

REVIEW ARTICLE



A REVIEW OF MENDELIAN/NON-MENDELIAN NEUROLOGICAL DISORDERS COMMONLY REPORTED FROM PAKISTANI POPULATION

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RESEARCH COMPLETION CERTIFICATE

It is certified that Ms. Shanzeh Tahir of BS Hons of session 2018-2022 (registration No. F18BGEN008), Department of Biotechnology has carried out research work entitled “**Rare and Common Neurological Disorders reported in Pakistani Population: A Systematic Review**”.

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DECLARATION

I, Shanzeh Tahir, hereby declare that the material printed in the thesis is my original work and has been carried out under the supervision of Dr. Shumaila Zulfiqar. To the best of my knowledge, this research work does not contain any material that has been submitted for obtaining similar degree from any other educational institute.

Shanzeh Tahir

Dedicated

To

My Beloved Father, Tahir Yasin

&

My dearest Mother, Sahar Tahir

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All praise be to Allah Almighty, Lord of the worlds. I am grateful beyond words for His countless blessings on me and my loved ones. I wish to express my heartiest thanks and gratitude to my parents for always believing in me and helping me in everything I wanted to accomplish. Their care and love for me is beyond explanation. A profound thanks to Dr. Shahnaz Choudhry, Academic Dean and Dr. Irum Anjum Head of Biotechnology Department, for providing me an excellent research facilities.

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ABSTRACT:

INTRODUCTION: Neurological disorders (NDs) are broad spectrum nervous system disorders with variable severity. Most of neurological disorders are genetically heterogeneous with overlapping clinical features making diagnosis challenging. NDs usually remain enclosed in Pakistan due to lack of proper health facilities, insufficient resources, illitracy, and associated stigmatization. A small scaled cross-sectional general population based survey, and meta-analysis, was conducted on an arbitrarily selected sample from Lahore and other urban areas of Pakistan, to analyze and interpret prevalence of these disorders such as; depression, migraine, schizophrenia, epilepsy, stroke, dementia, ADHD, autism. This study also aims to report majorly reported novel genes found in previous studies about the frequently present neurological disorders.

OBJECTIVES: This review highlights the prevalence of neurological and neurodegenerative disorders, novel genes reported in consanguineous families, and their mode of inheritance; monogenic/ Mendelian and polygenic/non-Mendelian inheritance reported in the Pakistani population since last ten years, and to provoke the need for epidemiological data for better findings. The survey and meta-analysis depicting which age groups are more likely suffering from these disorders and the public opinion about it. It was found out that most prevalent ND among Pakistani population was depression among young people frequently present in females.

METHODS: Studies reviewed were all held in between last ten years 2012-2022. The data extracted from these studies for different neurological research is compiled to obtain accurate and efficient extrapolations. Different databases and search engines were used to retrieve the data which included schihub, google scholar, web of science, NCBI. All figures were made through Biorender. An online small scale survey was conducted with the help of Google forms, from general population to speculate the prevalence of neurological disorders in urban areas of Pakistan from 110 different

households, the study included total of 153 people. Meta-analysis was conducted on results obtained from the survey by using statistical software IBM-SPSS.

RESULTS: It was found that the affected individuals mostly belonged to the age group of 15-30 were females mostly suffering from depression and were in non-consanguineous marriage or were unmarried, but getting easily stressed. Alongside this study also reports 41 novel genes of neurological degenerative and neurodevelopmental disorders among Pakistani population extracted from last ten years study.

CONCLUSIONS: Pakistan being a developing country has very scarce information reported for neurological disorders, these disorders are increasing day by day and mental health is affected of not only the patient but also of the ones surrounding him. It is the need of the hour to spread awareness and do more strategic work and studies. The government of Pakistan needs to promote genetic counselling, testing and campaigns to educate people about consanguineous marriages and its risk factors.

KEYWORDS:

Neurological disorders, neurogenics, consanguineous marriages, genetic disorders n Pakistan.

INTRODUCTION:

Genetic disorders are caused by mutation/s in genome. These are generally categorized as 1) monogenic (single gene mutation); 2) Polygenic (mutation in more than one gene—polygenes and environmental factors). Genetic disorders are further subdivided on the basis of inheritance pattern, mendelian (diseases that are either dominant or recessive) or non- Mendelian inheritance patterns (1).

Genetic disorders are highly prevalent in countries where consanguineous marriages are generally practiced. Significant reasons of consanguineous marriages are that people prefer these because they want their sociocultures and traditions to langlast

rather than any perceived economic assistance, either in comparatively reasonable amount of dowries or family consolidation or some family property, or due to misbeliefs and the desire that the family is well-known.

Unfortunately, these marriages are practiced more and more, critically higher rates are present in rural areas. Such marriages often lead to higher risks and threats of congenital abnormalities and autosomal recessive diseases. There are more than 6000 identified genetic disorders, approximately 65% of people have some type of genetic congenital mutations, and around 1 in 21 individuals is affected by rare genetic disorders. In 1983 it was the first time that a disease gene was mapped; Huntington's disease was detected on chromosome 4 using DNA polymorphisms isolated in 1993. It is inherited as an autosomal dominant pattern (2).

The development of the human brain is a complex mechanism having several cellular mechanisms. Any abnormality or delay in these pathways, mutations in genes cause neurological disorders, causing a defect in the proper functioning of in CNS or PNS, in an individual. The side effects and symptoms which appear due to these abnormalities are very diverse varying from disease or disorder to each individual. Neurological or neurodegenerative disorders are not confined to a single mode of inheritance they may follow Mendelian or non-Mendelian inheritance, affected by environmental factors significantly. These disorders not only affect the individuals suffering from it but also their families and close ones in many ways. Pakistan faces the majority of non-communicable neurological disorders which makes the situation even worse and the victims are stigmatized by society to seek help from professionals, which has become a serious concern in diagnosing and treating patients, which needs to be resolved (3).

The most prevalent neurological disorders in Pakistan include epilepsy especially Juvenile myoclonic epilepsy (JME), this condition is caused by GABRA1, most elevated predominance is found in individuals more youthful than 30 years old, for example about 2 million individuals and 1/tenth of the world weight of epilepsy is in

Pakistan. Headaches, according to a survey conducted in 2013 very serious percentage of 89.5% of the population suffered from it.. Strokes are widespread in Pakistan, its risks have been pumped, up to 100% in the past decade. A new gene has been discovered which is FoxF2 which increases stroke risk due to vessel issues in the brain. The frequency of these neurological disorders has been increasing day by day and Pakistan being the sixth most populous country in the world with an approximate population of 225,991,170 is at a very high rate of facing neurological problems leading to high death rates. It is predicted that by 2050 Pakistan will be the fourth most populous country in the world carrying high statistical percentages of psychological issues (4).

Sr #	NEUROLOGICAL DISORDER	PHENOTYPE	GENE/LOCUS/ LOCATION	INHERITANCE	DESCRIPTION
1	Stroke	Stroke, ischemic to Cerebral infarction	<ul style="list-style-type: none"> • F5 • 1q24.2 • PRKCH • 14q23.1 	<ul style="list-style-type: none"> • Mu • Classic Mendelian inheritance 	Causes deprivation of sensory and motor function due to neural tissue death in the brain. About 20% of strokes are hemorrhagic
2	Huntington	Huntington disease-like 1	<ul style="list-style-type: none"> • PRNP • 20P13 	<ul style="list-style-type: none"> • AD 	Rare familial disease, Causes nerve cells to degenerate in the brain, Can lead to

					psychiatric disorders.
3	Neuro-psychiatric disorder	Intellectual developmental disorder with neuropsychiatric features	<ul style="list-style-type: none"> • SLC45A1 • 1p36.23 	<ul style="list-style-type: none"> • AR 	Have average ID, can have seizures, anxiety, autistic characteristics, or other abnormalities.
4	Duchenne muscular dystrophe	Duchenne muscular dystrophe	<ul style="list-style-type: none"> • DMD • Xp21.2p21.1 	<ul style="list-style-type: none"> • XLR 	Can range from mild to severe, muscles degenerate, protein alters.
5	Creutzfeldt-Jakob disease	Creutzfeldt-Jakob disease Creutzfeldt-Jakob disease	<ul style="list-style-type: none"> • HLA-DQB1 • 6p21.32 • PRNP • 20p13 	<ul style="list-style-type: none"> • AD 	Is present in sporadic and inherited form, the brain gets degenerated and is fatal
6	Familial hemiplegic migraine	Migraine, familial hemiplegic, 1 Migraine, familial hemiplegic, 1, with progressive cerebellar ataxia	<ul style="list-style-type: none"> • CACNA1A • 19p13.13 	<ul style="list-style-type: none"> • AD 	Causes light and sound sensitivity with severe headache
7		Myofibromatosis, infantile 2	<ul style="list-style-type: none"> • 19p13.12 	<ul style="list-style-type: none"> • AD 	Most prevalent hereditary stroke

