronal loss and gliosis (scars) or other signs of tissue loss. The frequency of occurrence of these lesions is not fully known. Epileptogenesis refers to the transformation of a normal neuronal network into one that is chronically hyperexcitable [79]. There is a delay of months to years between an initial CNS injury such as trauma, stroke, or infection and the first seizure. The injury may lower the seizure threshold in the affected area until a spontaneous seizure takes place. In many genetic and idiopathic forms of epilepsy, epileptogenesis may be determined by developmentally regulated events [79]. The most common histological finding in the brains of epileptic patients is a bilateral loss of neurons in the CA1 segment (Sommer sector) of the pyramidal cell layer of the hippo-campus, extending into the contiguous regions of both the pyramidal layer and the underlying dentate gyrus. In a specific group of epileptic disorders, idiopathic epilepsy may be caused by a disruption of ion channels by neurotransmitter receptors [83]. A more complex genetic element is also identified in several childhood seizure disorders, for instance, (1) absence epilepsy with 3-per-second spike-and-wave discharges and (2) benign epilepsy of childhood with centrotemporal spikes. Both of these disorders are transmitted as autosomal dominant traits with incomplete penetrance, perhaps in a more complicated manner [83]. Gene mutations observed in symptomatic epilepsy appear to be associated with pathways affecting CNS development or neuronal homeostasis. In patients with symptomatic epilepsy, other neurological abnormalities, such as cognitive impairment, coexist with seizures. The challenge is to identify the multiple susceptibility genes that underlie the more common forms of idiopathic epilepsies.

Diagnosis

In the diagnosis of epilepsy, history is the key, because in most adults, the physical examination is relatively nondefinitive [83]. The examination of infants and children is of greater value, because the presence of dysmorphic and cutaneous abnormalities allows for the diagnosis of a number of highly characteristic cerebral diseases that give rise to epilepsy. When a patient is seen shortly after a seizure, the first priorities are attention to vital signs, respiratory and cardiovascular support, and treatment of seizures if they resume [79]. The physician's main means of diagnosis is to take a careful medical history, gathering as much information as possible about what the seizures looked like and what happened just before they began. The physician should also perform a thorough physical examination, especially of the nervous system, as well as an analysis of blood and other body fluids. Several laboratory studies are usually included in the initial diagnostic evaluation, such as a complete blood count, blood chemistry profiles, liver and thyroid function tests, an EEG, and a brain study, preferably with magnetic resonance imaging (MRI). Computed tomography (CT) scanning may be the only practical study in an emergency or for very young children [83]. Some patients may later require video/EEG or prolonged EEG monitoring, either in the hospital or with portable equipment in the home. Cardiac stress tests, Halter monitoring, tilt-table testing, long-term patient activated cardiac monitors, and sleep studies may also be performed. Any patient who has a possible seizure disorder should undergo EEG evaluation as soon as possible. Almost all patients with new-onset seizures should have a brain imaging study to detect any underlying structural abnormalities MRI is superior to CT for detecting cerebral lesions associated with epilepsy [79]. States of constitutional mental retardation and confusion associated with epilepsy present special problems in diagnosis [83]. Seizures are more common in those with mental retardation, but recurrent seizures themselves rarely cause intellectual deterioration [84]. When this situation does occur, an underlying degeneration or hereditary metabolic disease should be suspected. Migraine should not be mistaken for a seizure. A second battery of diagnostic tools includes another EEG to record brain waves. Electrical signals from brain cells are recorded during or between seizures and may show special patterns to determine whether the person has epilepsy. CT or MRI scans may be used to search for any growths, scars, or other physical conditions in the brain that might be causing seizures. In a few research centers, positron emission tomography (PET) is used to identify areas of the brain that are producing seizures.

Medical Treatment

Antiepileptic drug (AED) therapy, the mainstay of treatment for most patients, has four goals: to eliminate seizures or reduce their frequency to the maximum degree possible, to evade the adverse effects associated with long-term treatment, and to aid patients in maintaining or restoring their usual psychosocial and vocational activities, and in maintaining a normal lifestyle. The decision to start AED therapy should be based on an informed analysis of the likelihood of seizure recurrence, the consequences of continuing seizures for patients, and the beneficial and adverse effects of the pharmacological agent chosen [84]. Whether to initiate therapy in a patient with a single seizure is controversial [79]. A single seizure caused by an identified lesion such as a CNS tumor, an infection, or trauma, in which there is strong evidence that the lesion is epileptogenic, should be treated. The overall goal of AED therapy is to prevent seizures completely [79]. The relative risk of recurrence of epilepsy can vary, depending on the seizure type or syndrome [85]. Patients with epileptiform discharges on an EEG or with congenital neurological defects are at high risk of recurrence (approaching 90%) [84]. The patient's and family's views should also be considered when AED treatment is begun [86]. To prevent further seizures, it may be best to introduce AEDs early. Future seizure activity may be distressing for those who must drive, continue to work, or care for other family members. The probability of seizure recurrence varies among patients, depending on the type of epilepsy and any associated neurological and medical problems. Pharmacotherapy, however, carries a risk of adverse effects, at a rate approaching 30% after initial treatment [87]. Treating children presents additional problems, especially on brain development, learning, and behavior, when a drug is used chronically.

Selection of Antiepileptic Therapy

The ideal AED should suppress all seizures without causing any unwanted adverse effects [81]. Unfortunately, currently available AEDs not only fail to control seizure activity in some patients but also frequently produce adverse effects that range in severity from minimal impairment of the CNS to death from aplastic anemia or hepatic failure. The treating physician or practitioner must choose the appropriate AED or combination of drugs that best controls seizures with a satisfactory degree of untoward effects. It is generally accepted that complete control of seizures can be achieved in up to 50% of patients and that another 25% of patients improve significantly. Successful therapy is greater in patients with newly diagnosed epilepsy, and the success rate depends on type of seizure, family history, and extent of associated neurological abnormalities [88]. Initiating AED treatment can be based on the likelihood of seizure recurrence, the consequences of continuing seizures, and the beneficial and adverse effects of the agent in preventing recurrence[89].The relative risk of recurrence can vary, depending on the seizure type or syndrome[85].Patients with epileptiform discharges on an EEG or congenital neurological defects are at high risk (up to 90%) of recurrence[89].The risk of recurrence is also elevated in patients with previous symptomatic seizures, in those with cerebral lesions, and in patients with Todd's paralysis (a brief, temporary paralysis following a seizure) [90]. Approved AEDs used in epilepsy treatment in the U.S. are presented in Table 2.2 [79]. Because of the large number of drugs currently approved for the treatment of epilepsy, only the most relevant aspects of each drug's profile are presented here. For additional details on adverse events, contraindications, and warnings, readers may consult the references for each drug's prescribing information.

Table 2.2; Antiepileptic Drugs Approved for the treatment of Seizures

Primary Generalized Tonic–Clonic Seizures	Partial Seizures*	Absence Seizures	Atypical Absence Myoclonic, and Atonic Seizures
First-line agents			
Valproic acid Lamotrigine Topiramate	Carbamazepine Phenytoin Oxcarbazepine Valproic Acid	Valproic acid Ethosuximide	Valproic acid Lamotrigine Topiramate
Alternative agents			
Zonisamide† Phenytoin Carbamazepine Oxcarbazepine Phenobarbital Primidone Felbamate	Levetiracetam† Topiramate Tiagabine† Zonisamide† Gabapentin Phenobarbital Primidone Felbamate Eslicarbazepine Vigabatrin Lacosamide Pregabalin Rufinamide	Lamotrigine Clonazepam	Clonazepam Felbamate

*Includes simple partial, complex partial, and secondarily generalized seizures.
†As adjunctive therapy. Modified from Fauci AS, Kasper DL, Longo DL, eds. Harrison's Principles of Internal Medicine, 17th ed. New York: McGraw-Hill; 2008;2498–2512[79].

Materials and Methods

Study approval

Current study has been approved by IRB UCL UK.

Identification of families

Affected families were identified from different areas through Doctors, personal contacts and clinics.

Consent form

Informed consent was signed by parients/guardian of patients.Each participant received detailed explanation of the study's goals, objectives, potential advantages, and risks. Participants were asked to voluntarily give 3- 5ml of blood. Each participant gave informed consent to participants in the study before having their blood samples obtained. They had received assurances that the study results of their samples and their identities would remain private. Needle and syringes are used to collect blood samples. The type of needle and syringe used will depend on the size of the vein being sampled and the amount of blood needed. Blood collection tubes are used to store blood sample. The type of blood collection tube used will depend on the test that will be performed on the blood sample. Alcohol wipes are used to clean the skin before blood sampling. This help to prevent infection. Bandages are used to cover the puncture site after blood sampling. This help to stop the bleeding and prevent infection. Gloves are worn to protect the person collecting the blood sample from infection.

Inclusion

Individuals having any kind epilepsy are included in the study.

Exclusion

Individuals having other genetic disorders and epilepsy due to brain injury or trauma were excluded from the study.

