Prevalence of congenital deformities in Kot Addu district

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2023

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A Dissertation submitted in the partial fulfillment of the requirements for the degree of

Master of Philosophy

In

Human Genetics

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2023


بسم الله الرحمن الرحيم

CERTIFICATE

This dissertation "Prevalence of congenital deformities in Kot Addu district" submitted by **Mr. Sajjad Hussain** is accepted in its present form by the Department of Zoology, Faculty of Biological Sciences, Quaid-i-Azam University, Islamabad as satisfying the thesis requirement for the degree of Master of Philosophy in Human Genetics.

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Declaration

I hereby declare that the work accomplished in this thesis is the result of my own research work carried out in Human Genetics lab, Department of Zoology, Quaid-i-Azam University Islamabad. The epidemiological data were collected from district Kot Addu, Punjab, Pakistan. This thesis has neither published previously nor does it contain any material from the published resources that can be considered as the violation of the international copyright law.

Sajjad Hussain

Dedication

This dissertation is dedicated to

My parents

For their endless support, encouragement and

love. Theirprayers always paved the way of

success for me and

To my teachers

and For their support, encouragement

For being source of inspiration and enlightenment

ACKNOWLEDGEMENTS

In the name of Allah, the most merciful and beneficent. I bear witness that Holy Prophet Hazrat Muhammad (PBUH) is the last messenger of Allah Almighty. His (PBUH)life is perfect role model for a Muslim to be successful in this worldly life and hereafter. Without the blessing of Allah Almighty, I would not be able to complete my thesis.

I would like to acknowledge and express my deepest gratitude to my research supervisor ***Professor Dr. Sajid Malik*** *for his utmost guidance. Without his supervision and guidance completion of this dissertation would not be possible. I cordially thankful to him forhis kindness that is difficult to express in words. His skillful directions and dedicated advice have really guided me throughout the course of my research.*

I want to pay my special thanks to Professor ***Dr. Amina Zuberi, Chairperson****Department of Zoology for providing me all privileges during the completion of my dissertation.*

I also want to express my gratitude to all the affected families for their cooperation who helped me to complete this study.

My acknowledgement would not be completed unless I offer my humble appreciation to ***my parents*** *for their supportr throughout my educational career, and endless love.I am especially thankful to my friends,* ***Khalid Mehmood, Muhammad Adnan and Dilshad Hussain*** *for their support during my field work.*

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List of Abbreviations	Full form
CD	Congenital deformities
CNS	Central nervous system
CP	Cerebral palsy
CVS	Chorionic villus sampling
DALYs	Disability adjusted life years
dbHL	Decibles hearing level
DDH	Developmental dysplasia of hip
ICD	International Classification of Diseases
KPK	Khyber Pakhtunkhwa
MRI	Magnetic resonance imaging
NTD	Neural tube defect
OMIM	Online Mandelian Inheritance in Man
US	Ultrasound
WHO	World Health Organization

Abstract

Congenital deformities (CD) also known as birth defects arise due to functional or structural abnormalities during the developmental process in the intrauterine life. CD is caused by many factors like a defect in a gene, chromosomal aberrations, environmental teratogens, and micronutrients deficiency. About 50% of CD are of unknown aetiology. These are considered as the main cause of disability and mortality among children in developing and developed countries.The objective of this study was to explore the prevalence of CD and their association with various demographic variables in Kot Adu district. In this epidemiological study, a total of 295 families/ index subjects were ascertained. There was no proper data on CD available in the hospitals, the only source to collect data and to find subjects with certain CD was door to door survey. This method was completely dependent on cooperation and coordination between researcher and study population. The subjects with CD were diagnosed with the help of medical practitioners and the diagnosis was confirmed through online databases like OMIM. The ascertained deformities and index subjects were classified into six major categories. The representation of neurological disorders was highest, i.e., 30% (n=88). The second most prevalent CD was neuromuscular defects 28% (n=82), followed by sensorineural/ear defects 18% (n=53), eye/visual impairment 9% (n=28), musculoskeletal defects 7% (n=21), limb defects 6% (n=17) and 2% other defects. Among the ascertained index cases, 69% (n=204) were male and 31% (n=91) were female. The low contribution of female subjects may be attributed to the restricted sampling approach in rural areas. Sporadic cases, 72% (n=214) were more prominent than the familial cases 28% (n=81). Isolated cases representation was higher 61% (n=181) than syndromic 39% (n=114). Many index subjects fall in the poor economic quartile. The representation of the index subjects was highest at 27% (n=81) in the age range of >10-20 years. The highest incidence concerning birth order was recorded with 1st parity 28% (n=60) in case of sporadic cases. Among 81 familial cases 66% (n=54) were segregated in one generation. Consanguineous unions recorded were 69% (n=204). The current study provides valuable information about the prevalence of CD in the

study area, which will be useful for future research. Awareness campaigns regarding CD, genetic counselling, and prenatal diagnosis can help to reduce disease risks. The high frequency of CD in developing countries imposes a significant socioeconomic cost due to low per capita income. High consanguinity and a high occurrence of sporadic cases suggest the involvement of both, genentic and non-genetic factors and a high potential for primary prevention. This study provides a baseline for future molecur genetic study for the broader understanding of CD.

Chapter # 1

Introduction

1.1 What are congenital deformities?

According to the World Health Organization (WHO) fact sheet of 2012, congenital deformities (CD) are structural and functional deformities. It also includes different metabolic disorders that appear at the time of birth (WHO, 2012). Congenital deformities were classified into major and minor deformities. Based on their expression, they were divided into lethal, severe, and minor deformities, whereas the severe and lethal are known as major deformities (Samina et al., 2010; Czeizel, 2005)

Congenital deformities are classified into two types: structural and functional. Typically, structural deformities manifest during the first trimester of embryonic development (Desilva et al., 2016). While structural CD refers to conditions in which the body's shape is altered, such as cleft palates, limb abnormalities, and neural tube defects. Functional CD refers to conditions in which a specific organ or body portion is impaired (Taylor et al., 2020). Birth defects can be isolated deformities or syndromic that increases the risk of newborn mortality and morbidity (Francine et al., 2014). These are the leading cause of disability and death in both developing and developed countries.

Structural deformities were classified on the basis of tissue development. Some of them arose before the development, like malformation and dysplasia, while others arose after the tissue development occurred, for example, deformation and disruption (Laury et al., 2007). Some of the CD only affect a single organ system, while others affect more than one body part or system (Sawardekar, 2005; Walden et al., 2007).

1.2 Prevalence of congenital deformities

According to a population-based surveillance program, 2% of births have structural deformities (Feldkamp et al., 2017). But this ratio increases during the first year in the form of deformities in different body organs like the heart, urinary tract, and other structural deformities (Priya et al., 2018). These are more common in stillborn infants than in live-born infants. There is a higher chance of chromosomal deformities in around half of the spontaneous abortions (Liao et al., 2009).

The prevalence rate varies as well among low- and middle-income countries, and developed countries also show similar results. In developed countries, the prevalence rate for all genetic deformities was 39.7 per 1,000 cases, while it was 82 per 1,000 in low-income countries (Butt et al., 2013).

The prevalence rate of congenital deformities varies from country to country across the world. In Japan, it was reported at 1.07%, while in Taiwan, it was as high as 4.3%. It varies from region to region because of the involvement of different factors like social, etiological, and economic factors (Temtamy et al., 1998; Biri et al., 2005).

The prevalence of the organ-specific deformities also varies from region to region. The overall prevalence of neurological disorders was found to be 6.5%, with the exception of an increase in their incidence. The incidence of congenital deformities was found to be 3–7%. South Africa has 1.49%, England has 2%, and the United States has 2-3%. In India, overall, it varied from 0.3% to 3.6% (Parmer et al., 2010; BBS, 2011).