	CADASIL	Cerebral arteriopathy with subcortical infarcts and leukoencephalopathy 1 Lateral meningocele syndrome			disorder
8	Parkinsons	Parkinson disease 6, early-onset	<ul style="list-style-type: none"> • PINK1 • 1p36.12 	<ul style="list-style-type: none"> • AR 	Disorder of the brain causes motor and coordination abnormalities.
9	Depression	Major depressive disorder	<ul style="list-style-type: none"> • SLC6A4 	<ul style="list-style-type: none"> • Non-Mendelian 	Caused by genetic and environmental factors can lead to the severeness
10	Schizophrenia	Schizophrenia Schizophrenia Schizophrenia	<ul style="list-style-type: none"> • MTHFR • 1p36.22 • SCZD12 • 1p36.2 • CH13L1 • 1q32.1 	<ul style="list-style-type: none"> • AD 	Chronic in nature causes delusions and speech issues
		Basal ganglia		<ul style="list-style-type: none"> • AD 	Causes physical problems, due to

11	Basal ganglia	calcification, idiopathic, 1	<ul style="list-style-type: none"> • SLC20 A2 • 8p11.2 1 	failed suppression of unwanted movements
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Neurological disorders are significant reasons for morbidity and mortality, around the world. A significant obstruction in defining a powerful wellbeing strategy is the absence of a strong epidemiological examination in Pakistan. This review aims to enlighten the need to develop and install a strategized infrastructure, hiring specialized neuro-specialists, geneticists, psychiatrists, and researchers. Although we have very limited and scattered information about Pakistan and other low-income countries, disease prevalence, severity, and patterns are only diagnosed via cultural, geographical, social, ethnic, and religious aspects. The focus of this review is to target neurological disorders among inbred couples and also the patients which are affected due to consanguineous marriages, to highlight novel mutations and the prevalence of these disorders. In addition to this provide a need for revised healthcare guidelines for management, administration, and availability of epidemiological data (5-8).

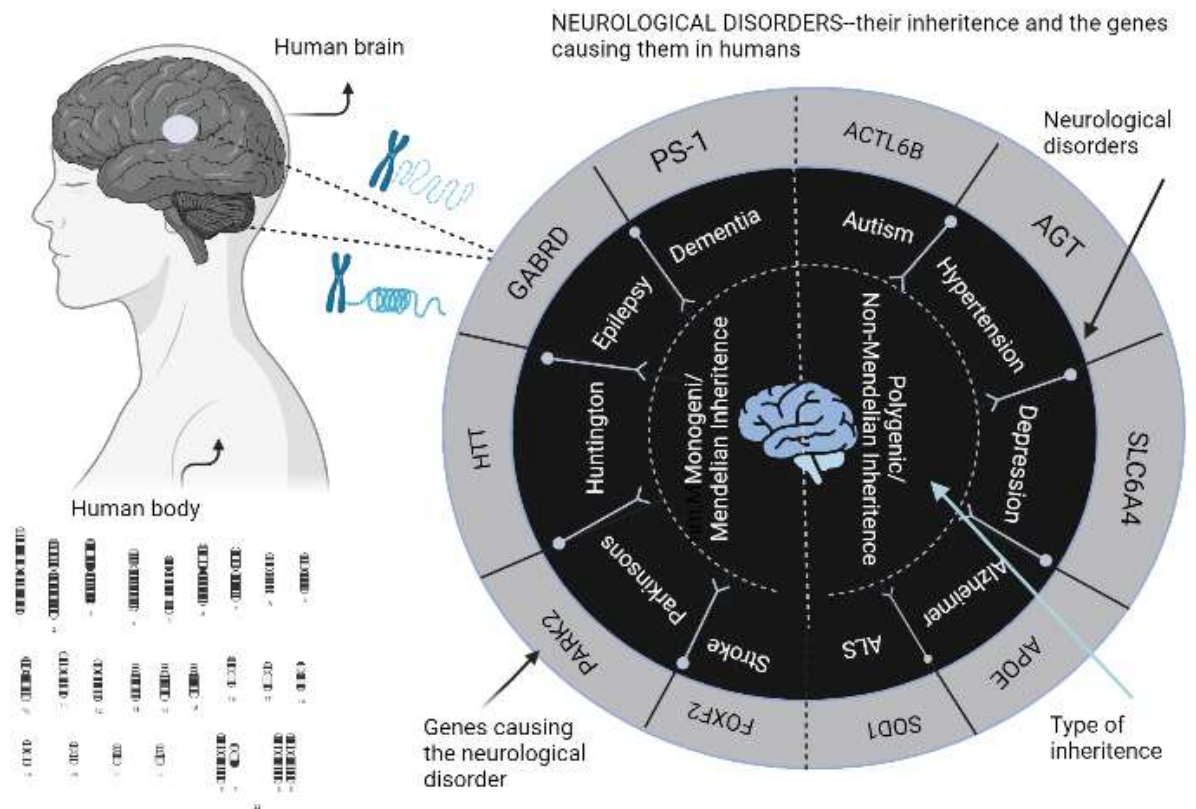


Figure 1 A demonstrative image showing neurological and neurodegenerative disorders categorized into monogenic/ Mendelian and polygenic/non-Mendelian patterns of inheritance along with the gene causing the neurological disorder. Created with Biorender.com

A genetic syndrome or disorder is a malfunction in either a specific part or in the whole sequence of DNA distinguishing it from the normal one. These are categorized as 1) monogenic (single gene mutation) 2) Polygenic (mutation in more than one gene—polygenes) 3) Multifactorial (mutation in more than 1 gene and includes environmental factors as well). Genetic disorders can follow mendelian (diseases that

are either dominant or recessive) or non- Mendelian inheritance patterns. Neurological disorders can also be genetic or as a result of other complex factors (9).

While discussing the prevalence of neurological disorders, it has been reported in the latest study conducted in 23 local hospitals of Pakistan, which estimate covered 75% of the population estimated, consisting of 57,664 individuals out of which 35.3% were females and the rest males, suffering from psychiatric or multiple neurological disorders. The most prevalent among them was schizophrenia presenting a comparatively higher ratio in men about 30.4% whereas in women for 25.2%. Other prevailing disorders were epilepsy and psychiatric issues, especially depression, major reasons stated include high divorce rates in the population (8, 10).

Alzheimer's disease (AD), Amyotrophic lateral sclerosis (ALS), Frontotemporal lobar degeneration (FTD), and Parkinson disease (PD), to some extent have an overlap of molecular and pathological features. All these neurodegenerative disorders either follow a non-familial or mendelian inheritance patterns. AD affects 5.5 million Americans and 2-6% in Pakistan, being the most common neurodegenerative disease (11).