Sampling area

Patients having epilepsy are registered from Hazara division (Alai ,Thakot) of KPK and invited to participate in the current study.

Battagram District

Battagram is a district in Hazara Division of Khyber Pakhtunkhwa province in Pakistan. The headquarter is Battagram, which is about 75 km from Mansehra. The district of Battagram is located at a latitude of 34.41 and longitude 73.1. It is surrounded by Kohistan District to the north, Mansehra District to the east, Kala Dhaka (now Torghar District) to the south, and Shangla District to the west. It has a land area of 1,301 square kilometres (502 square meter). Battagram obtained the status of district in July 1993, when it was upgraded from a Tehsil and separated from Mansehra District.

THAKOT

Thakot or Takot is a tribal town on the Indus River in Battagram District of Khyber Pakhtunkhwa, Pakistan. It is also one of twenty Union Councils of Battagram District, and one of twelve in Battagram Tehsil. Thakot is located midway between Battagram town in the south and Besham town (Shangla District) in the north, at a distance of about 30 km from both. Thakot is a small village/town along the Karakorum Highway in Khyber Pakhtunkhwa Province of Pakistan. From Thakot begins the road along the River Indus this it is the starting point of Karakorum Highway along the Indus valley. After Thakot the mountains start to rise above 6000 meters. Thakot is also the point where Chinese built first suspension bridge on Indus [92].

Allai District

Allai District is a district in the Hazara Division of Khyber Pakhtunkhwa, Pakistan. The Allai district covers an area of 521 sq km and has a population of 180,414 according to the 2017 census. It consists of eight union councils including Banna, Batila, Batkul, Biari, Jumbera, Pashto, Rushing and Shakargah. Allai was previously a tehsil within the Battagram District of the Hazara division [92].

Sampling:

With the assistance of skilled phlebotomist, 3-5ml of blood sample was extracted in EDTA tube from 9 families and sent to Neurogenetic Lab London (UCL) for genetic analysis by Dr. Henry Houlder and Dr. Vincenzo Salpatiero.

Questionnaire

A detailed questionnaire was designed to get demographic details of the patient.

Personal Information:

a. Full name
b. Date of birth
C. Gender
d. Contact information (phone number, address, email)

Accessibility:

a. How do you prefer to receive information in public settings (e.g., events, announcements)?
b. Are there any specific situations where you have experienced challenges accessing information?

Medical History:

a. Do you have any existing medical conditions?
b. Are you currently taking any medications?
c. Have you had any surgeries in the past?

Support system:

a. Do you have a support system in place (e.g., friends, family,support groups)?
b. Are there any areas where you feel you need more support?

Emotional Well-being:

a. How do you generally feel on a day-to-day basis?
b. Do you face any emotional challenges or concerns?

Communication Experience:

a. How comfortable do you feel communicating with non-epileptic individuals?
b. Have you faced any communication barriers in your daily life due to your epilepsy?

Area Requiring improvement:

1) Accessibility:

Accessibility remains a significant challenge for epileptic individuals in Pakistan. Public spaces, transportation, and infrastructure should be designed to accommodate the needs of people with epileptic disabilities.

2) Inclusive Policies:

There is a need for comprehensive policies and legislation that promote the rights and well-being of epilepsy patients, including provisions for their education, employment, and accessibility rights.

Clinical characters:

Clinal characters are recorded.

Detailed information on data collected from patients is here

University College London Hospitals NHS
NHS Foundation Trust

The National Hospital for Neurology and Neurosurgery
Queen Square, London WC1N 3BG

MRC Centre for Neuromuscular Diseases

CENTRE FOR NEUROMUSCULAR DISEASE
The National Hospital for Neurology and Neurosurgery
Queen Square, London WC1N 3BG
Tel: 0845 155 5000

Chief Investigator: Professor Michael G Hanna
Name of Principal Investigator: Professor Michael G Hanna
REC reference number: 07/Q0512/26
UCLH Project ID Number: 07/N018
Form version: 9.2
Date: 27/04/2016

Participant Identification Number for this study:

CONSENT FORM

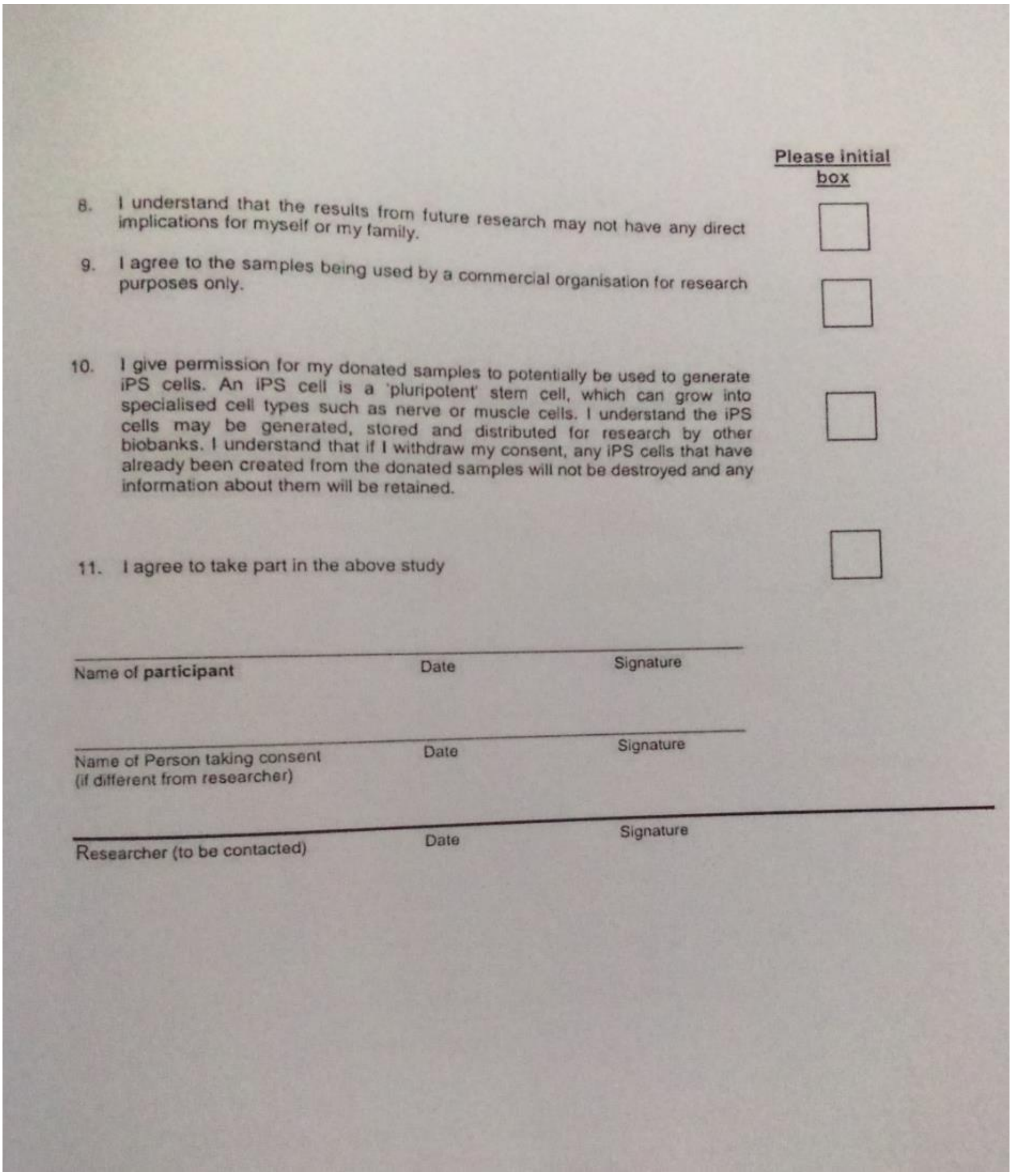
Title of project: Investigation of human neurological ion channel and episodic neurological disorders

Please initial box

1. I confirm that I have read and understood the information sheet dated 30/03/2016 (version 9.1) for the above study and have had the opportunity to ask questions. ☐
2. I confirm that I have had sufficient time to consider whether or not want to be included in the study. ☐
3. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
4. I understand that sections of any of my medical notes may be looked at by responsible individuals from (company name) or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐
5. I understand that all provided clinical information and tissue samples (e.g. Blood samples, muscle and skin biopsies) will be considered a 'gift' to the National Hospital for Neurology and the Institute of Neurology and may be used in subsequent research projects. ☐
6. I agree that my pictures and videos could be kept by the research team and may be used in subsequent research projects. ☐
7. I agree to the samples being used within the UK and internationally for future ethically approved research projects into the causes of genetic conditions and treatments for such conditions. ☐

UCL HOSPITALS

The National Hospital for Neurology and Neurosurgery is part of UCL Hospitals NHS Trust which also includes The Eastman Dental Hospital, The Elizabeth Garrett Anderson and Obstetric Hospital, The Heart Hospital, The Hospital for Tropical Diseases, The Middlesex Hospital, The Royal London Homeopathic Hospital and University College Hospital.