Giamipietro et al., (2009) described that the vertebral deformities had a prevalence rate of 0.5–1 per 1,000 cases. But it did not include stillbirths and terminated pregnancies. According to other studies, the prevalence of congenital limb deformities ranges from 4.9 to 13 per 10,000 live births (Mano et al., 2018). According to a report, in Brazil, 24,000 newborns were found to be associated with congenital deformities between 2010 and 2019. Among them, the most cases were related to limb defects (24.4 cases per 10,000 live births). Heart defects accounted for 8.4 of every 10,000 cases, while oral defects accounted for 6.1 of every 10,000. Organ deformities were 4.6 per 10,000 live births (cardos-dos-santos etal., 2021).

A study was conducted in a hospital in Nigeria, where the admitted neonates with random diseases were taken into account. The duration of the study was 5 years, and during that period, a total of 1057 patients were reported. There was a high ratio of patients with congenital deformities, accounting for 67% of the total cases observed. Among those cases, the most frequent were those related to cardiovascular defects, which accounted for 20.9% of the total cases observed. Following that, digestive system anomalies were found to account for 17.9% of all cases (Ajao and Adeoye, 2019).

1.2.1 Mortality and morbidity rates of congenital deformities

The mortality and morbidity rates in low- and middle-income countries are high as compared to those in developed countries. A total of 95% of the deaths due to CD occur in low-income countries (Chinta et al., 2014; Ndibazza et al., 2011). An estimated 504,000 deaths were recorded across the world because of congenital deformities. It was reported by the Global Burden of Disease 2010 (Murray et al., 2012).

A recent report discussed that congenital deformities contribute 7% of neonatal deaths and 25.3–38.8 million disability-adjusted life years (DALYs) across the world. According to WHO, congenital deformities were ranked 17th in the Global Burden of Disease (Guthold et al., 2021).

A report was generated from Guatemala; according to that report, one-third of the deformities were because of the lack of prenatal care, and 2% of the neonatal deaths were because of congenital deformities. In that report, 67% of the cases had neurological bases, and 15% were cleft lip and cleft palate cases (Figueroa et al., 2020). Another report from India indicated that 8–15% of perinatal deaths and 13–16% of neonatal deaths were due to congenital deformities. Those deformities lead to mortality, child morbidity, and adult morbidity (Taksande et al., 2010). Modell et al., calculated the mortality rates because of the congenital deformities, and they found that mortality ratios under age 5 were underestimated by fourfold compared to the original numbers.

According to the World Health Organization's statistics, the mortality rates for children in the African region were 5%. In South Asia and East Asia, it accounted for

7%, while it reached up to 19% in the European region. In China, it was estimated at around 11%. (Soleman, 2020). In Indonesia, congenital deformities accounted for around 5.7% of the total infant mortality and 4.8% of the child mortality.

A study was conducted in Malta, where congenital deformities contributed 36.7% of the neonatal mortality (Gatt et al., 2015). Another study was conducted in Nigeria, where neonatal mortalities with congenital deformities were recorded at around 10.4% (Ajao and Adeoye, 2019). According to WHO, congenital deformities were the leading cause of neonatal deaths, accounting for 11% of all neonatal deaths (Boyle et al., 2018).

A study published in 2016 by the current birth defect surveillance programme found that the data was unreliable and that congenital deformities were underreported when compared to estimated data (Lebese et al., 2016). A comparative study was conducted that compared the past and present scenarios of the mortalities caused by congenital deformities; according to that, the deaths have decreased to 2.4 million in 2019 compared to 4.7 million in 1990. But the proportion of deaths among children under age 5 increased to 46% as compared to 37% in 1990 (Bhutta et al., 2014).

According to the Pan-American Health Organization, CD is thought to be responsible for 20% of all child fatalities (Roncancio et al., 2018). In Argentina, CD is reportedly responsible for 28% of all baby deaths (Bronberg et al., 2019). Infant death rates in Iran have a 21% CD rate (Maryam et al., 2017). Around 3.3 million children under the age of five die from birth abnormalities, while 3.2 million are permanently disabled (Juliet et al., 2011).

1.3 Types of congenital deformities

Congenital deformities are categorised on the basis of the part of the body they are associated with, like neurological, musculoskeletal, neuromuscular, vision, sensory neural, limb defects, and deformities associated with the kidney, heart, and urinary tract.

1.3.1 Deformities of central nervous system

Congenital deformities of the central nervous system are those of the brain and spinal cord that occur during the developmental process. The majority of central nervous system (CNS) disorders occur due to the inability of the neural tube to close during the third and fourth weeks of the developmental process. Different neural tube defects include spina bifida occulta, meningocele, milo meningocele, and encephalocele. The most prominent of them is spina bifida, which has two types: spina bifida occulta and spina bifida cystica. Spina bifida occulta is a defect of the vertebral arches that does not involve meningeal protrusion, whereas spina bifida cystica does (catibusic et al., 2008).

Annually, 300,000 babies are born with neural tube defects (NTD); among them, 88,000 face death, while the remaining face disabilities for the rest of their lives (Pandey et al., 2021). The incidence of foetal CNS deformities was about 0.1%–0.2% in live births, but its occurrence was relatively high in the case of stillbirth, which reaches 3–6% (Milani et al., 2019).

According to research conducted, the incidence of neural tube defects around the world is 1 in 1000 live births). The most common cause of neural tube defects is a

combination of genetics and environment. Some other minerals, like folic acid deficiency, play a crucial role as well. Other maternal factors are equally important, such as obesity, maternal diabetes, and the medicines taken by the mother, such as antiseptic drugs (Yerby, 2003; Huang et al., 2017).

In the CNS, neurological disorders are the most prevalent. The most prevalent and significant CD is a neurological disorder (Eke et al., 2016). A typical neurological condition known as mental retardation or intellectual disability results from deformities in the structure or function of the brain. The frequency of intellectual disability is 1-3% worldwide, with underdeveloped nations having the highest prevalence due to malnutrition, environmental factors, and inadequate health care. A diagnosis of intellectual disability can be made by identifying specific phenotypic symptoms such as delayed speech and seizures (Redin et al., 2014). Genetic disorders such as aneuploidies, copy number variants, tandem repeats in particular genes, and chromosomal aberrations like Down syndrome, Edwards syndrome, and Patau syndrome are among the many factors that contribute to intellectual disability (Ilyas et al., 2020). The most frequent cause of mental retardation in humans is Down syndrome, which is a trisomy of the 21st chromosome (Ghosh et al., 2009). Down syndrome occurs in 1 in 800 live births worldwide. The two main causes of Down syndrome are meiotic non- disjunction and advanced maternal age (Patil et al., 2014). Meiotic non-disjunction causes Down syndrome in around 95% of instances.

It is necessary to detect these brain deformities, but their detection is a very complex process. Anatomy scans during the second trimester can detect certain brain deformities, but they have their limitations. Magnetic resonance imaging (MRI) is a technique used to diagnose defects in detail. Although brain deformities can be

detected using a highly complex ultrasound (US) screening procedure, Anatomy scans during the second trimester can detect certain brain deformities, but they have their limitations. Magnetic resonance imaging (MRI) is a technique used to diagnose defects in detail. Although brain deformities can also be detected through screening ultrasounds (Kruger et al., 2019).