RARE NEUROLOGICAL DISORDERS:

Hereditary Spastic paraplegia:

Hereditary Spastic paraplegia (HSP) is a genetic following classical monogenic mendelian inheritance pattern, c having 80 different types of HSP. Its clinical symptoms include muscle weakness and tightness (spasticity) in the lower limbs. Causative genes were identified among two consanguineous Pakistani families which were completely unrelated with 2 types of HSP. In 1 family ZFYVE26 variant was recognized for the first time to be reported from Pakistan, whereas the CYP2U1

variant was identified in 4 affected patients having symptoms of SPG56 which were reported for the second time in Pakistan (12, 13).

In another study, two consanguineous Pakistani families, unrelated, were reported, in family 1, CYP2U1 gene with a novel homozygous variant (c.604G>A) with SPG56 features, while in family 2 features of SPG11 were observed among 3 affected patients, with the help of Sanger sequencing and whole-exome sequencing (14, 15).

Early infantile epileptic encephalopathy (EIEE)

EIEE is an age-related form of epileptic encephalopathy and is a very serious form of neurological disorder. The clinical symptoms appearing for patients suffering from this disorder include muscle contraction onset since the age of 3 months, occurring countless times per day, and may cause psychomotor impairment and eventually death of the child. EIEE-39 is caused due to a mutation in the SLC25A12 gene which is present on chromosome number 2q31(16).

Schizophrenia:

It is a mental-psychological illness which is characterized by hallucinations and depressive episodes following multifactorial mode of inheritance. Approximately 24 million of the worlds total population is affected by schizophrenia, it is a ND which involves recurrent or chronic psychosis, in severe cases it can also lead to long-term functional disability. Unfortunately, 50% of the affected individuals donot receive appropriate care due to lack of awareness, financial burden, stigmas, among which 90% people belong to developing countries like Pakistan. In account to global prevalence and the draft of ‘ Assessment of Health Status & Trends in Pakistan’, the estimated ubiquity of people suffering from schizophrenia in Pakistan is around 1-2% among general population. According to the census of 1990 approximate loss in disability-adjusted life years (DALYs) due to schizophrenia and linked NDs was estimatedly 13million with 1% burden of schizophrenia holding 26th position on list whereas by 2020 it gained 20th position and, DALYs loss by 17million. In Pakistan its

frequency is higher in males than females whereas globally it is 1:4. The currently calculated estimation of schizophrenia being inherited is 80%, alongside environmental factors also play a very important role in the onset, severity and treatment of it for example stress, smoking, alcohol consumption disturbed upbringing.

Both adoption and family studies suggest that various loci are involved in genesis of schizophrenia. Linkage analysis have been performed on schizophrenic genes on chromosomes 2q, 3p, 4p, 5q and 22q globally. The first reported study from Pakistan also performed linkage disequilibrium analysis and haplotype association of DISC locus (1q24.1) with a risk of schizophrenia and they reported the effect of it on human genome region 1q24.1 in transmission and association of schizophrenia in the population of Pakistan. According to another research conducted in Lahore, Pakistan, GWAS identified several common CNVs and gene variants which were linked to psychiatric illnesses. The genes associated with schizophrenia are FURIN which participates in neurodevelopment, CHD7 it regulates neuronal differentiation, SORCS3 and NMUR2 which regulates receptors signaling and sorting present in neurons (17-20).

Intellectual disability:

Intellectual disability (ID) is counted as among one of the most uncommunicable syndromes in patients especially in children globally but a high ratio has been observed in under-developed countries. ID is considered a novel neurological syndrome in countries where consanguineous marriages are very prevalent. It is a heterogeneous neurological disorder associated with hundreds of genes and many chromosomal abnormalities leading to monogenic forms. It is an autosomal recessive genetic disorder affecting around 3% of the total population and has been gaining momentum with increasingly consanguineous marriages, malnutrition, and disturbed surrounding environments for the individual. High ratios of intermarriages have led to the increased ubiquity of genetic disorders, such families help in the identification of

recessive novel genes. Research conducted in different ethnicities of Pakistan studied 121 families, among which 111 families had cousin marriages. Novel pathogenic variants of ARID genes were reported, missense, frameshift, splice site, and non-sense mutations were also reported varying among families. While evaluating two consanguineous marriages an alteration in splicing of ATP9A was found. In another study where 5 individuals were studied from families which were not related to one another from Pakistan and Saudia-Arabia, suffering from the same clinical symptoms were examined. A novel mutation was found in genes IQSEC1 manufacturing altered proteins, which belong to 3 related genes. The genes IQSEC2 and IQSEC3 depicted seizures, developmental delay, short stature, and intellectual disabilities, whereas all the patients in this cohort belonged from families of inter-marriages (21-24).

Epilepsy:

Epilepsy is a ND in which the activity of brain becomes abnormal, it causes unusual behaviour and seizures. Around 30-40% epilepsy is caused by genetic factors having comparatively higher risk by 9-12% if it runs in the family, but it is also caused by the combination of environmental and genetic factors that influence the health of the individual. Epilepsy follows Mendelian inheritance pattern in several cases. Globally 977 genes associated with epilepsy have been reported, 84 epilepsy causing genes, 536 epilepsy related genes and 73 neurodevelopmental associated genes. The genes associated with it have been lately identified, benign familial neonatal convulsions by mutations in KCNQ2 and KCNQ3, Autosomal dominant nocturnal frontal lobe epilepsy is caused by mutations in CHRNA4 and generalized epilepsy with febrile seizures plus by mutations in SCN1B.

The tendency of having epilepsy in Pakistani population is approximately 9.99/1000 individuals. Its frequency is higher in age group of 30years, slightly decreasing in people of 40-59 years of age. (24-28) Epilepsy has four main types :

- Generalized

- Focal
- Generalized and focal
- Unknown/ cryptogenic

Juvenile myoclonic epilepsy follows polygenic/mendelian inheritance predominantly and is heterogeneous, whereas in some cases it is reported to follow autosomal dominant inheritance pattern and some mutations including GABAA. Males and females both are affected by this disease equally and triggers in twenties. The factors that precede include alcohol consumption, stress, sleep deprivation. JME is the most commonly occurring type of epilepsy and affects 10-30% of the population worldwide, in India only it causes around two million cases whereas the prevalence in Pakistan has lack of epidemiological record but it is estimated to be 9.99/1000. In a study conducted for the first time in Pakistan from two unrelated families, for JME affected individuals, 3 exons were selected of EFHC1 causing mutations. 3 variants; R159W, V460A, P436P, and 1 insertion were reported, among these V460A was uncommon and was also identified in an un-phenotype American individual. The study showed that the majority of mutations of EFHC1 varied among different ethnicities and are unevenly distributed globally (29, 30).

Neuronal ceroid lipofuscinosis:

NCL (Neuronal ceroid lipofuscinosis) is a neurodegenerative genetic disease-causing lysosomal storage. Its clinical symptoms include movement decline, seizures, and poor vision. The mutation in CLN5 causes NCL, a study was conducted in Punjab, Pakistan to find the novel gene variants present in two consanguineous Pakistani families who were unrelated and, diagnosed with NCL. Two novel homozygous variants were discovered with the help of whole-exome sequencing (31).

Autism spectrum disorder (ASD) :

ASD (autism spectrum disorder) is a neuropsychiatric and multifactorial neurodevelopmental disorder present in children following either monogenic or polygenic mode of inheritance.. Its clinical symptoms may range from mild to severe, such as difficulty in socializing and communicating. A study conducted for the Pakistani population observed the association of many different genes with SNP's categorized for ASD varying among the populace. It scrutinized that in the Pakistani population, the SNP's are not the major cause of ASD in children but other factors play significant roles (32).

Attention deficit hyperactivity syndrome (ADHD):

ADHD is a genetic condition in which some areas of the brain are comparatively smaller or take longer than normal to grow and develop in children, vitamin D deficiency can also lead to babies with high risk of having ADHD. It is one of the most frequent neurodevelopmental disorder in children and often around 30-40% of them are referred to child mental health practitioners due to its severity. But due to scarcity of resources in Pakistan they are referred to adult psychiatrists and paediatricians. ADHD causes a wide range of abnormalities in the development and growth of the individuals personality, ADHD follows a tenacious pattern of hyperactiveness, impulsiveness, inattention and disturbed behaviour. Around 2.49% people are living with ADHD in Pakistan. Boys are significantly more prevalent as compared to females by 2:1 to 9:1. Substantially people believed that ADHD outgrows when a child reaches adolescence but now it has been cleared that around 2/3 of children will have ADHD as adults and its treatment will continue throughout their life.