Please initial box

8. I understand that the results from future research may not have any direct implications for myself or my family. ☐

9. I agree to the samples being used by a commercial organisation for research purposes only. ☐

10. I give permission for my donated samples to potentially be used to generate iPS cells. An iPS cell is a 'pluripotent' stem cell, which can grow into specialised cell types such as nerve or muscle cells. I understand the iPS cells may be generated, stored and distributed for research by other biobanks. I understand that if I withdraw my consent, any iPS cells that have already been created from the donated samples will not be destroyed and any information about them will be retained. ☐

11. I agree to take part in the above study ☐

Name of **participant**	Date	Signature
Name of Person taking consent (if different from researcher)	Date	Signature
Researcher (to be contacted)	Date	Signature

Results

In our studied population total of 11 patients from 9 families were registered from the Hazara division.

Consanguinity

In our study group, the consanguinity rate was 33.3%.

Family history

Family history is 0%. None of the individuals had a family history of Epilepsy before.

Mental health and facilities available for Epileptic individuals in the Hazara Region

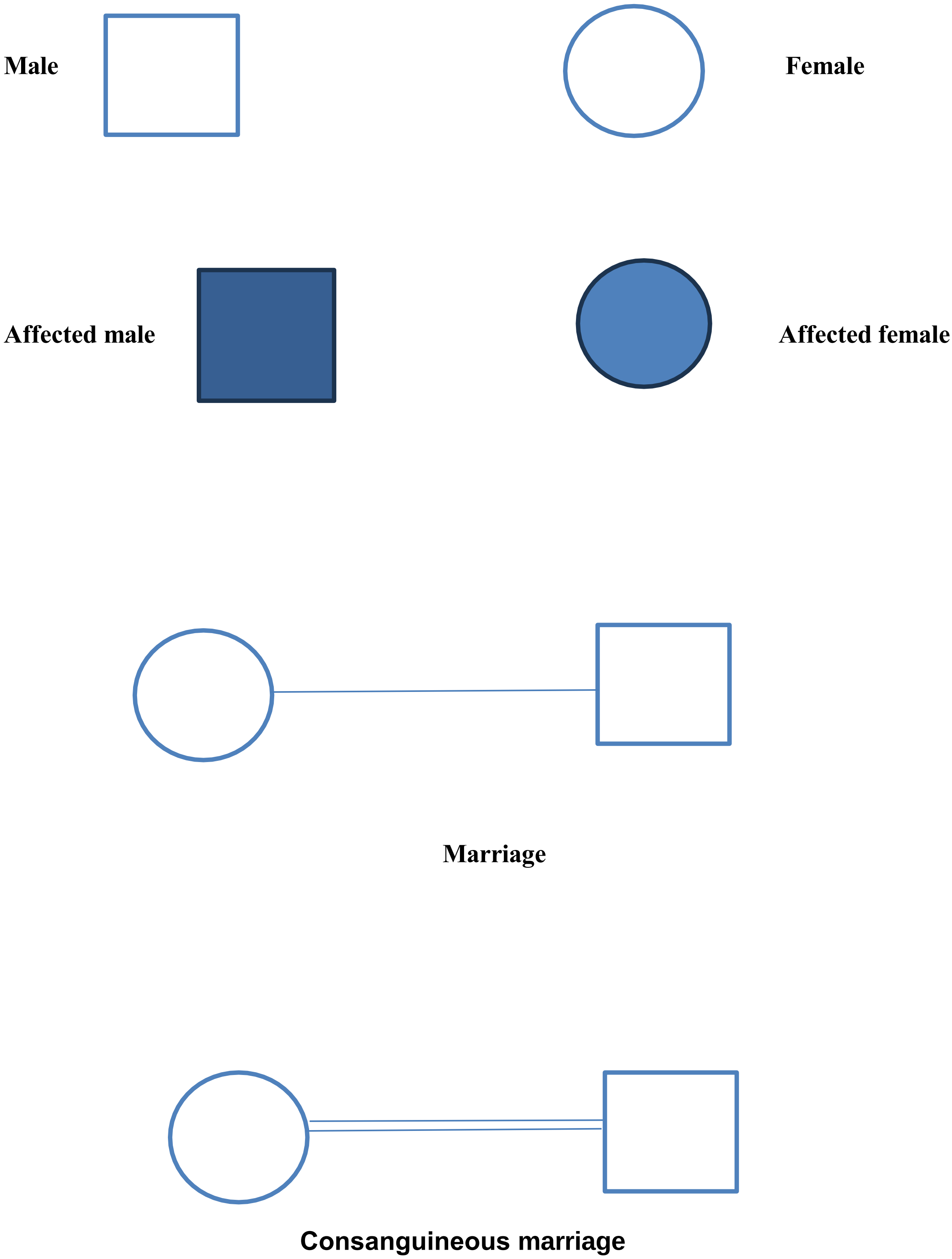
Mental health and basic facilities were assessed in the studied population. When mental health and basic facilities were assessed in affected individuals, it was found that most of the individuals were depressed. They were not aware of the basic facilities provided by the government of Pakistan related to health for children with disabilities.

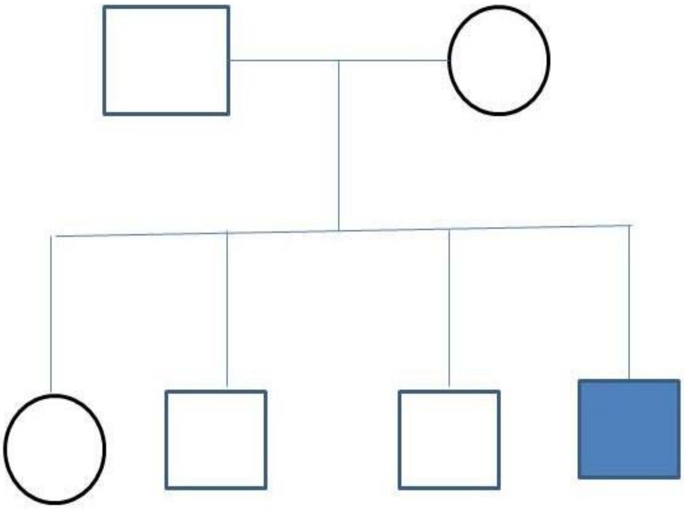
Table 4.1: Clinical information of patients

Sample ID	Name	Family ID	Gender	YEARS	Clinical Information and family relationship	Consanguinty	Family History
A1987293	Gull Zareen	TH 2	Male	9 years	Epilepsy (P1)	NO	NO
A1987221	Tayab ul Haq	TH 2	Male	15 Years	Epilepsy (P2) +Autism	NO	NO
A1093706	Musanif	TH 3	Male	12 Years	Epilepsy (P1)	NO	NO
A1093793	Sami ullah	TH3	Male	9 Years	Epilepsy (P2)	NO	NO
A1092701	Umir Rahmn	AL 5	Male	16 Years	Epilepsy only seizure (P1) (dismorphic)	YES	NO
A1092071	Adal Rahman	AL 6	Male	30 Years	Epilepsy (P1) (dismorphic)	YES	NO
A1093755	Bahadar sher	AL 8	Male	50 Years	Epilepsy (P1)	YES	NO
A1093756	M. Yasir	AL 9	Male	18 Years	Epilepsy (P1)	YES	NO
A1093748	Nazmul haq	AL 12	Male	25 Years	Epilepsy (P1)	NO	NO
A1093667	Taj Muhammad	AL 14	Male	34 Years	Epilepsy (P1)	NO	NO
A1092929	Shah faisal	AL1	Male	36 years	Autism, Bipolar (P1)	NO	NO