Table 1.1 Worldwide prevalence of central nervous system deformities

Prevalence of CNS deformities				
Prevalence rate	**Sample size**	**Country/Continent**	**Year**	**Reference**
28%	124	India	2022	(Sinha et al.,2022)
23%	365	Malaysia	2022	(Tan et al., 2022)
1.00%	72	Nigeria	2016	(Eke et al., 2016)
34%	72	West-Nigeria	2015	(Singh et al., 2015)
2/1000	12000	Europe	2010	(Dolk et al., 2010)
28%	275	Brazil	2016	(Almeida et al., 2016)
41%	1189	Pakistan	2022	(Bibi et al., 2022)

1.3.2 Sensorineural/ear defects

The sensorineural defects are also prominent congenital deformities. The ear is divided into three parts: the external, the middle, and the internal. Ear defects can be structural, like the absence or underdevelopment of the pinna of the ear, but more prominently, these defects are due to the loss of function of the middle or internal ear. According to recent studies, ear defects cause a 50% decrease in ear volume, a 19% decrease in ear length, and about a 28% decrease in ear width. External ear defects lead to a decrease in the self-confidence of the patients and cause problems in their communication abilities (Kim et al., 2019).

Congenital deafness can affect one ear (unilateral) or both ears (bilateral). According to a recent study, unilateral causes affect 29% of cases while bilateral causes affect 71% of cases (calkoen et al., 2019). Congenital loss of hearing occurs in 1-3/1000 live births. The normal hearing threshold is 20 dB HL (decibels hearing level). Around 3 in every 1000 people have hearing loss greater than 20 dB HL. When there are other risk factors present, the incidence increases. The risk factors that are found to be associated with this congenital deafness are the family history of the subject, other deformities linked with the deafness, and the other infections of the host (Gettlefinger and Dahl, 2018).

1.3.3 Congenital limb defects

The majority of the congenital limb defects are sporadic (they do not run in families), while few of them are familial (Lenz, 1980). While looking at the etiological bases, limb deformities are classified into chromosomal, environmental, and genetic deformities (Gold et al., 2011). In the broadest categorization, limb defects are divided into transverse and longitudinal limb defects (Wilcox, 2015).

Although there are different types of limb defects, one of them is limb reduction. It is defined as the shortening or total absence of a limb or the absence of a specific part of a limb. The most common form of limb reduction is upper limb reduction, which accounts for 59% of the limb reduction deformities (Dillingham et al., 2002).

Syndactyly also comes under the category of congenital defects of the limb. It is the osseous fusion of the adjacent digits in the upper or lower extremities. It results in "super" or "webbed" digits. It may be simple or complex. If there is fusion of bones, it is called complex; otherwise, it is simple. It may also be complete or incomplete. If it extends toward the tip of the digits and also involves the fusion of nails, then it is called complete syndactyly. However, if it does not extend to the tip of the digit and there is no involvement of nail fusion, it is referred to as incomplete syndactyly. But if there are accessory bones or phalanges in it, then it is described as complicated syndactyly (Buck–Gramcko, 2002). It is found in 1 in every 2,000 live births. It contributes 20% of the total hand deformities, and it is the most common hand anomaly (Little and Cornwall, 2016). Mano et al., (2018) discussed in research that the prevalence of congenital limb deformities was 4.9–13 per 10,000 live births.

A paper published in Europe discussed the prenatal mortality along with the upper limb deformities, lower limb deformities, and both limb deformities. The results explained that there was the highest number of terminations when there was the presence of both limb deformities, and the occurrence of live birth was rare when both limb deformities were found (Farr et al., 2020).

1.3.4 Congenital eye/visual impairment

According to the International Classification of Disease 11 (ICD 11), vision impairment is classified into two groups: distance vision impairment and near vision impairment. Distance vision impairment is further classified into mild, moderate, severe, and blindness types. People with vision impairments do have either congenital or acquired vision loss (ICD 10). According to WHO, at the start of 2020, around 19 million children under the age of 15 were visually impaired, and 1.4 million cases were irreversible. It was estimated that 1.4 million cases were preventable (Ackland et al., 2017).

In low- and middle-income countries, the prevalence was found to be 0.2–7.8 per 10,000 people, but in developed countries, it was around 6 per 10,000 in children under the age of 15 (Courtwright et al., 2010; Rahi and Gilbert, 2010). There is a high prevalence of additional disabilities in children with visual impairments. According to a study, it was found to be around 68%. According to a community-based study in India, the prevalence of childhood blindness was 0.6/1000 to 1.06/1000, and for visual impairments, it was 2.5/1000 to 13.6/1000 (Kemmanu et al., 2016; Tityal et al., 2003).

There were certain causes associated with the visual impairments. Some of them had both hereditary and intrauterine causes (Hayakawa et al., 1999). A comparative study was conducted in Pakistan in which blindness and vision impairments in 1990 and 2017 were taken into account, and as a result, the visual impairments in 2017 were found to have increased by 55% as compared to 1990. It was the 10th highest increase among other causes of health loss (Hassan et al., 2017).

Vision is a key factor that communicates with people socially. It shows the

importance of this natural sensory modality (Jindal, 2004). Impairments in vision can increase the risk of disability by increasing the likelihood of being involved in an accident. Visual impairments also lead to severe personal life experiences like loneliness. A person also faces issues with social interactions.

1.3.5 Neuromuscular congenital defects

These are the defects that affect the functions of the muscles due to problems with the nerves and muscles in the body. It involves one kind of heterogeneous group of a disease known as cerebral palsy.

1.3.5.1 Cerebral palsy

Cerebral palsy (CP) is a group of permanent, but not changing, disorders of movement and motor function that are due to non-progressive interference or abnormalities of the immature brain (Cans et al., 2007). It is a rare condition that affects muscle functioning. In cases of cerebral palsy, prenatal risk factors were found to be 75%, and neonatal risk factors were 10–18% in all CP cases (Reddihough and Collins, 2003).

The prevalence of cerebral palsy around the world is approximately 2 in every 1,000 live births. But in Europe, it is found to be slightly less, at 1.64 per 1000 live births (Stavsky et al., 2017; Periera et al., 2020).

1.3.6 Musculoskeletal defects

A congenital musculoskeletal defect is actually a defect of muscle or bone that affects the extremities or the vertebral column. It affects both the upper and lower extremities. It involves different types of muscular dystrophies, like Duchene and Becker muscular dystrophies.

1.3.6.1 Duchene muscular dystrophy

It is the most severe form of inherited muscular dystrophy. It results in muscle fibre degeneration due to a mutation in the dystrophin gene. It starts with muscle weakness, progressively increases in intensity, and finally results in restricting the patients to wheelchairs (Bello and Pegoraro, 2019). It is an X-linked recessive disorder affecting 1 in 5,000 to 1 in 6,000 live male births. Its prevalence is 10 cases per 100,000 males, and it remains the same between the different regions across the world (Ryder et al., 2017; Mah et al., 2014). Patients with this disease require intensive care. In the UK, special services are given to the patients, and community therapies are provided (Cany et al., 2021).

One study in India reported that musculoskeletal defects accounted for one-third of all congenital deformities. Another study in Iraq indicated that musculoskeletal defects were found around 27.5% of the time (Sarkar et al., 2013; Vatankhah et al., 2017). This type of deformity creates a huge burden on the personal, social, and family relationships of the individual. If not treated properly, the person becomes completely dependent on others for daily life activities. Musculoskeletal defects involve disorders like developmental dysplasia of the hip (DDH), talipes equanivaris, congenital scoliosis, and pectus excavatum.

1.4 Causes of congenital deformities

There are so many factors that play a role in the occurrence of a congenital deformity. When it comes to prenatal deformities, it appears that multifactorial causes are one of the main concerns. Multifactorial causes are those in which more than one factor contributes. A less common factor is genetics; here, genes play an important role and continue to express themselves in future generations. Some environmental factors also play a crucial role, sometimes increasing or decreasing the expression of the particular deformity. Some causes are idiopathic (those with unknown origin). Genetic factors contribute 10–30% of the different congenital deformities, whereas environmental factors contribute 5–10%. Different multifactorial inheritance accounts for 20-35% of causes, with the remaining 30-45% being idiopathic (Kumar, 2008).