A gene based analysis performed showed 6 genes in 4 loci (ST3GAL3, FRAT1/FRAT2, CGB1, and RNF225/ZNF584) which were linked significantly to persistence with ADHD. ANK3 gene which encodes ankyrinG is mainly involved in neuronal signalling and development, it has been reported in cases of schizophrenia, bipolarity, ID and autism. Another study reports the inactivating mutations in

ANK3 gene expression causing disruptions in all isoforms of this gene by a balanced translocation, in patients with ADHD (33-35).

COMMON NEUROLOGICAL DISORDERS:

Stroke:

According to World Health Organization (WHO), and the Global burden of the disease study group, stroke is no longer considered as a cardiovascular disorder but now as a neurological disorder. WHO stated that by 2030 approximately 80% of all strokes will occur in developing-low-income countries. The significant factors contributing to this neurological disorder are hypertension, depression, and advanced age. Strokes about their genetic aspects have been hardly focused and reported, although an epidemiological study of families of twins which were heterozygous and homozygous exhibit genetic tendency towards stroke, this study was conducted in Pakistan having 250 individuals as a control group and 200 under observation, it concluded an associated link between ischemic stroke and SNP83. However another study regarding gene-gene and gene-environment about stroke reveals that abnormalities in the loci of these 3 genes COL4A2, COL4A1 and HTRA1 have influence on stroke phenotypes which follow Mendelian inheritance (36-39).

Migraine:

Headaches and migraines are becoming more and more prevalent globally, several factors include stress, excessive usage of electronic technology, and many others. A cross-sectional study conducted in PEMH-Rawalpindi, Pakistan of individuals who were diagnosed with migraine, showed that 90.1% of individuals from a total of 201 patients had symptoms of premonitory phase, the study included both genders, males to females in a ratio of 1:3. The findings report that these premonitory phase

symptoms had a very high frequency among migraine patients, requiring an effective treatment (40).

Major depressive disorder:

Depression and anxiety are hot topics around the globe nowadays, especially after the Covid-19 pandemic. It is one of the non-communicable diseases, it is often neglected in rural areas, major factors include financial-social status, family concerns, trauma, and, are highly prevalent in most of the countries especially Pakistan, India, and other developing countries. (MDD) Major Depressive Disorder also known as mood disorder in DSM-5, it follows a non-Mendelian inheritance pattern and is polygenic and monogenic in some cases. This disorder affects an estimated 322 million people worldwide leading to severe psychological health concerns and at times may become suicidal. Pakistan reportedly has very few specialized psychiatrists and visiting them is still considered a norm, the patients and their families are stigmatized if they consider seeking help from professionals, being judged, and given different anonymous titles by society, affecting patients' dimensions of living and thinking. A study depicts novel and common gene variants causing MDD in the Pakistani populace, it was found that BCR, PABPC1 (stress-causing), and BCR play significant roles in MDD pathogenesis (41, 42).

Dementia:

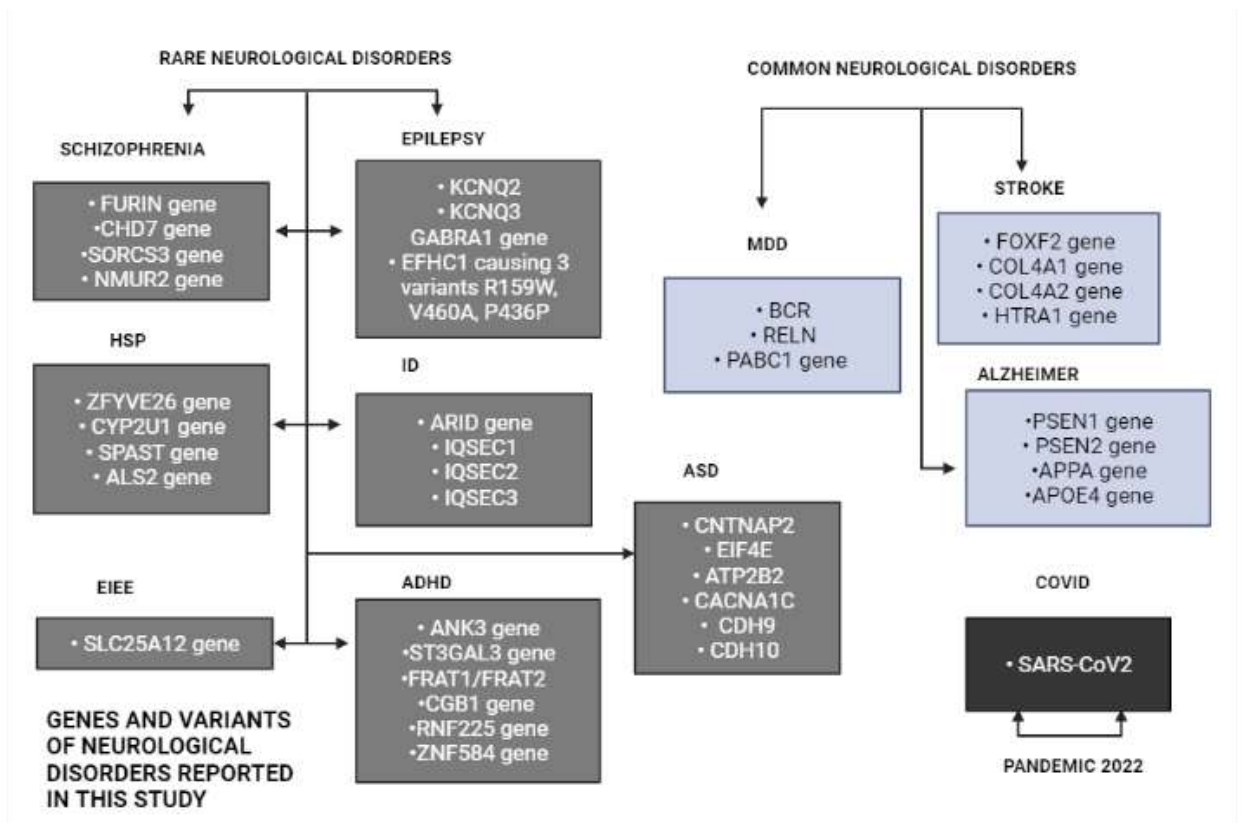
Dementia is also called as a major neurocognitive disorder. It is particularly not a disease but a wide range of disorders such as Alzheimer, Parkinson's, Huntington, which are characterized by several cognitive deficits, memory loss, irreversible and progressive brain injury eventually leading to mortality. By 2005 approximately 24.3 million people were suffering from dementia and 4.6million cases are added each year since then. As Pakistan is the 6th most populous country it faces many difficulties and challenges for managing aging and diseases related. Estimatedly 150,000-200,000 individuals are living with dementia in Pakistan, while its prevalence increases to 2-

6% in elderly (greater than 65 years). The psychiatric Diagnostic and Statistical Manual (DSM 5) gave dementia another name 'major neurocognitive disorder' (43-45).

Alzheimers:

Alzheimer is one of the most frequent type of dementia. It is mild cognitive impairment. Neurogenetics becoming advanced with time has identified some genes associated with Alzheimers disease such as alterations in PSEN1 gene which causes onset of AD in young people (presenilin 1), PSEN2 gene which causes onset of AD in elderly and APPA gene (amyloid precursor protein)involved in commonly causing familial AD, where as frequency of APOE4 gene in Pakistani population is yet unknown (45).