Pedigree Analysis

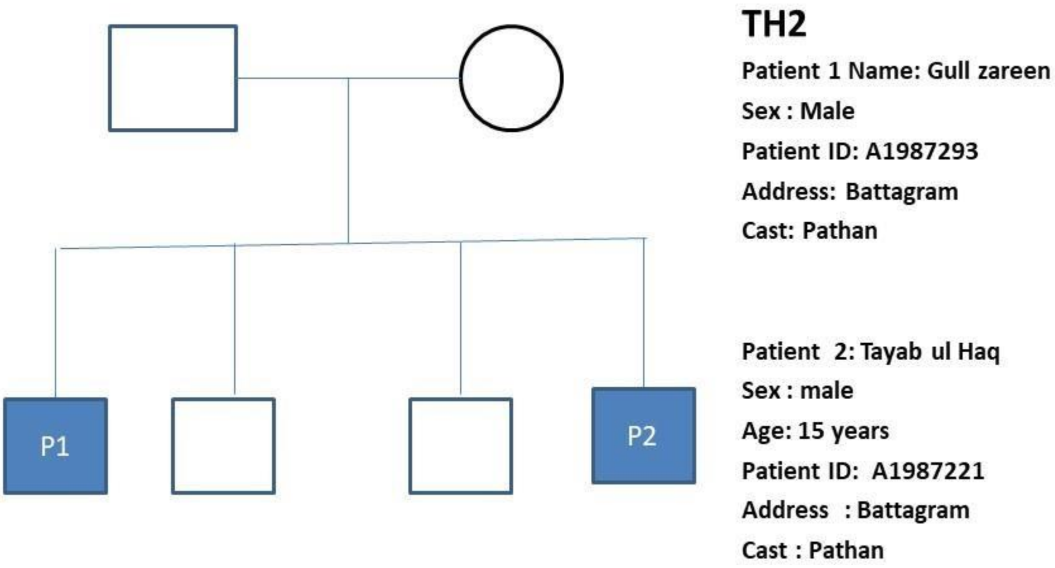
Symbols

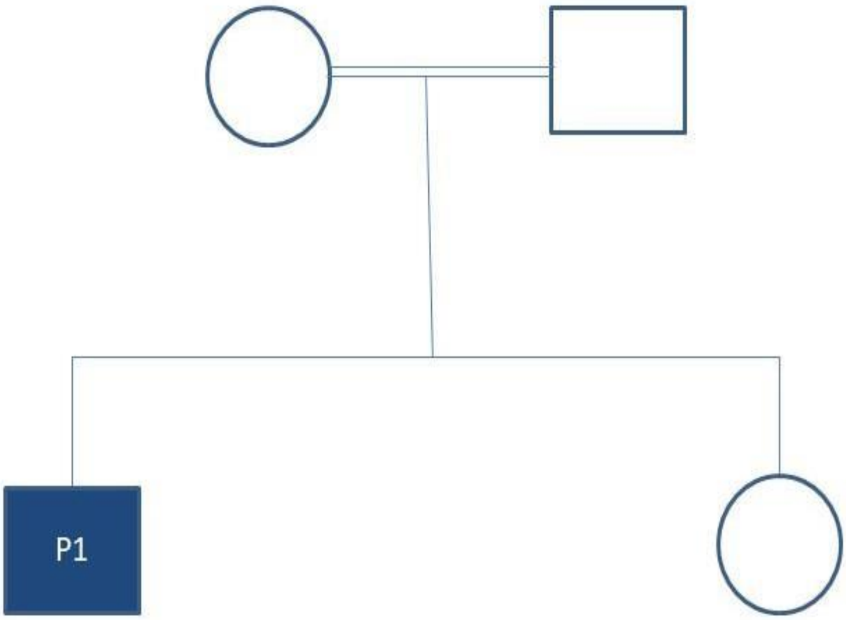

Male
Female
Affected male
Affected female
Marriage
Consanguineous marriage



- **AL1**

Ptient name: Shah Faisal
Sex : Male
Patient ID : A1092929
Address : kanai Batkool


TH2
Patient 1 Name: Gull zareen
Sex : Male
Patient ID: A1987293
Address: Battagram
Cast: Pathan
Patient 2: Tayab ul Haq
Sex : male
Age: 15 years
Patient ID: A1987221
Address : Battagram
Cast : Pathan
P1
P2



- **AL 5**

Patient Name: Umair rehman

Sex: Male

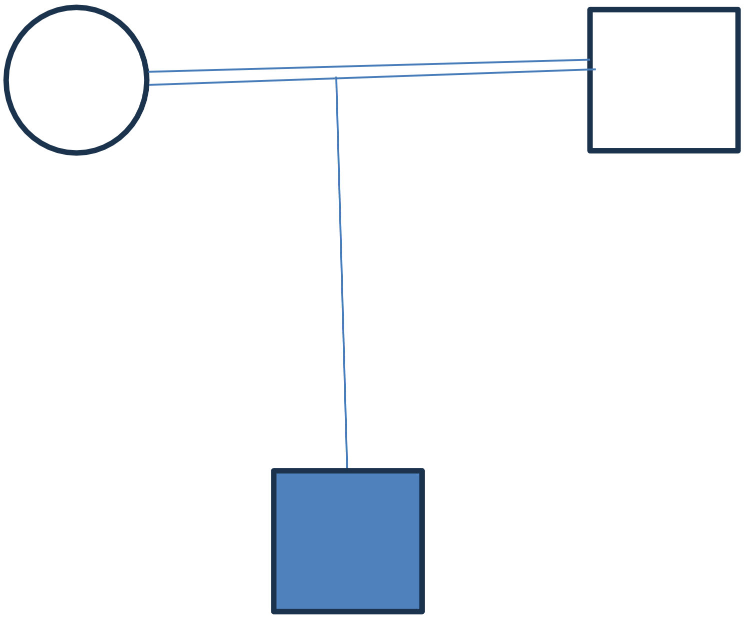
Age : 16 years

Patient ID: A1092701

Address: Kanai Batkool

AL6

Patient Name: Adal Rehman Sex: Male /Age 30 years Patient ID: A1092071 Adress: Kanal Batkool