Some other factors that are involved in causing these congenital deformities are socioeconomic (those depending on the living conditions of the patients). Certain demographic factors are also important (vary from region to region and country to country). Nutritional factors, including the health and fitness of the mother, are also equally important. Exposing the mother's body to different radiations and chemicals also plays a major role in increasing the intensity of these defects.

According to a report from Birmingham Women's Hospital in Boston, the various causes of congenital deformities were chromosomal mutations (involving an increase or decrease in the chromosomal number or addition and deletion in some part of the chromosomal structure). Certain multifactorial factors and environmental factors were also evident. Some other rare factors were also taken into account. Among those factors, vascular disruption and complications of the twinning process

were common. The duration of the study was 40 years (Toufaily et al., 2018).

Chemical substances like lead, mercury, and arsenic were also found to be associated with the congenital deformities. Those chemicals were very hazardous and produced different kinds of deformities in the newborns. Mercury was found in some fish. If consumed as food by the mother, it resulted in some serious defects related to mental deformities. It was found to be associated with CP and other kinds of mental retardation. Lead was reported to cause some neurological issues and growth retardation (Shaw et al., 2003).

It was a reported fact that those populations with consanguineous marriages (marriages among very close relatives, like cousin marriages) had more congenital deformities than the populations without consanguinity. So it was also one of the main causes of those congenital deformities (Baird et al., 1991).

Recently, a study was conducted in Ethiopia to find out the associated risk factors with different congenital deformities. The study showed that there were 45% cases related to the health issues of the mother (mother's health was not good before the child delivery or she was struggling with some infection).

1.5 How To diagnose and prevent congenital deformities?

1.5.1 Diagnosis

For the management and rehabilitation of patients with congenital deformities, it is necessary to find out the actual cause or causative agent of these deformities. As a result, only the actual cause identification can lead to anomaly prevention. It would be relatively simple to deal with those deformities, and it would be satisfactory to take calculated measures to prevent and avoid these deformities in future generations, as well as to reduce their severity in current cases of congenital deformities (Usman et al., 2014).

There is a lot of difficulty in diagnosing and estimating the actual cause of congenital deformities because there is a lack of diagnostic capacity, and many of those cases are not reported properly, and in some cases, there is underreporting. There is also another factor in that there is a lack of awareness among different populations where these defects appear, and people really don't know how to deal with these kinds of situations. All these factors make it more difficult to diagnose these cases (Ndibazza, 2011; Lawal et al., 2015).

There were some techniques available in the past where there was some possibility of diagnosing those defects, but they were valid up to a certain point. Fetal anomaly scanning was one of them, which was quite helpful in reducing the chances of certain serious deformities and was used to maximise the survival rate of those who were born with those serious issues (Sairam et al., 2001).

Prenatal diagnosis was helpful in some cases and helped improve the preoperative conditions, but in other cases, it was not meant to be helpful at all. For

the pregnancies at increased risk for chromosomal deformities, chorionic villus sampling (CVS) was used during the first trimester of pregnancy, while during the mid-trimester another technique, amniocentesis, was in use for the prenatal diagnosis (Gibbs, 1992). But the current methods of diagnosing congenital deformities are highly dependent on imaging methods such as ultrasound (US) or magnetic resonance imaging (MRI). However, one of the limitations of the US is that it has been discovered to be highly sensitive and can harm the fetus. For some cases, like congenital diaphragmatic hernia, the sensitivity level reaches up to 70%. So, it makes it highly unreliable to use (Burgos et al., 2018).

The most reliable and trusted method of diagnosis is foetal diagnosis using maternal body fluids. Circulating placental mRNA during the 4^{th} week of gestation can be used to diagnose any kind of deformity present in the fetus. It is much safer than the other techniques (Dennis et al., 2007). Micro RNAs (short sequences of 22 nucleotides in length) were found to be associated with foetal development, and they were used to diagnose congenital heart diseases. They were found to be an efficient method of diagnosing these sorts of deformities (Smith et al., 2015).

Few new techniques are under consideration, namely microarrays and genome sequencing. These are being used in a few countries to identify different kinds of genetic deformities with precision. So, these are the ones with future perspectives.

In order to identify the CD in the foetus caused by chromosomal abnormalities, nuchal translucency screening is employed. Chromosome abnormalities are linked to increased nuchal translucency thickness between the 11th and 13th weeks of pregnancy (Steinhard, 2010). Results for nuchal translucency are only as accurate as the examiner's abilities. Even normal karyotypes with thickened

nuchal translucency can be associated with chromosomal abnormalities (Jackson and Rose, 1998). Trisomy 21 (Down syndrome) is frequently diagnosed via nuchal translucency measurement (Wald et al., 2008).

1.5.2 Prevention

The removal of risk factors can ultimately lead to the prevention of congenital deformities. So, after a proper diagnosis, the next step is actually dealing with these risk factors to minimise them, if not totally eradicate them. Another approach is to maximise survival factors. If the protective factors are increased, this will ultimately lead to an increase in the patient's survival against the potential threats. Some daily life habits, such as eating a proper and healthy diet and maintaining a healthy body weight, can help the patient fight the disease and its risk factors. Consumption of essential vitamins also improves immunity. Certain minerals, such as folic acid intake, can be quite valuable as well.

Protecting the body against environmental poisons like radiation, different kinds of pesticides, and harmful chemicals can help protect against congenital deformities. Avoiding certain sensitive drugs during pregnancy can also help protect against potential risk factors (WHO, 2016).

In some cases, after a prenatal diagnosis, the only way to avoid an anomaly is to terminate the pregnancy (because delivering such a child may result in more disastrous consequences than terminating the pregnancy). However, there are a few other options, such as vaccination or immunisation of the mother against some serious issues. In the USA, to avoid congenital Rubella syndrome, immunisation was taken into account (Cutts and Vynnycky, 1999).

1.6 Aims and objectives of research

As described earlier, there was not much work done on the topic of congenital deformities in tehsil Kot Addu, so aim was to conduct research in respective tehsil to know about different kinds of congenital deformities and their prevalence.

There are a few objectives associated with this aim as well. These are:

- To find out the prevalence patterrn of different types of congenital deformities in Kot Addu tehsil,
- To find out the familial/sporadic ratio of the congenital deformity cases,
- To learn about the consanguinity of the parents of the congenital deformities,
- To know the role of different socioeconomic and demographic factors with respect to congenital deformities,
- To know the relation of parental age with respect to congenital deformities,
- To know the prevalence of sporadic/familial cases among the congenital deformities.

1.7 Congenital deformities in Pakistan

In Pakistan, the prevalence of congenital deformities is relatively high as compared to the overall world statistics. It is due to various factors such as the fact that close marriages are quite common in Pakistan and people prefer to marry within their close relatives. Low socioeconomic factors are also equally important because the people in most of the areas are poor and struggling to achieve their basic rights. Some maternal factors, such as maternal health and prenatal maternal care, are also involved. Mothers also face some nutritional deficiencies as well. In Pakistan, congenital deformities contributed to 6–9% of the perinatal deaths (Khan et al., 2015; Bhatti et al., 2019).

Congenital deformities are under the control of some factors. Among those factors, the genetic factor is quite evident. Some genes are involved that play a vital role in the occurrence of certain genetic deformities that usually run in families and affect the upcoming generations. Other factors, such as the environment, are less important in some cases. The environment may help in increasing or decreasing the intensity of the cause. An environmental cause is when the mother may be affected by or exposed to certain infections, resulting in the neonate's health deteriorating. Hardly 10% of congenital deformities are under the control of this environmental factor. But a less common cause of genetic deformities' occurrence is the genetic one.