Table 1 different genes and variants involoved in various neurological disorders from previous studies conducted in Pakistan



Epidemiological study of congenital and hereditary abnormalities in Sialkot:

An epidemiological study was conducted in Sialkot, Pakistan for scrutinizing individuals with neurological and limb disorders, with around 241 patients it was found that approximately the majority of them had neurological disorders such as microcephaly, intellectual disability, down syndrome, cerebral palsy e.t.c. this study also showed that not only genetic but also etiological factors played a significant role in their present conditions which could ultimately be improved with better management and administration of the healthcare system (46).

COVID-19 pandemic and its neurological-psychiatric side-effects on patients:

COVID-19 is a global pandemic and a serious health concern among individuals worldwide. Coronavirus disease 2019 (COVID-19) an infectious disease having varying strains caused a pandemic and took millions of lives globally, it affected the psychological state of patients their families, students, and especially health workers. A cross-sectional study was conducted in a hospital in Karachi, Pakistan in the year 2020, the study excluded patients having any prior neurological disorder. 114 patients were included in the study, 42.9% patients ranged less than 50yrs and 57.1% more than 50 years, among which were 54.4% males and 45.6% females. Patients suffering from neurological complaints were 24.5%, dizziness (17.5%) was among the most typical symptom, others included headache (15.7%), impaired consciousness (8.7%), and skeletal muscle injury (10.5%). Three patients also suffered from a stroke, a factor involving hypercoagulability which may also cause a stroke. ACE2 (Angiotensin-converting enzyme 2) was also identified as a receptor in SARS-CoV-2) whose expression can be a possible reason for causing neurological symptoms in patients suffering from covid-19 through several mechanisms. Several studies also show that SARS-CoV-2 infection led to the aggravation of varying neurological events, faced by

patients post-covid, including (OMS) Opsoclonus-myoclonus syndrome, a rare neurological disorder, characterized by motor and behavioral imbalances which could be treated with IVIG and corticosteroids (47, 48).

An online survey conducted from several universities from Pakistan for students regarding their online exams and schooling showed that 65% of individuals were not satisfied with their system and classes while 41% of them faced stress and were psychologically affected (49).

Prevalence of Consanguinity and its adverse consequences:

Numerous factors nurture the practice of consanguineous marriages in Pakistan. Aspects regarding the security of knowing-well the spouse, strengthening bonds among relatives, and dowry have spiking rates with children being born with higher chances of being affected. The custom of inter-marriages has been in practice for a long time, being recurrent in developing Asian countries like Pakistan. Pakistan being the 6th most populous country has the highest rates of cousin marriages. Certain studies highlight that 60% of marriages exhibit consanguinity out of which around 80% of the couples were first cousins. The ratio of inter-marriages is predominantly high in Muslim countries. Pakistan has been ranked among one of the leading countries practicing consanguinity by around 70% of such marriages. Regions such as Sargodha, Punjab, and KPK, rural areas, and places with low-literacy rates have alarming percentages of this customary practice. Such marriages lead to drastic effects that are needed to be highlighted such as stillbirths and abortion or congenital abnormalities, especially in the case of familial neurogenic disorders, leading to the expression of autosomal recessive diseases and other genetic disorders such as microcephaly and neonatal mortality. These inter-marriages are often linked to several rare recessive genetic disorders, which are usually suppressed in members of the same family, and the chances of them being expressed increase dramatically, causing high

ratios of learning disabilities, a single gene associated neurological disorders. Recently it was concluded by a team of scientists in Pakistan that the prevalence of mental retardation is due to cousin marriages, further leading to a discovery of 30 novel genes causing this anomaly. Even though a decrease in inter-marriages have been observed regarding modernization and socio-economic development in Africa, some part of Asia, and the western world, but has remained a common practice in Pakistan, hence highlighting the high risks of affected individuals not only with neurological disorders but many other genetic disorders too (50, 51)

Socio-economic burden:

The ongoing discussion around the country that health will automatically lead to a more stabilized economic-social growth and development cannot be supported by present-day facts and evidence. Without doing investments and having sufficient resources, desirable and up-to-mark cures and treatments cannot be provided. Implementation of strategic plans and investments at a national and international level are required to enhance and upgrade the databases and hence leading to better diagnosis, treatment, and prevention. The population of Pakistan has been facing economic uncertainty, socio-political instability, and strong faith in superstitions for many decades. Pakistan like many other countries has higher rates of mental illness in women as compared to ones in men, such as hypertension, anxiety, depression, headaches, vaginal discharge, other menstrual issues. in various studies, it was observed that most women belonging to such areas faced social, financial, and disturbing family issues caused by uncountable expectations of their roles in society. Often patients with such neurological disorders go untreated, being victimized by discrimination and stigmatization, and are refrained from social activities. Such patients go unrecognized and unfortunately code a very large ratio, due to different beliefs that the parent or family has been cursed or the patient is suffering from black magic, such cases are largely found in poor populaces of the country, where people are illiterate and unaware. As the number of non-communicable neurological disorders

increases among people, it also implies the demand for considerably improved management of resources. Such issues are now emerging as public health concerns in such countries (5, 8, 52).

Scarcity of epidemiological data:

One of the prime obstacles faced while formulating an effective long-lasting health policy is the shortage of epidemiological research in Pakistan and many other developing countries. People with neurological disorders are present all around the globe, but they are comparatively more prevalent in developing countries than the developed, due to numerous reasons including low-literacy rates, strong belief in superstitions, therefore, lacking the epidemiological data regarding neurological disorders. The data is very limited due to several reasons including lack of trials to prevent and treat according to patient needs, funding by the government, lack of interest in updating epidemiological studies, and limited resources. This data is most of the time collected by physicians and doctors of respectable hospitals for their records and not a representation for the whole nation. China, Pakistan, and India collectively form around 65% of the population of Asia, and the data collected from these regions vary in various aspects according to their lifestyles. According to another study, some concerns are brought into attention which shows that some drug combinations prescribed require addressing to lower mortality and morbidity examining the need for some medicines for some patients. Now is the need to remodel our infrastructure and standardize approaches for patients with neurological disorders and disturbed mental health in hospitals and the health ministry of government shall get fully involved to standardize the treatments being provided. Pakistan being a low-income country does not have sufficient specialists in the field of neurology. The burden of more patients and fewer resources has become a burden for physicians and doctors, hence requiring restructured neurology training programs as well as genetic counselors as neurogenic disorders are very prevalent caused by consanguineous marriages. It is the utmost need of the hour to collect reliable authentic data from all

over Pakistan to conduct studies based on this data, which could then be used to access the prevalence, and lower the burden of neurological disorders from the country. It shall be very resourceful and helpful to have a national survey conducted among all regions of the country to access the needs of the people and to monitor the health, and probable risks among the populace (6, 8, 10, 53).

Methodology:

This review will target the following databases to access scientific journals. The PubMed search engine on NCBI, Google Scholar, Scihub, Scopus, and Web of science will help access articles about biomedical sciences. The selected articles will target the prevailing neurological disorders in the Pakistani population and the need for research on it. Research journals will be retrieved from science hub or science direct.

The already obtained articles have been selected based on their target study and the articles will be selected from the last 10 years (2012) and onwards to provide updated data. The findings being reviewed should enlighten growing neurological disorders, the genes causing mutations behind them. Additional studies on awareness among the populace and research in this field can help estimate the efficacy of the proposed treatment plan. To avoid ambiguity and clutter of data, this review will avoid detailing medicines prescribed.

An online small scale survey was conducted with the help of Google forms, from general population to speculate the prevalence of neurological disorders in urban areas of Pakistan from 110 different households, the study included total of 153 people. Meta-analysis was conducted on results obtained from the survey by using statistical software IBM-SPSS.

Unfortunately, no data has been published so far indicating the prevalence of both rare and common neurological disorders in Pakistan. This review will help to identify both reported neurodevelopmental and neurodegenerative disorders in Pakistan, their prevalence recorded in the survey held at 21st April 2022. Research on a neurological

disorder will also incorporate its brief genetic background which will enable researchers to understand the most frequent neurological disorders in Pakistan.