- **AL 8**

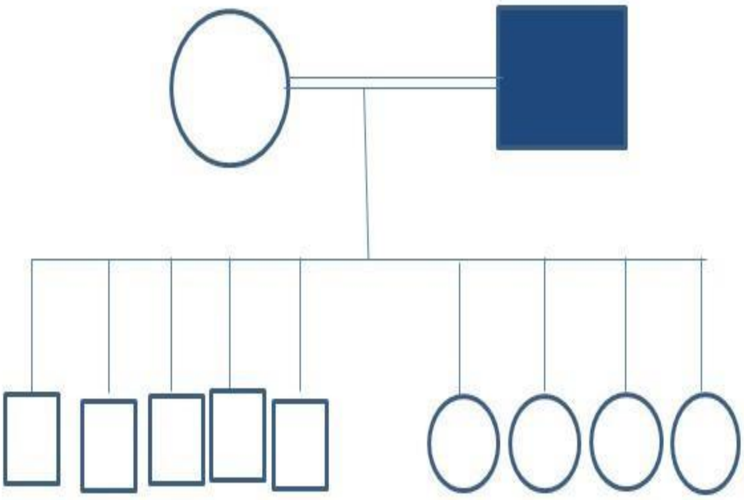
Patient Name:Bahader sher

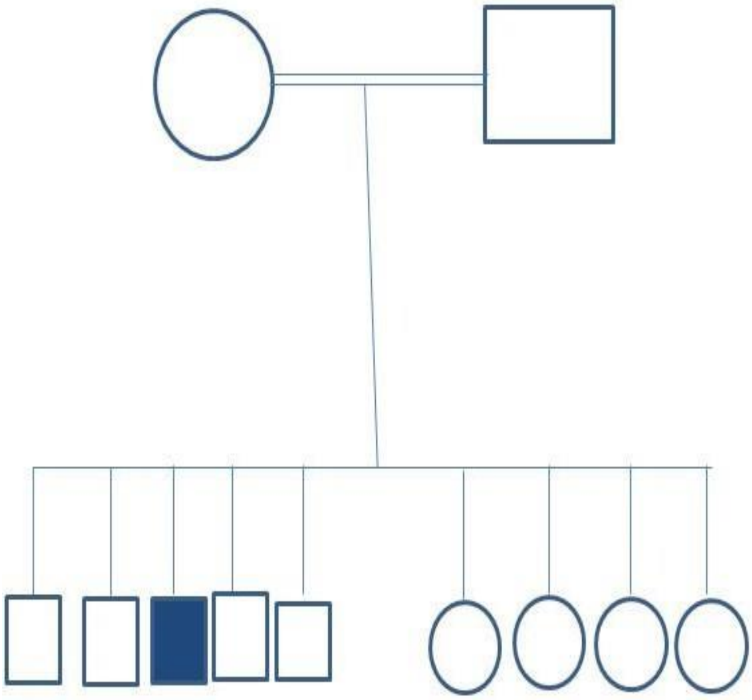
Sex : Male

Age: 50 Years

Patient ID: A1093755

Addrsss: Kanai Batkool



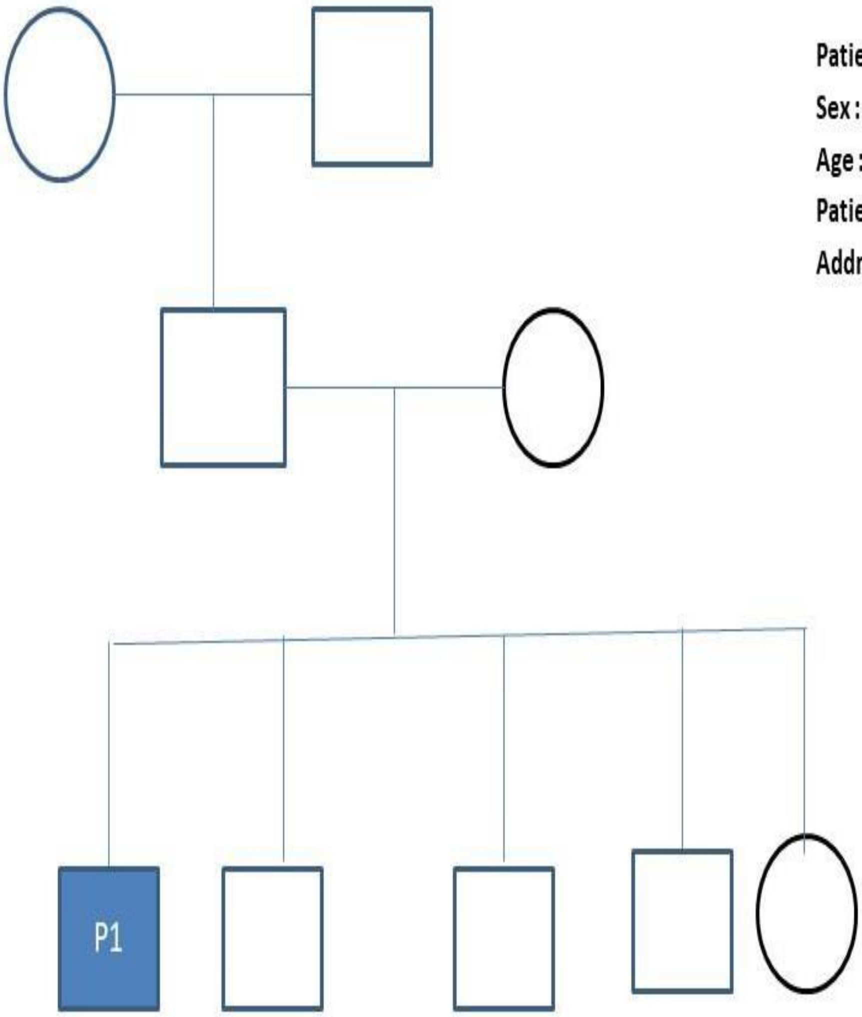


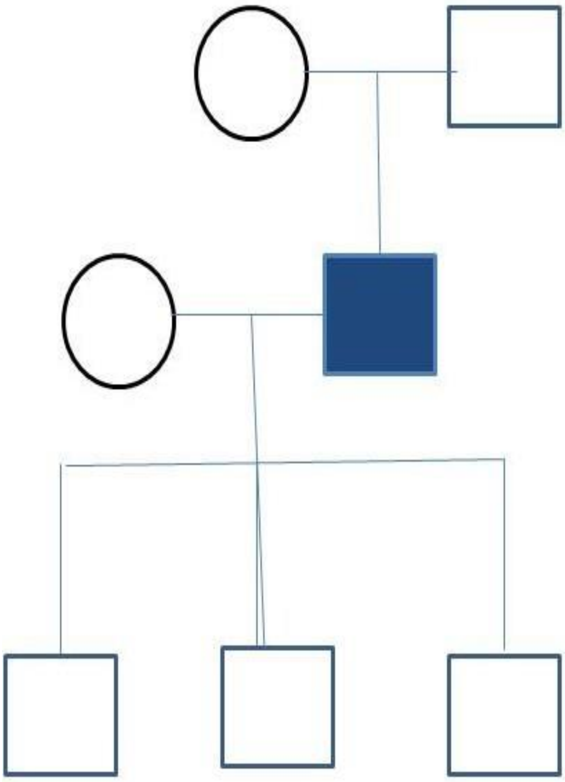
- AL 9

Patient Name: M Yasir
Sex : Male
Age: 18 Years
Patient ID : A1093756
Address: Kanai Batkool

- **AL 12**

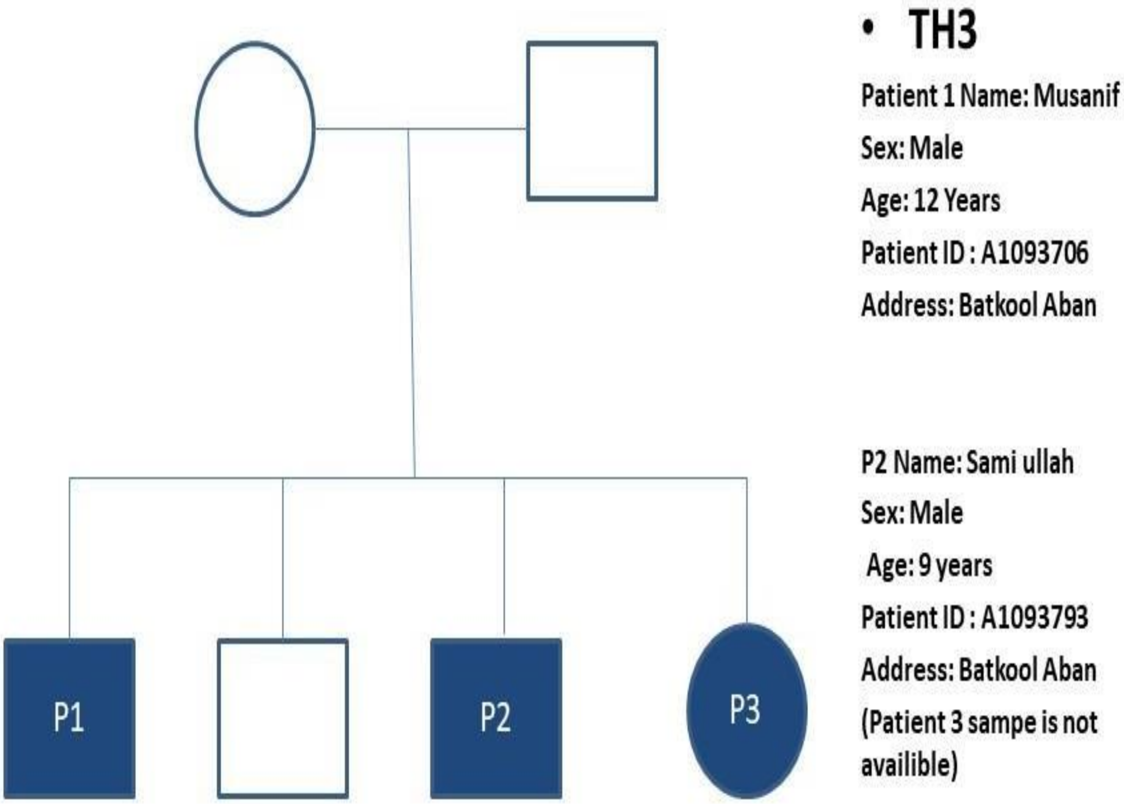
Patient name: Nazam ul Haq
Sex : Male
Age : 25 Years
Patient ID: A1093748
Address: Thakot Batkool Kanai





- **AL 14**

Patient Name: Taj Muhammad
Sex : Male
Age : 34 Year
Patient ID : A1093667
Address: Kanai Batkool


P1
P2
P3
• TH3
Patient 1 Name: Musanif
Sex: Male
Age: 12 Years
Patient ID : A1093706
Address: Batkool Aban
P2 Name: Sami ullah
Sex: Male
Age: 9 years
Patient ID : A1093793
Address: Batkool Aban
(Patient 3 sampe is not availible)

Epilepsy awareness questionnaire

To investigate the public openion about epilepsy, a google survey was performed and about 110 students were participated in it and the statistical data of the survey are given bellow:

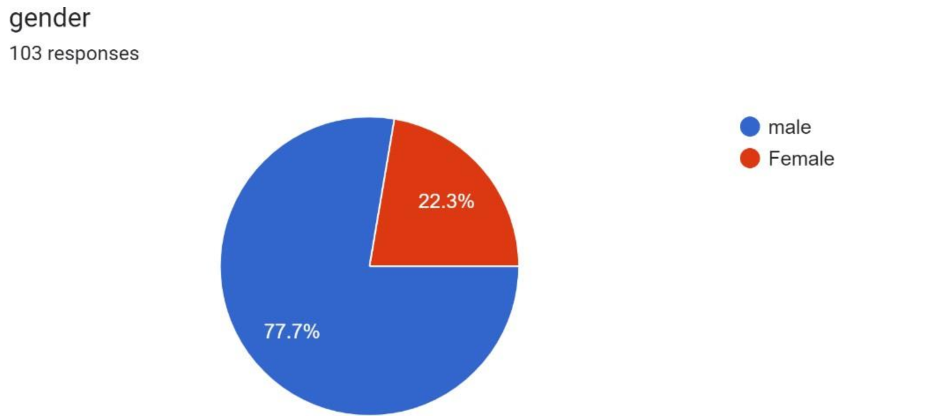


Fig4.2: Gender participation in survey.

Among 103 respondents 22.3% were females and 77.7% were males (Fig. 4.18).