Chromosomal mutations are also a factor that plays a crucial role in causing different congenital deformities. In this regard, the mutation in chromosomal number results in the addition or deletion of chromosomes, as a result of which certain chromosomal abnormalities occur, such as Down syndrome. Mutations also result

from the addition or deletion of certain parts of chromosomes or chromatids .

According to a recent paper, a study was conducted in a civil hospital in Karachi, where the prevalence of congenital deformities was noted to be 2.22%. There were certain kinds of deformities that were more frequent as compared to the others. Most of the deformities that were dominant were related to the central nervous system (CNS), of which anencephaly was the most dominant. Other congenital deformities were also present but in a slightly lesser ratio, such as deformities related to the kidney, gastro-intestinal tract, and skeleton (Anbreen et al., 2021).

Recently, a paper was published describing a study conducted in Khyber Pakhtunkhwa (KPK), where the total number of cases taken into account was 1,189. There were different categories of congenital deformities reported. There were some cases that were discovered to be more common than others.The majority of reported cases involved CNS deformities with neurological origins.They were accounted for by almost 40.9%, and the second-highest defects were related to the limb and were around 24.6%. Other musculoskeletal defects accounted for 8.9% of the total. Some congenital deformities, accounting for 8.5%, had a sensory neural basis. The visual impairments and blindness were also present, but in lesser amounts as compared to the other defects. Those were 3.3%. There were also certain other factors reported as well, like the presence of close marriages among the parents of the patients with congenital deformities. There was 66% consanguinity among the congenital basis deformities, which was quite high (Bibi et al., 2022).

Another study was conducted on the congenital limb defects in the Sindh province of Pakistan; according to that, 165 cases of congenital deformities were taken into consideration, bringing the total number of affected individuals to 315

(when familial cases were taken). According to the study, the most common limb defects were polydactyly, which accounted for 48% of all cases reported.The second-highest deformities were found to be associated with the cases of syndactyly that accounted for around 20 cases, or 6% of the total (Lal and Malik, 2015).

A research project was done in the north-west areas of Pakistan, where the main focus was to observe the congenital defects of the limb. There were a total of 153 individuals; the most frequent cases that were reported belonged to the category of polydactyly. They were 95% of the total number of cases. The other cases were related to syndactyly, which accounted for 9% of the total cases observed (Ullah et al., 2015).

Rasool et al., (2021) carried out research in a tertiary-care hospital for the congenital deformities of kidney and urinary tract infection, where a total of 150 cases were taken into consideration, and of those, 10 individuals were found with deformities. The most cases were related to kidney deformities (80%). Ultrasonography was applied to those deformities. Hydronephrosis was the most commonly observed anomaly.

Another study was carried out to determine the prevalence of congenital deformities in paediatric patients in the Punjab. According to that study, cousin marriages (of the subject's parents) were the most common factor among the patients with congenital deformities. Moreover, the most frequent cases were related to the cleft palate. Other cases were related to hydrocephalus, cleft lip, Down syndrome, and polydactyly. The most important thing about the research was that there was a 1% increase in the prevalence rate per year. Cousin marriages accounted for 69.7% of the deformities. The prevalence of congenital deformities was 14.7%. The main causes of

those deformities were cousin marriages and a lack of prenatal diagnosis due to a lack of facilities in those areas (Langah et al., 2022).

1.7.1 Study Gaps

As far as tehsil Kot Addu is concerned, no work on congenital deformities has previously been done. So, there was a need to establish some research here to know about the different types of congenital deformities. It was important to find out the prevalence of different types of congenital deformities and to know about different demographic variables found to be associated with congenital deformities. So, this will be the first research project in tehsil Kot Addu.

2.1 Studying congenital deformities in district Kot Addu

Kot Addu is a tehsil in the Kot Addu district (it was previously part of the Muzaffargarh district but was recently elevated to the status of a district) in Punjab, Pakistan. It is now divided into 32 (formerly 28) Union-councils.

This tehsil is known as the geographical centre of Pakistan and is located at 30° N (latitude) and 70° E (longitude). This region is 430 feet above sea level. The total length of the tehsil is 3553.1 $^{km2.}$ According to an estimation, 50% of its area is used for agriculture. The most cultured crops are wheat, cotton, and sugarcane. According to the 2017 census, its total population was calculated at around 808,438 people. According to the census, it is the 67th largest city in Pakistan, with a population density of approximately 425.5 people per square kilometre. (Statistics, 2017).

Although different languages and cultures exist here where Saraiki, Punjabi, and Urdu are the most commonly spoken languages, the Saraiki language is the one spoken quite often. The Saraiki culture dominates here, and Punjabi customs are followed here. It is an industrial area where one of Pakistan's famous industries lies. There are only a few power plants here. Kot Addu Power Company (KAPCO) and Lal-Peer Thermal Station are the most famous. The Pak Arab Oil Refinery (PARCO), Pakistan’s largest oil refinery, also lies here. The Tounsa Barrage, located on the Indus River (Pakistan's largest river), is another well-known landmark. There are also a few sugar mills, like Fatima Sugar Mill.

This tehsil was chosen as area of study because it is hometown and birthplace of the researcher. That is why this specific area was selected to study the prevalence

of congenital deformities. Being a resident of the area, it was comparatively easy to deal with the locals.So, data collection was easy. Another reason for choosing this tehsil was that there had not been enough work done on that particular topic previously. So, it was something new to look for and study.