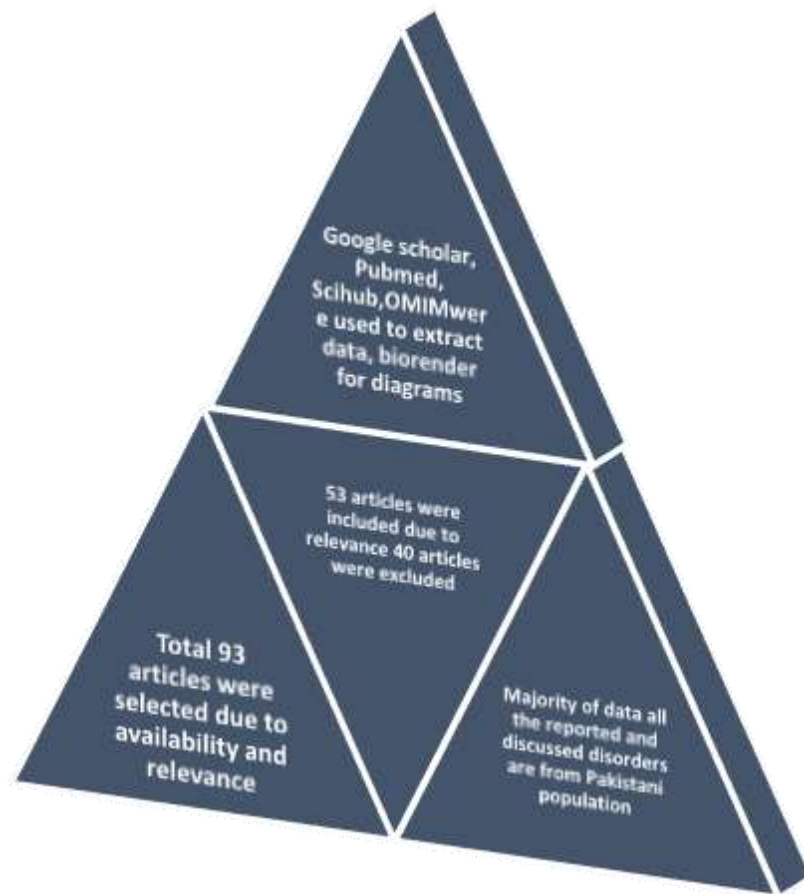


Figure 2 This figure demonstrates the methodology and article selection criteria opted for this study

RESULTS:

SURVEY:

Mental health is the most important concern of an individuals health. Unfortunately neurological disorders are present worldwide but its frequency is noticeably high in countries like Pakistan. They lead to disability, loss of freedom to live and productive life. Pakistan being a growing country has very scarce reported data and research in this field. Hence a small-scale general population based survey was conducted from randomly stratified general population from Lahore and people living in other urban areas of Pakistan in Lahore, in order to determine the prevalence, frequency of consanguinity in affected individuals and understanding of neurological disorders and if they had opted for genetic counselling or testing. The survey included a total of 153 individuals belonging to 110 different households and of different age groups and genders. The survey was irrespective of the class, status or religion of the individual hence restraining from racism or superiority or inferiority complex.

AGE GROUP:

The age group of the affected person was divided into five categories such as below 15 yrs, 15-30 yrs, 30-45 yrs, 45-60 yrs and 60 yrs above. Noticeably significant individuals belonged to the age group of 15-30 years old.

		AGE_GROUP			Cumulative
		Frequency	Percent	Valid Percent	Percent
Valid	>15	7	4.6	4.6	4.6
	15-30	113	73.9	73.9	78.4
	30-45	18	11.8	11.8	90.2
	45-60	8	5.2	5.2	95.4
	60<	7	4.6	4.6	100.0
	Total	153	100.0	100.0	

Figure 3 Frequency table of age groups

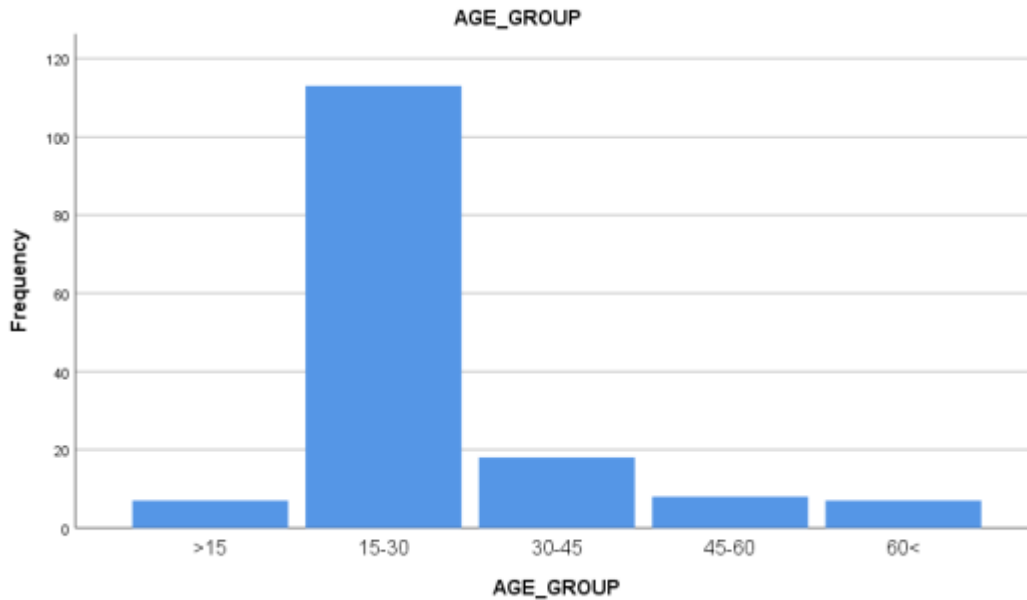


Figure 4 bar graph showin age groups and their frequency in the survey

GENDER:

They survey provided options for male, female and other. Among them females were the ones mostly suffering from neurological disorders which is 130 and males 23, others 0 out of 153 individuals.

		GENDER			Cumulative
		Frequency	Percent	Valid Percent	Percent
Valid	male	23	15.0	15.0	15.0
	female	130	85.0	85.0	100.0
	Total	153	100.0	100.0	

Figure 5 Frequency table for gender

CITY:

Survey was conducted in Lahore and was also filled by people belonging to other urban areas of Pakistan. 128 individuals were from Lahore while 25 were from other cities of Pakistan.

		CITY			
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	lahore	128	83.7	83.7	83.7
	urban_areas_of_Pakistan	25	16.3	16.3	100.0
	Total	153	100.0	100.0	

Figure 6 FREQUENCY OF INDIVIDUALS BELONGING TO LAHORE AND OTHER URBAN AREAS OF PAKISTAN

NEUROLOGICAL DISORDERS:

Depression was the most prevalent among all the individuals comprising of 66 cases, followed by migraine 25 people , other 8 people (Parkinsons, anxiety, epilepsy, panic attacks), autism 4 people, stroke and schizophrenia 3 people each, dementia 2 persons and 1 for ADHD, where as 41 were normal out of total 153 individuals.