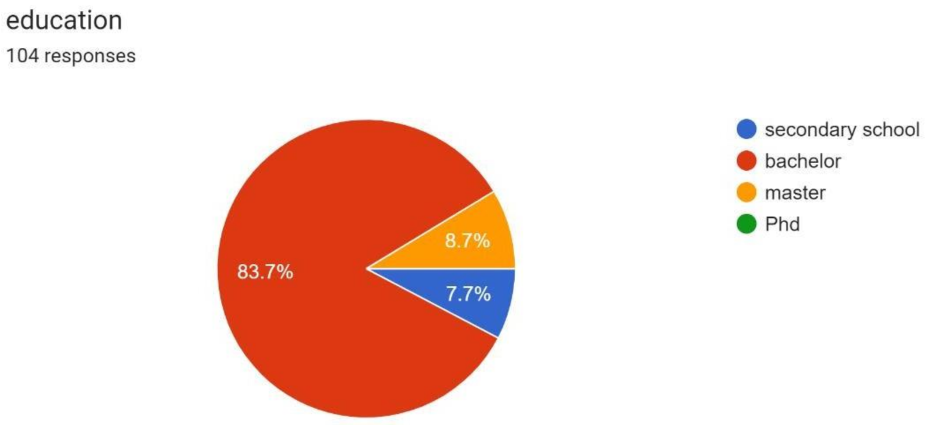


Fig 4.3: Education of participations

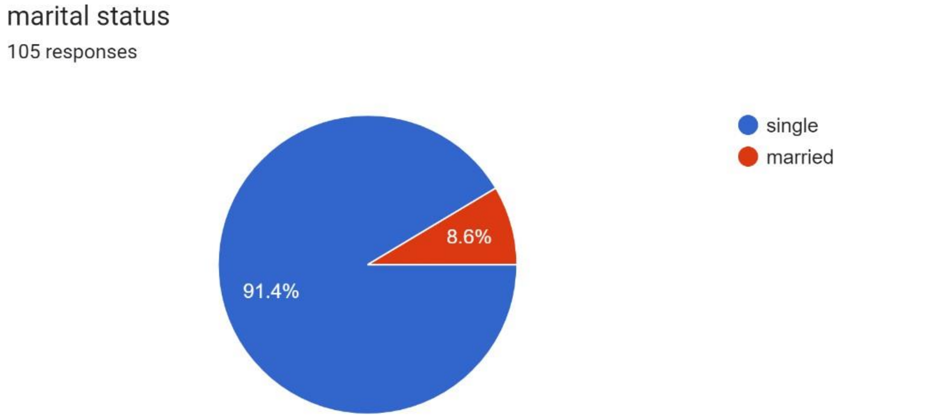


Fig 4.4: Marital status of participants

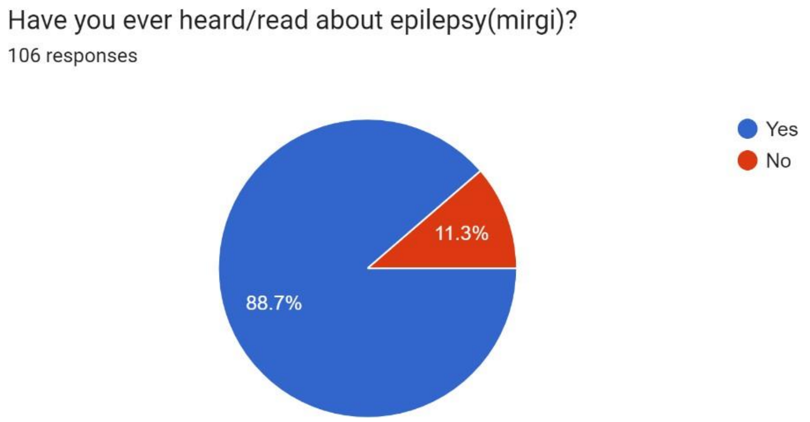


Fig 4.5: Idea about epilepsy

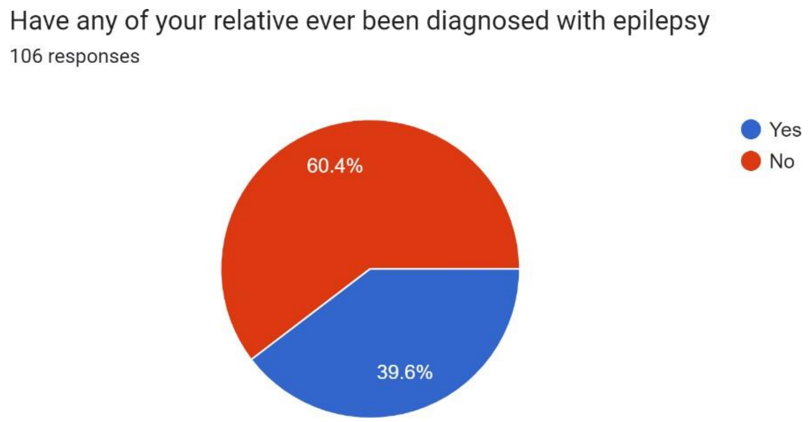


Fig 4.6: Prevalence of epilepsy in relatives

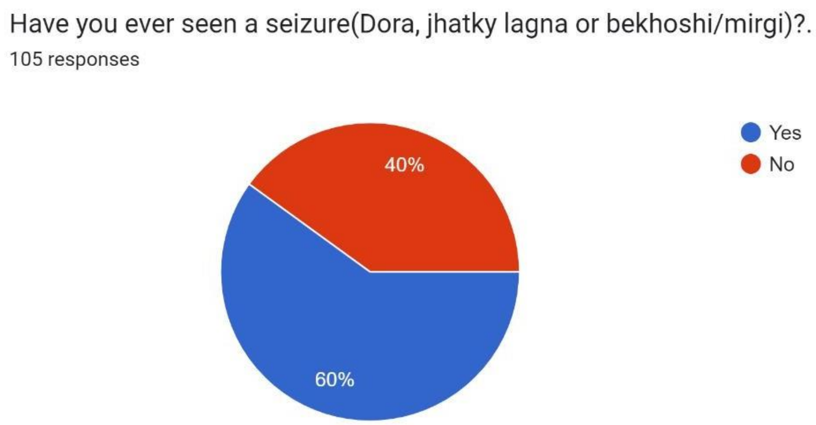


Fig 4.7: Seizure experiences

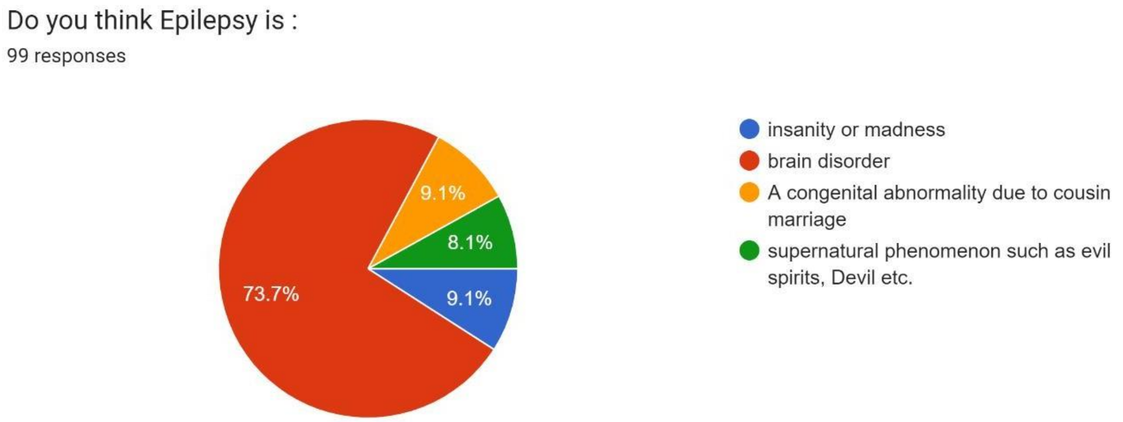


Fig 4.8: Information about epilepsy.

Among 99 responders, 73.7% thought that epilepsy is brain disorder (Fig. 4.8).