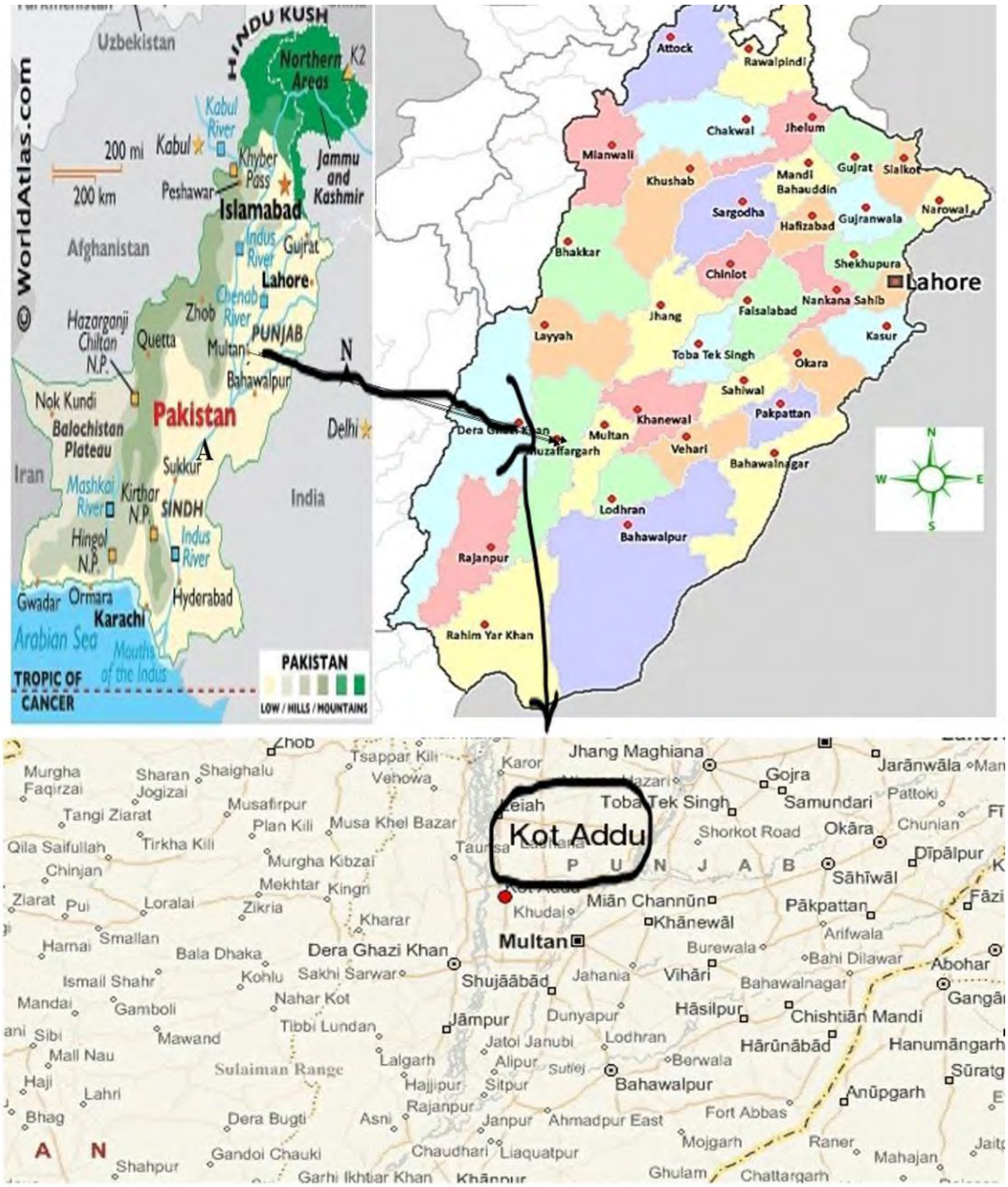

Fig. 2.1. Map of Kot Addu, Punjab, Pakistan.

Source (google maps)

2.2 Methodology

Methodology covers all the processes through which research gone and data was collected and analysed to achieve results. Because the entire procedure was lengthy, it is divided into several steps, which were as follows:

2.2.1 Generating data collection performa

Prior to going for the data collection, it was necessary to generate a performa that included all the questions needed to be asked while collecting the data for the patients with CD. Although it was already available in the Human Genetics Department (Biological Sciences) of Quaid-i-Azam University, Islamabad, still there was a need to add some extra rows for the additional information that was a requirement for the fieldwork. So, a few extra columns were added. The performa covered all aspects of the subject (having a congenital deformity), including the name of the patient, the local address of the subject, the union-council of the subject, origin (whether the subject belonged to a rural or urban area), and the age of the subject. The performa also covered information regarding the cast (Qoum or Biradri) of the subject, the mother tongue of the subject and his relatives, and the marital status (married or single) of the subject. It also involved a few socioeconomic factors as well, like, economic situation of the subject and his family (whether poor, low, mid, low-mid or high). It also included the subject's or his caretaker's occupation (means of earning). There was also information regarding whether the photo of the subject was taken or not. There was also some information about the sporadic (only one person in the family was affected) or the familial (more than one person of the family was suffering from the same type of congenital anomaly). Parental age at the time of the

subject's birth (age of the mother and father) was also part of that particular performa. Information regarding the consanguinity of the parents was also part of the questionnaire. Data waere also taken about the nature of different consanguineous relationships like father–brother-daughter (F.B.D.), father-sister-daughter (F.S.D.), mother-sister-daughter (M.S.D.), mother-brother–daughter (M.B.D.), 2^{nd} cousin, and no consanguinity at all. There was also some information regarding whether there had been any pregnancy events of the subject or not. There was also a discussion about the parity order of the subject. The performa also described the total number of affected individuals in the pedigree and the total number of affected individuals in the subject generation. Data about the total number of households, the number of males and females, and the number of people under the age of 18 were also taken into consideration.

2.2.2 Ethical approval

After the proper performa setting, there was a need to ask for permission for the research from the Ethical Board of Quaid-i-Azam University, Islamabad. As a result, the ethical board of the concerned university granted this Human Genetics project ethical approval. According to that permission, project was only allowed to collect data while keeping in mind all the ethical values of the concerned families. The project was granted permission to collect data as per the terms and conditions.

2.2.3 Consent approval from family

After approaching the family, the first and most important part of the research was to inform them about the research purpose for visiting their place. It was an important part of the research to get their confidence in the research, and it was necessary to tell them that all their ethical values would be kept in mind. Oral consent approval was obtained. There was a mixture of reactions among the different families: some of them allowed wholeheartedly to take the data, some of them were ready to share the personal information of the subject but not allowed to take their photos; and a few of them were reluctant to share their information at all. So, keeping in mind the ease and comfort of the family, data was taken from the families.

2.2.4 Sampling method

It was a kind of population-based study of congenital deformities, and patients were approached through door-to-door surveys. The study was conducted across 7 different union councils: Daira Din Pannah, Ahsan Pur, Kot Addu, Pattal, Haider Ghazi, Hinjrai, and Drigh. The duration of the study was 4 months, from June 2022 to

September 2022.

2.2.5 Journey to field visit

After receiving permission, it was a long journey to go on a field trip and look for patients with congenital deformities. It was a kind of door-to-door survey where research was carried out union-councilwise. First of all, hometown union council was visited. It was a very time-consuming process because, prior to approaching the affected family, it was necessary to sort out that family. After sorting it out, as it was a door-to-door survey, there was a need to approach the family while using different contacts and resources. After approaching the family, it was necessary to share all the information and purpose of the research. It was also critical to obtain their willingness to share the information and to persuade them of the importance of their family information for this research. After all the information and discussion, it was really up to the family whether they wanted to share their valuable information or not, because the ease and comfort of the family was the primary objective. With the consent of a willing family, data was collected with all the necessary information. All the data about the name, address, union council, age, marital status, socioeconomic status, father's occupation, family history of deformities, parental age at the time of the subject's birth, and the parental consanguinity and pregnancy event of the subject (if any) was obtained.

While collecting the data, it was necessary to notice all the signs and symptoms of the subject and to write those signs and symptoms on the backside of the questionnaire. It was necessary for the proper identification of the family. Gathering all the information about the subject's life, way of living, and the kinds of difficulties subject faced.

2.2.6 Pedigree construction of affected family

Pedigree construction was also part of the plan. A pedigree provides a brief summary of the family and its members, as well as information about the affected individuals. A three-generation pedigree was constructed for all the subject families, involving the generation of the subject, his father's or mother's siblings, their grandparents, and their children (if any). Square boxes in the pedigree showed males while the circular boxes displayed females, and filled boxes indicated the number of affected individuals in the family. On the backside of each performa, a 3-generation pedigree was drawn. Pedigree also included information about the consanguinity of the parents of the subject and the different nature of consanguineous relationships, which was also written along with the horizontally drawn marriage lines.

2.2.7 Data Storage, analysing and statistical analyses

Along with the performa filling, there was a requirement to save the data gathered from various performas. So, for that purpose, MS-Excel was used to save the data gathered from various performas. The data was stored in the form of so many columns and rows, covering all the aspects of the questionnaire information. The excel sheet shows different columns like: subject name, family ID (a specific number was given to the family for proper identification), local address, respective union-council, rural or urban, occupation of the subject father or subject, the socioeconomic condition of the family, family type (single, nuclear, or extended), contact numbers, family history of anomaly, photos taken or not, parental age at the time of subject birth, parental consanguinity and any pregnancy event of the subject. The total number of affected individuals in the generation, sibship, parity order, and the sporadic or familial

nature of the case was also taken into consideration. It was very similar to the performa.