		NEUROLOGICAL_DISORDER			
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	depression	66	43.1	43.1	43.1
	other	8	5.2	5.2	48.4
	migraine	25	16.3	16.3	64.7
	schizophrenia	3	2.0	2.0	66.7
	dementia	2	1.3	1.3	68.0
	stroke	3	2.0	2.0	69.9
	ADHD	1	.7	.7	70.6
	autism	4	2.6	2.6	73.2
	none	41	26.8	26.8	100.0
	Total	153	100.0	100.0	

Figure 7 FREQUENCY OF NEUROLOGICAL DISORDERS IN LAHORE AND OTHER URBAN AREAS OF PAKISTAN

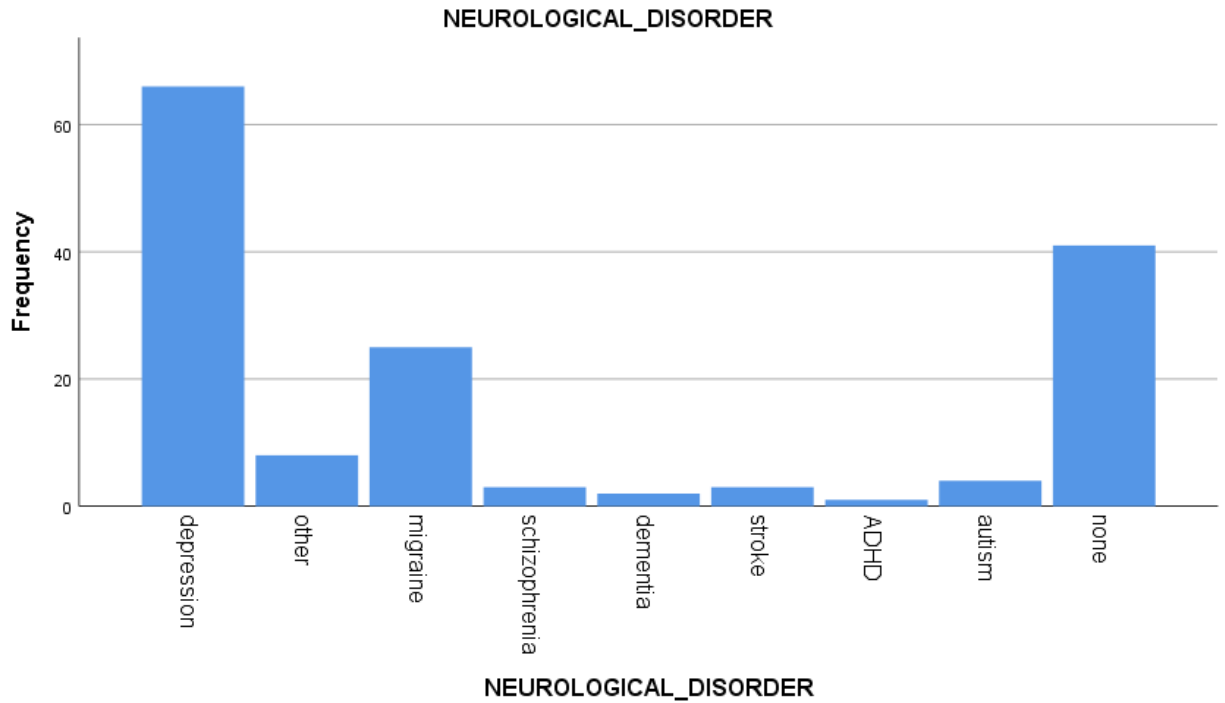


Figure 8 bar graph showing neurological disorders and their frequency in survey conducted in Lahore-Pakistan

PREVIOUSLY PRESENT IN FAMILY MEMBERS:

Among 153 individuals 112 had a family history of the disease which they were carrying while 41 had no such medical history.

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	yes	112	73.2	73.2	73.2
	no	41	26.8	26.8	100.0
	Total	153	100.0	100.0	

Figure 9 frequency of medical history of the disease

ENVIRONMENTAL CONDITIONS:

It was asked in the survey that in what environment was the affected individual raised, two options were provided among which 33.6% of the individuals were raised in good environment whereas majority of them 66.4% were raised in poor environment (as shown in the fig 9). It can be speculated from these results that the environmental conditions in which a person or a child is raised leaves a significant impact on that person and his mental as well as physical health. There are both genetic and environmental factors involved for the onset of the disease. It was also found out that what kind of relation did that person shared with his family, friends and loved ones now and it was noticeably good in majority of the people with 54.7%, 36% had disturbed relation whereas 9.3% had poor relations with their surrounding ones (as shown in fig 9).

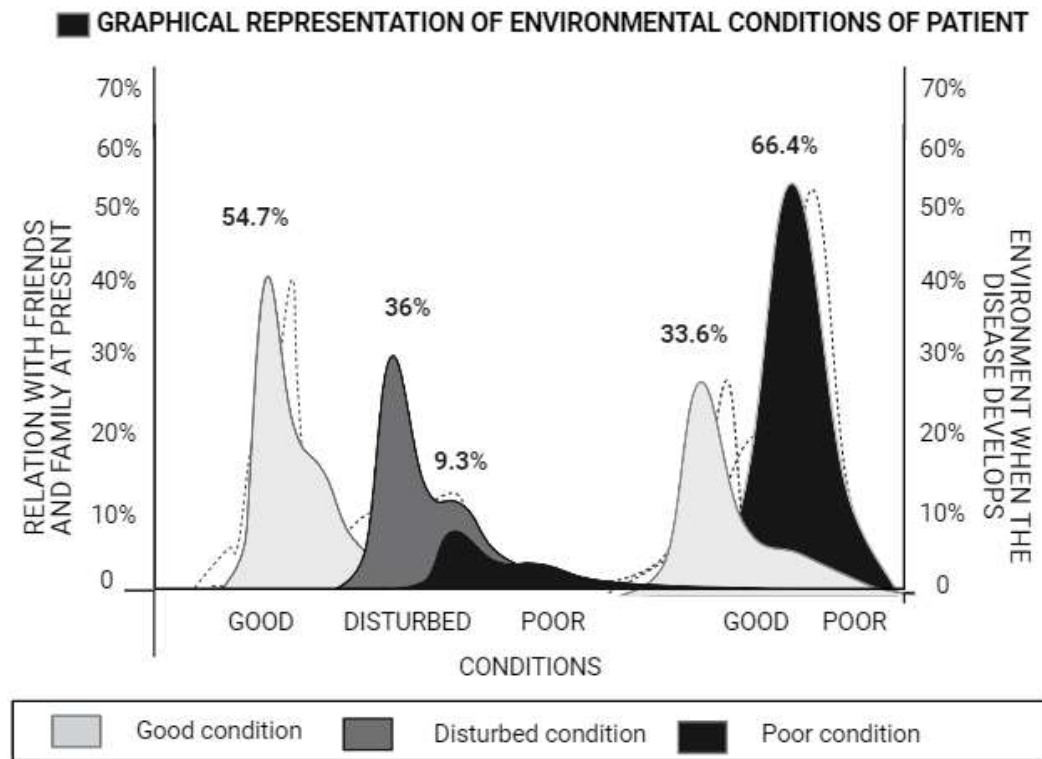


Figure 10 A graphical representation of environmental conditions of the patient. The left side depicts the relation of the individual while having the disease with his family and friends, whereas the right side shows the environment in which he developed the disease. A scale is given to distinguish the categorical conditions faced by the population.

GRAPH FOR PREVALENCE:

Different neurological disorders were mentioned in the survey including the following options with their prevalence observed by the general population in the year 2022 (as shown in fig 10)

- Schizophrenia 3.29%
- Depression 42.76%
- Migraine 16.45%
- Epilepsy 0.68%

- ADHD (attention deficit hypertension disorder) 0.66%
- Dementia 1.31%
- Stroke 2.63%
- Autism 2.63%
- None 26.97%
- Other(it was filled by the respondents, the answers including Parkinson's disease, anxiety and panic attacks) 2.62%

These percentages show that depression is the most prevalent disease in Pakistani population where as migraine and headaches are second. There may be several factors contributing to them including family matters, financial issues or social problems. People having depression are often faced stigmas and taboos and refrained from seeking professional help.