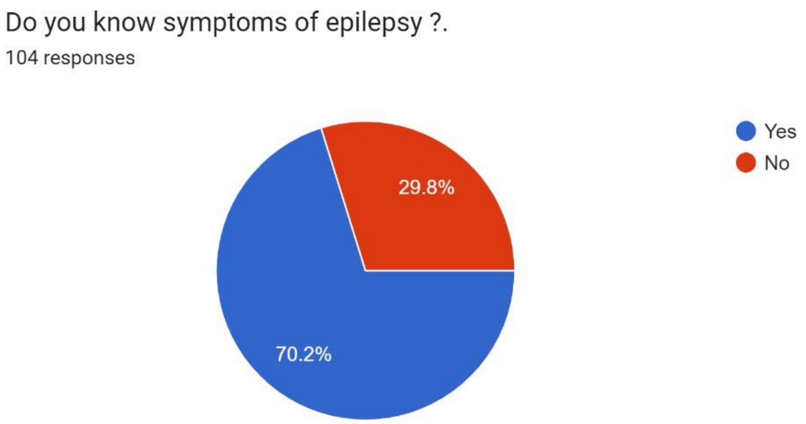


Fig 4.9: Symptoms awareness

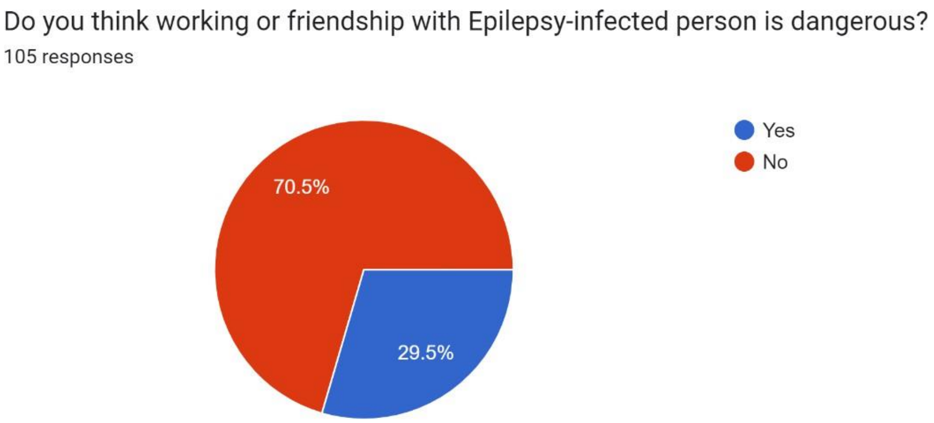


Fig 4.10: People interaction with epileptic patients

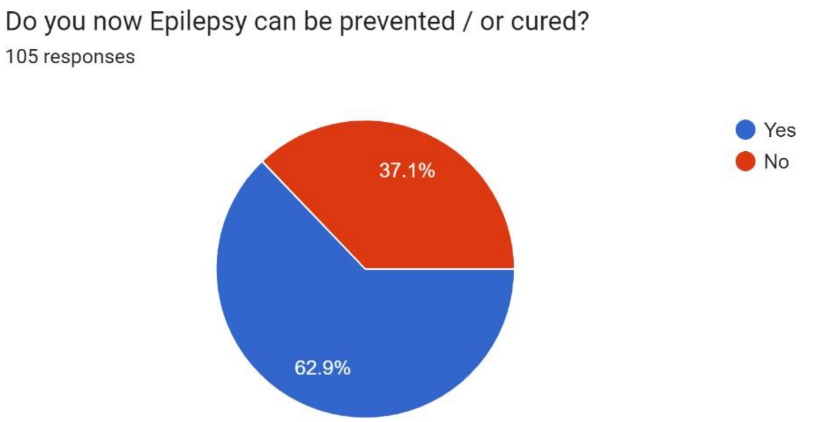


Fig 4.11: Awareness about prevention and cure.

Among 105 respondents 62.9% knew about epilepsy already, while 37.1% did not (Fig. 4.11).

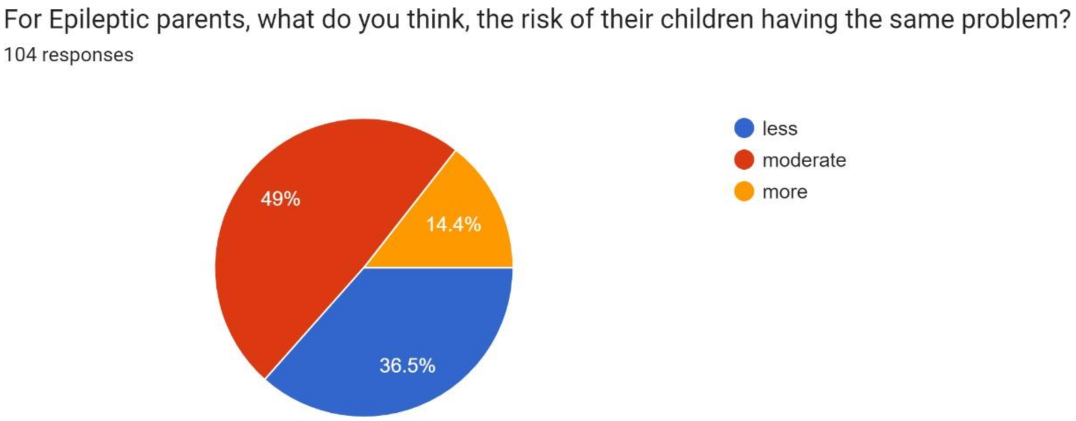


Fig 4.12: Risk of epilepsy in offspring

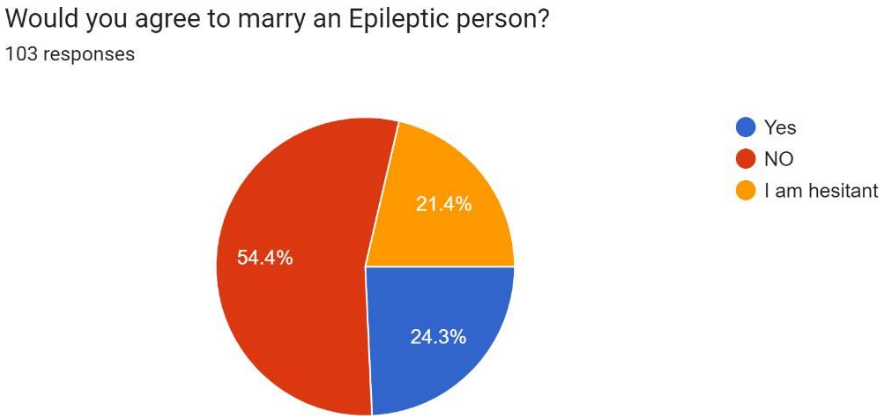


Fig 4.13: Tend to marry an epileptic person.

Among 103 respondents 54.4% were not agreed to marry a person having epilepsy, while

24.3% were agreed (Fig. 4.13)

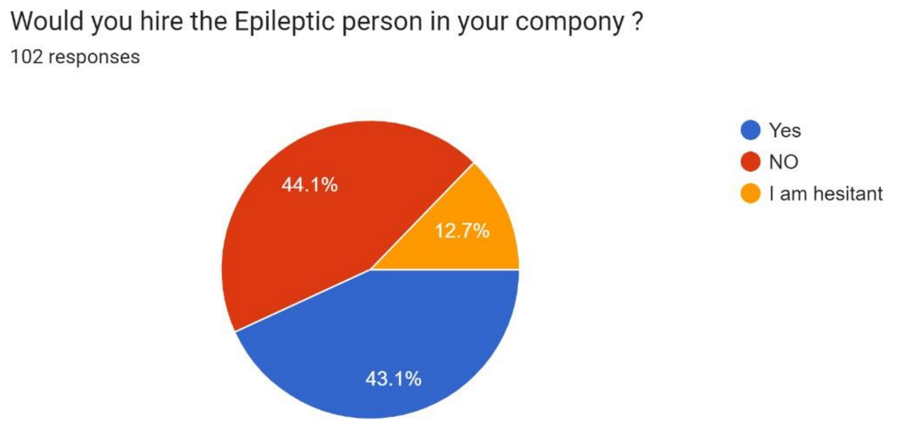


Fig 4.14: Hiring of epileptic patients.

44.1% respondents were not ready to hire patients of epilepsy in their company (Fig. 4.14).

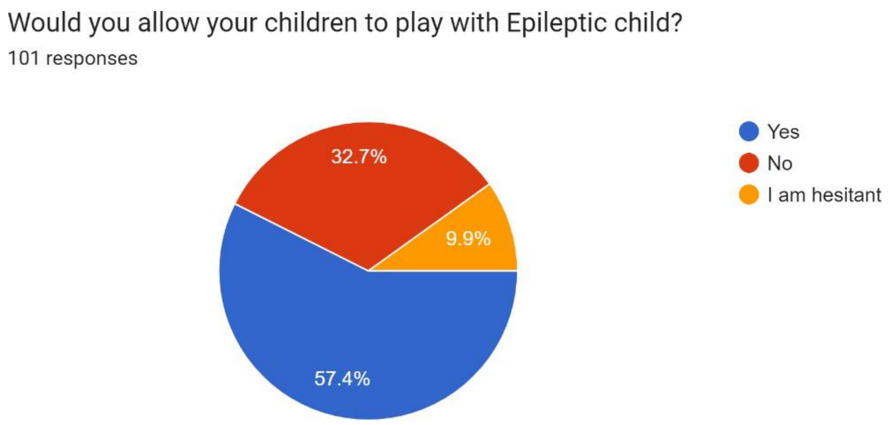


Fig 4.15: Community behavior towards epileptic children.

Among 101 respondents, 32.7% were not agreed to let their kids to play with patients of epilepsy while 57.4% were ready (Fig. 4.15).