2.2.8 Classification scheme of congenital deformities

Congenital deformities were claassified into different types on the basis of the part of the body they affect. They are basically divided into six types: congenital deformities of the central nervous system (CNS) or neurological disorders, Sensorineural/ear defects, congenital limb defects, congenital eye/visual impairments, neuromuscular defects, and defects of musculoskeletal origin. Congenital deformities of the CNS involve deformities affecting the brain and spinal cord, involving cases of mental retardation. Sensorineural defects include ear defects and deformities associated with speech problems. It includes the deaf and mute categories. Limb defects include various deformities of the upper and lower limbs. It also involves cases of polydactyly and syndactyly. Congenital impairment of vision includes cases of blindness and other eye deformities where people can see things partially. Congenital defects of neuromuscular types have cases of cereal palsy. Congenital musculoskeletal defects cause a variety of muscular dystrophies. There are some other cases that do not fit into any of these categories, like, oral defects etc. This classification is made after the proper identification of all the cases. A doctor was approached for the identification of different categories of cases. For further confirmation, International Classification of Disease 10 (ICD 10) and the Online Mendelian Inheritance in Man (OMIM) were used.

A total of 295 independent index cases with certain types of genetic deformities were observed in district Kot Addu.

3.1 Demographic distribution of index subjects

3.1.1 Distribution of subjects with respect to gender and familial/sporadic nature

The representation of male subjects was found to be very high as compared to the female subjects in both the rural and urban areas. The percentage of male subjects was 78% (n=230), whereas the percentage of female subjects was 22% (n=65). Most of the cases were sporadic representing 72% (n=214) while familial cases were 28% (n=81) (Fig. 3.1). The distribution of gender wise and familial/sporadic was not statistically significant (Table 3.1).

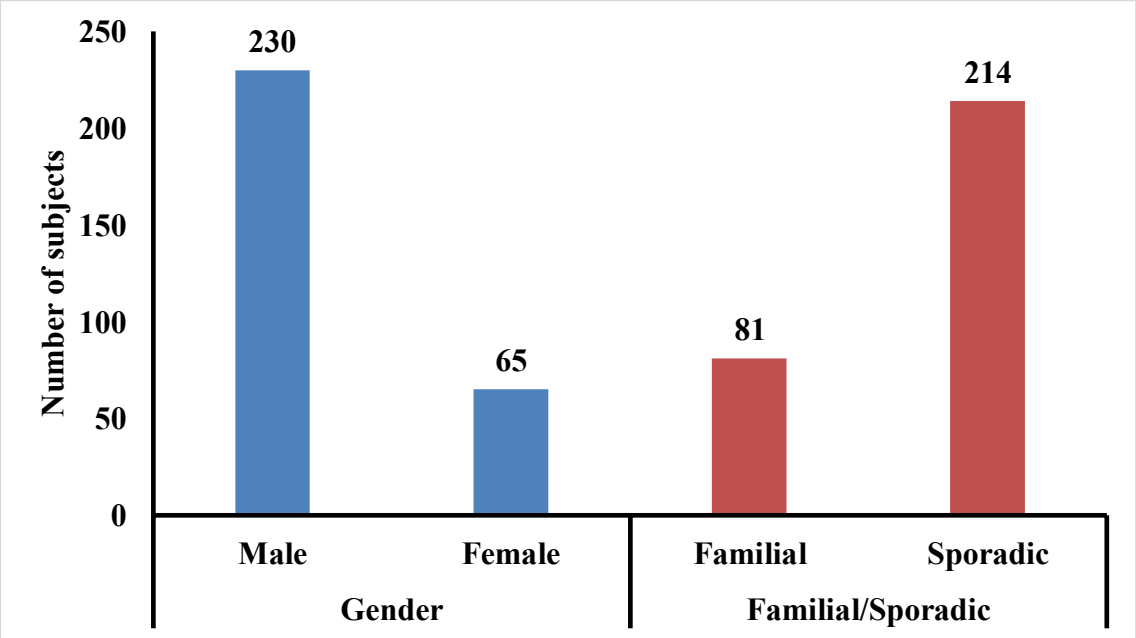

Fig. 3.1. Distribution of subjects with respect to gender and familial sporadic/nature

3.1.2 Distribution of subjects with respect to rural and urban origin

Most of the cases belonged to the rural parts of the district counting 94% (n=277) while urban cases only accounted 6% (n=18). On the other hand, sporadic cases were predominant in rural areas as compared to familial cases and contributed 72% (n=200), while familial cases were 28% (n=77). Similarly, sporadic cases were also dominant in the urban areas and contributed 78% (n=14) whereas familial cases were recorded 22% (n=4) (Fig. 3.2). The distribution of gender wise and familial/sporadic was not statistically significant (Table 3.1).

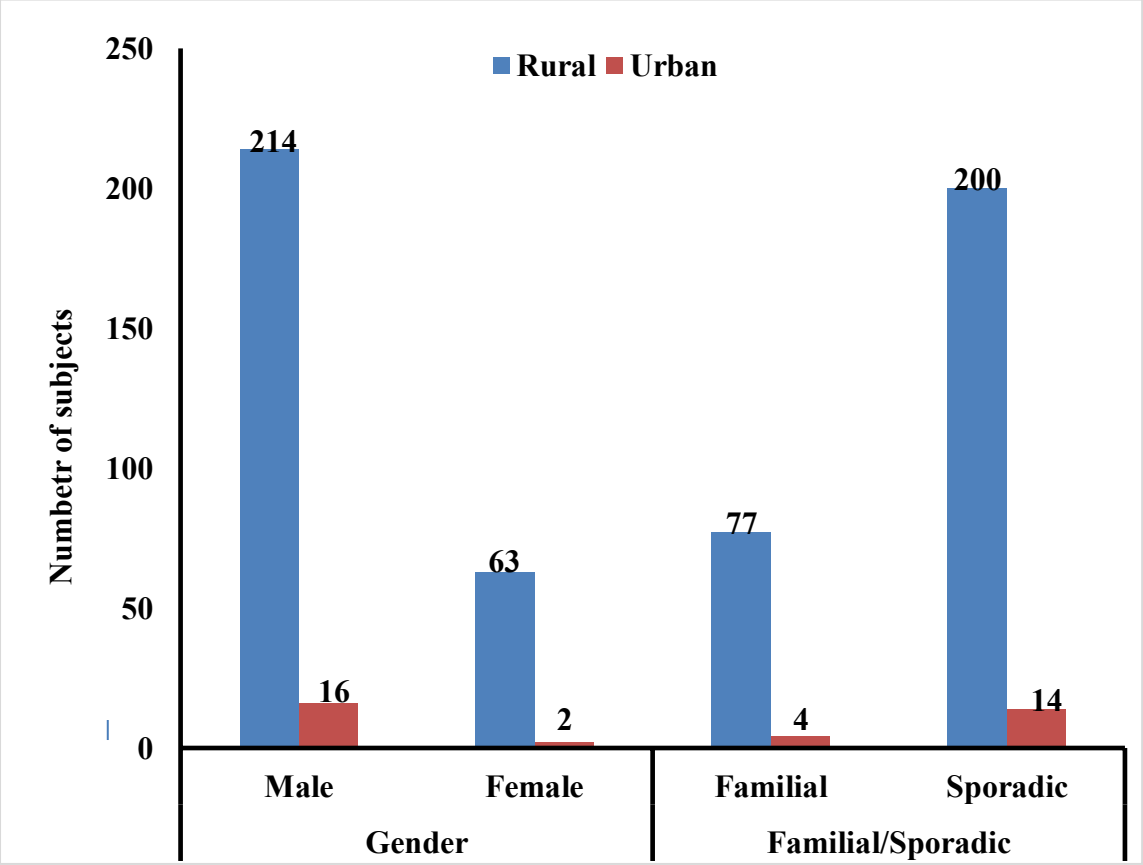

Fig. 3.2. Distribution of subjects with respect to the origin, gender and familial/sporadic nature

3.1.3 Distribution of the subjects with respect to age categories

Subjects were classified into 5 different age categories based on their age categories. The highest number of cases was found in the age category of 11-20 years with a percentage of 36% (n=105). An estimated 25% of cases (n=73) were from the category of age 6-10 years. While 15% (n=44) were from the age category of above 30, followed by 14% (n=42) from 21-30 years and 10% (n=31) from the age category below 5 years (Fig. 3.3). The distribution of gender wise was statistically non-significant but the distribution of familial sporadic was statistically significant (Table 3.1).