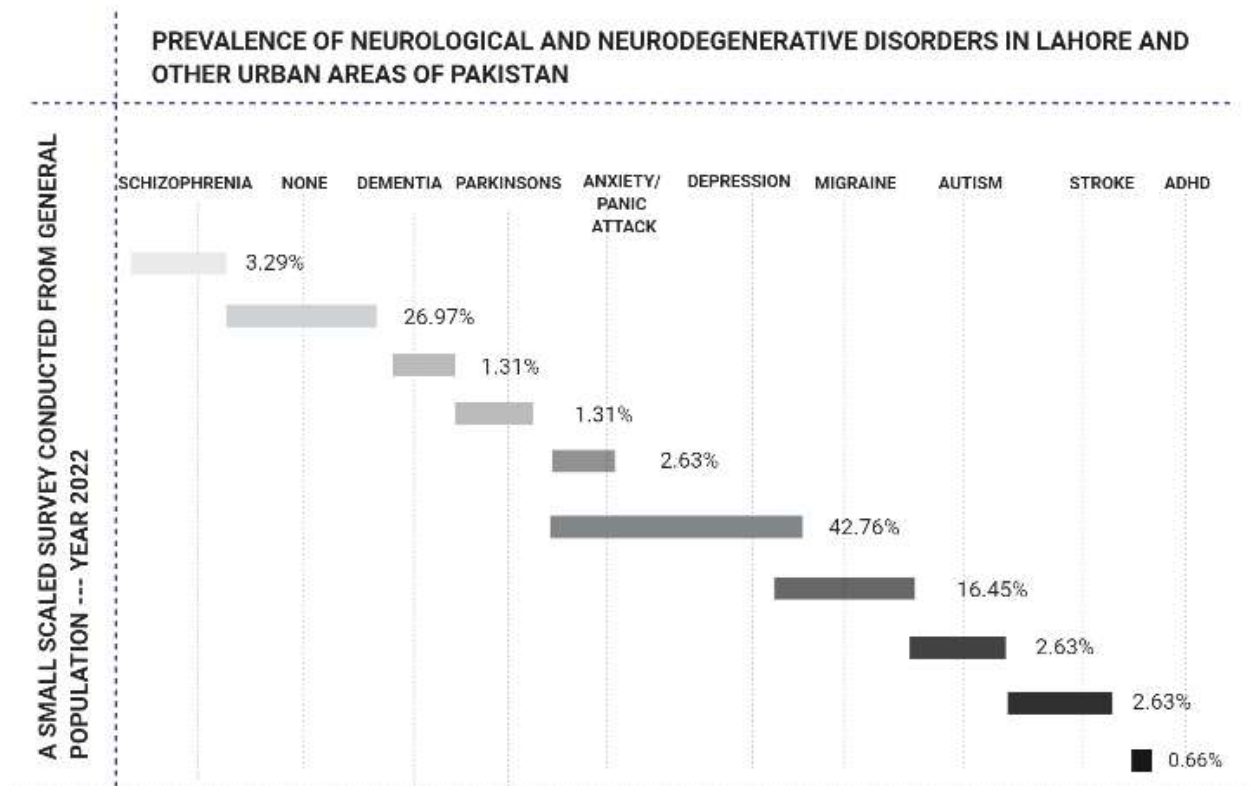


Figure 11 A demographic graph showing prevalence of neurological disorders in urban Pakistan and their prevalence in the survey.

PUBLIC OPINION ON PREVALENCE, STIGMATIZATION, SOCIO-ECONOMIC BURDEN AND AWARENESS:

In the survey people were asked about their opinions whether if they think that neurological disorders are becoming increasing prevalent in Pakistan according to which 72.4% people thought that they are highly prevalent, 21.7% people were neutral about their spread whereas 5.9% people thought that they are not prevalent. Increase in prevalence shows that people are getting aware about the increasing frequency of neurological disorders by observing it in their surroundings. When asked that if the people suffering from different neurological disorders are stigmatized or considered a taboo in response 68% people agreed, 25.5% were not sure whereas 6.5% people disagreed to it. Stigmatization can often lead to adverse critical outcomes for the

patient which can worsen his/her health and refrain them from seeking professional help which can eventually help them to deal with their difficulties. When asked that did they believe that socio-economic pressures lead to greater risks of these neurological disorders 86.6% people agreed while 13.4% disagreed. In some cases these issues are the main cause of depression and migraine in patients, as Pakistan is an under-developed country people face financial issues and mostly do not have health insurances to go for treatment, while living hand to mouth. When asked about awareness 97.4% people thought that the government of Pakistan shall regulate some campaigns about spreading awareness programs about mental health and neurological disorders whereas 2.6% people were not in favour (as shown in fig 11).

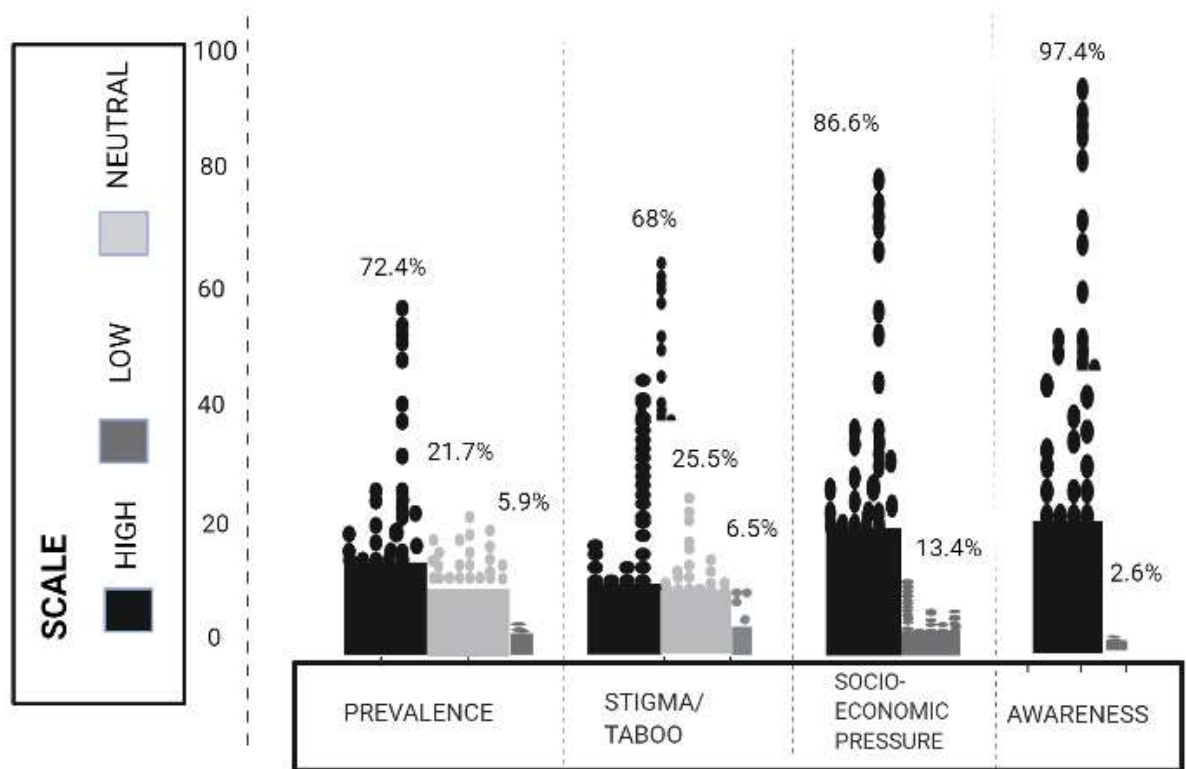


Figure 12 opinion of respondents in regard to prevalence, stigmatization, socio-economic pressure and awareness about neurological disorders.

Conclusion:

Neurological and neurodegenerative disorders are present globally but their prevalence is getting much higher in countries like Pakistan and India where the society has imposed stigma to the individuals and their respective families to seek help from professional health-care, rather are preferred to do superstitious rituals, hence most of the cases go undiagnosed and untreated in the non-communicable diseases. The rate of consanguineous marriages has been increasing day by day, especially in rural areas where there is a low literacy rate and a high ratio of genetically transmitted neurological disorders. This review focuses on novel mutations found in neurological disorders over the last 10 years and provokes the need for updated epidemiological data and research to be conducted in this field.

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