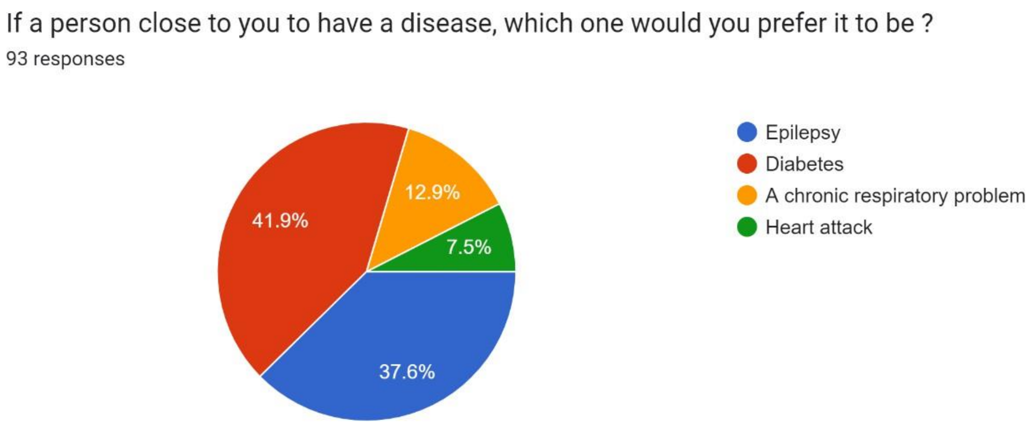


Fig 4.16: Preference towards epilepsy

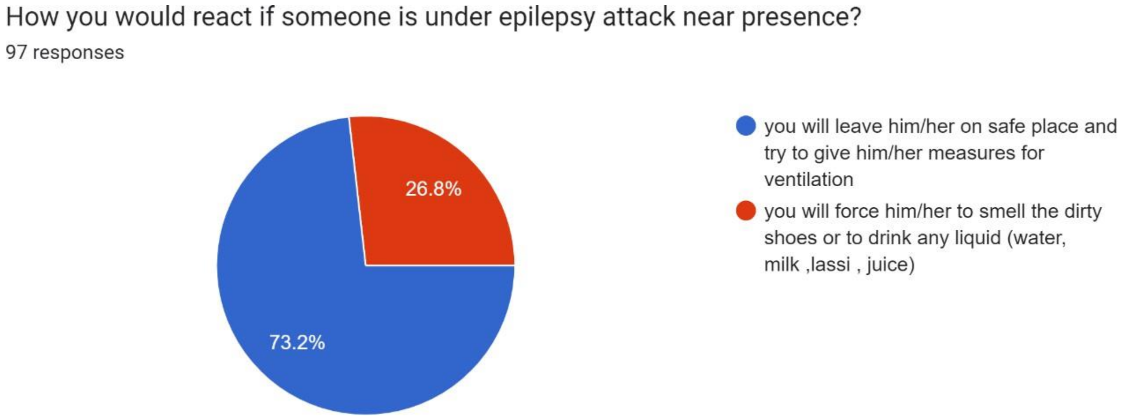


Fig 4.17: Management of epilepsy attack

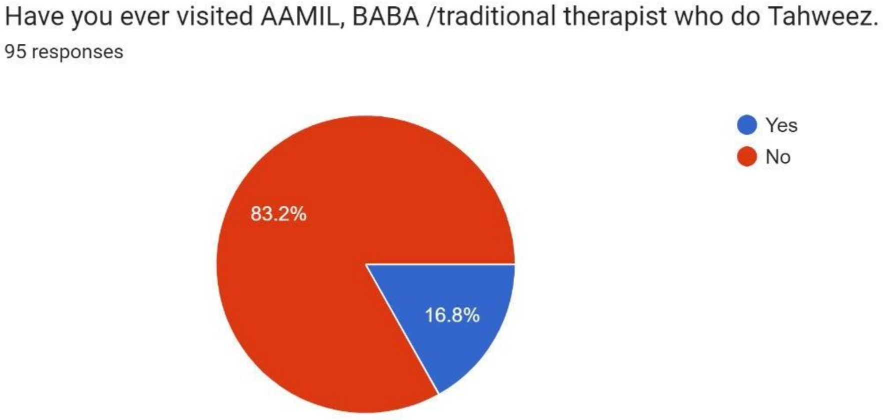


Fig 4.18: Believes of people on traditional therapist.

Among 95 respondents, 83.2% have visited to traditional therapist to treat epilepsy (Fig. 4.18).

Discussion

Epilepsy is one of the common human neurogenetic disorders, in which abnormal electrical activity in the brain occurs which leads to recurrent seizures. In our studied population in Hazara division patients of 1-20 years age and all males are diagnosed with idiopathic epilepsy were include from paediatric out patients, admitted cases and private clinics. The prevalence of epilepsy varies region to region. Low and middle-income countries tend to have high prevalence comparatively to High-income countries, due to limited health facilities. The world wide prevalence of epilepsy is 7.60% per 1000 people and the prevalence in Pakistan is 9.99 per 1000 people.

About 70% patients have idiopathic epilepsy, the normal brain is capable of experiencing a seizure under certain conditions, and individuals vary in their susceptibility or threshold for seizure.

Seizures may be induced by a high fever in children who are otherwise healthy, who have a structural defect, or who have genetic risk factors. A severe, penetrating head trauma or injury is associated with almost a 50% risk of subsequent epilepsy. In older patients, Alzheimer's disease and stroke may precipitate epilepsy. Viral and parasitic infection can also induce the risk of

epilepsy.
We collected samples from the Hazara division, the clinical characteristics and medical history of each patient were recorded and the samples was sent to University College London for genetic analysis.
When age-wise distribution was analysed it was found that 16.67% in between 1-10 years, 33.33% in between 11-20 years, 16.67% in between 21-30 years, 16.66% in between 31-40 years and 8.33% in between 41-60 years.
When mental health and basic facilities were assessed in affected individuals, it was found that most of the individuals were sad and depressed. They were not aware of basic facilities provided by the Government of Pakistan related to health for children disabilities.

Organizations for Epileptic People International organizations

The International Bureau for Epilepsy (IBE)
The International Bureau for Epilepsy (IBE) was established in 1961 as an organization of laypersons and professionals interested in the medical and non-medical aspects of epilepsy. The IBE addresses such social problems as education, employment, insurance, driving license restrictions and public awareness.

The International League Against Epilepsy (ILAE)

The International League Against Epilepsy (ILAE) was founded in 1909 and is an organization of more than 120 national chapters.
ILAE's **mission** is to ensure that health professionals, patients and their care providers, governments, and the public world-wide have the educational and research resources that are essential in understanding, diagnosing, and treating persons with epilepsy.

Organizations in Pakistan

The organization of epilepsy care in Pakistan involves a combination of governmental initiatives, non-governmental organizations (NGOs), healthcare institutions, and community- based efforts aimed at raising awareness, improving access to care, and providing support to individuals living with epilepsy. Here are some key aspects of the organization of epilepsy care in Pakistan:

1. Government initiatives:
   The government of Pakistan, through the Ministry of Health and regional health departments, plays a role in setting policies, guidelines, and regulations related to epilepsy care.
   Government-run healthcare facilities provide epilepsy diagnosis, treatment, and follow-up care, particularly in urban and rural areas.
2. Non-government organizations (NGOs):
   Several NGOs in Pakistan are dedicated to raising awareness about epilepsy, providing support services, and advocating for the rights of individuals with epilepsy. These organizations often collaborate with healthcare providers, educational institutions, and community leaders to promote epilepsy awareness and improve access to care.
3. Healthcare institutions:
   Hospitals, clinics, and healthcare centers across Pakistan provide epilepsy diagnosis, treatment, and management services. Neurologists, epileptologists, and other healthcare professionals specializing in epilepsy play a crucial role in assessing patients, prescribing medications, and coordinating care.
4. Community-based programs:
   Community-based programs and outreach initiatives are essential for reaching underserved populations and raising awareness about epilepsy at the grassroots level. These programs may include health camps, educational workshops, and training sessions for healthcare workers and community volunteers.

Facilities For Epilepsy in Pakistan

1) **Shifa international Hospital:**

Shifa International Hospital, Islamabad is among only few healthcare providers in Pakistan providing advanced minimally invasive neurosurgical treatment options to Pakistani patients suffering from complex Brain and Spine problem.

2) National Epilepsy center Karachi:

NEC is located on the premises of Jinnah Postgraduate Medical Centre (JPMC), Karachi under a signed MOU between the NGO and JPMC as a public private Project.

NEC's goals are to provide holistic management of epilepsy to the all affected, especially those with poor resources, create public awareness about the treatability of this highly stigmatized disorder, fight stigma associated with it by changing the

nation's is mind-set. It also works towards enhancing epilepsy education amongst professionals and epilepsy research. 17000 patients per annum are managed holistically and provided medicines.

3) Awareness Program

The Epilepsy Foundation promotes education and awareness about epilepsy. Our goal is to help everyone understand what a seizure looks like and what to do if they see someone having a seizure. The more everyone talks about epilepsy, the less people living with the condition have to fear discrimination, worry about receiving improper first aid, or keep their epilepsy hidden in the shadows.

4) Epilepsy Foundation Training and education:

The Epilepsy Foundation offers a variety of educational training programs on epilepsy and Seizure First Aid for both professionals and anyone who interacts with the public**.**

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