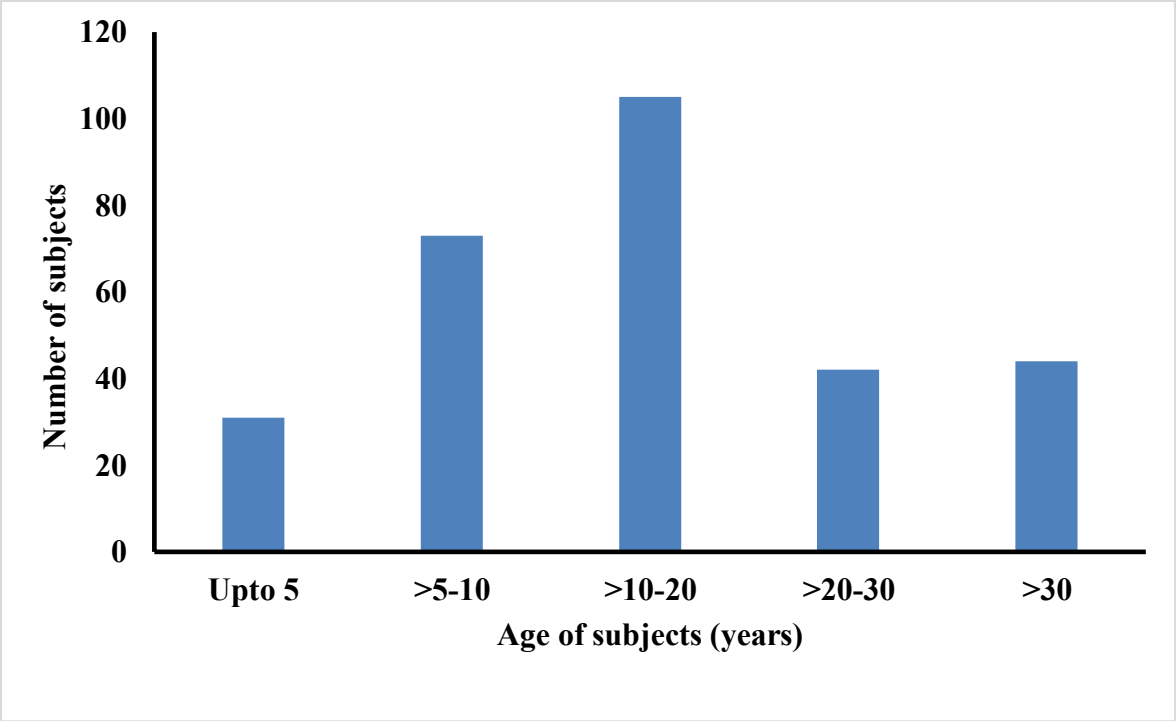

Fig. 3.3. Distribution of subjects with respect to age categories

3.1.4 Distribution of subject with respect to literacy level

The subjects below the age 5 years category were not included and 94% (n=279) subjects were considered for this category of distribution based on literacy level. Most of the cases were illiterate and contributed 86% (n=241) as compared to the illiterate 14% (n=38). From the illiterate category 77% (n=186) were male while 23% (n=55) were females. Literate subjects were further divided into four groups based on their level of education Primary schooling, Middle schooling, High schooling and above High school categories. Middle school category was 47% (n=18) followed by Primary schooling 40% (n=15), above high schooling 8% (n=3) and high schooling 6% (n=2), respectively (Fig. 3.4). The distribution of gender wise and familial/sporadic was not statistically significant (Table 3.1).

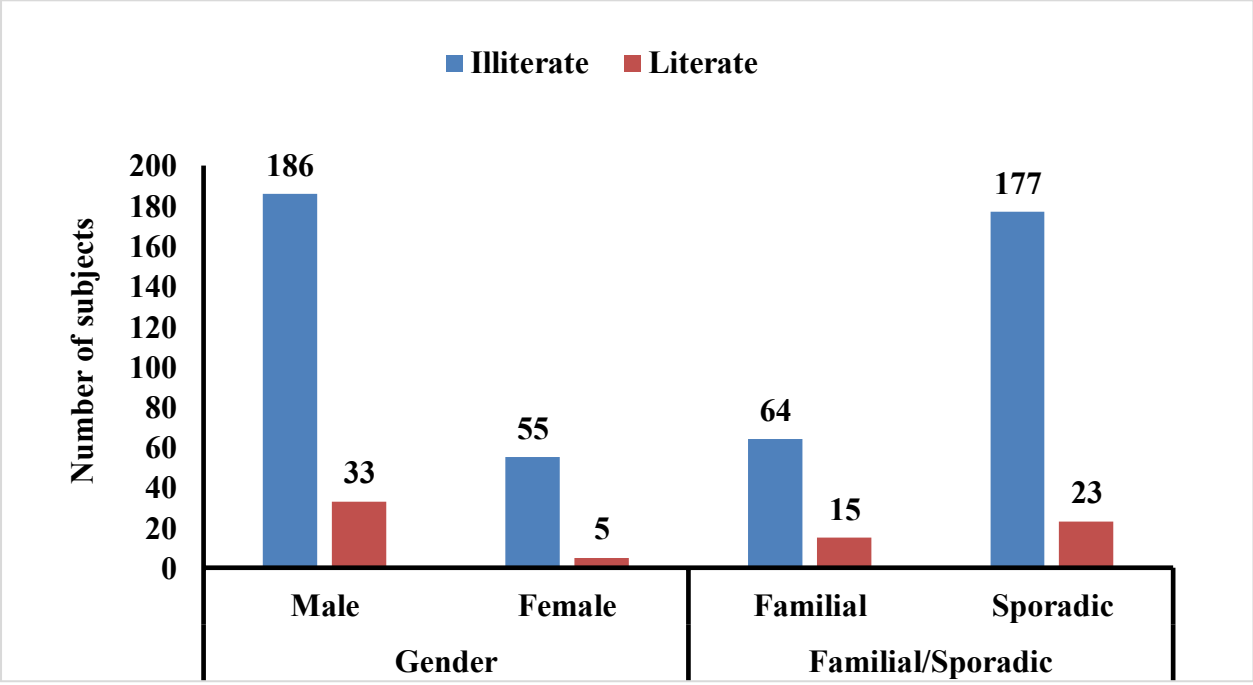

Fig. 3.4. Distribution of subjects with respect literacy level

3.1.5 Distribution of subjects with respect to their guardian's occupation

The occupation of the guardian was considered for this distribution of the index cases. They were divided into 5 categories: Labor, Unemployed, Farmer, Shopkeeper and others. Labors were 31% (n=91). There were 26% (n=78) cases when a guardian was found to be unemployed. The guardians of the 21% (n=61) cases were farmers while 15% (n=43) were shopkeepers and 7% (n=22) belonged to other categories. Other categories included Private teachers and other small Businessmen (Fig. 3.5). The distribution of gender wise and familial/sporadic was not statistically significant (Table 3.1).

Fig. 3.5. Distribution of subjects with respect to guardian occupation

3.1.6 Distribution of subjects with respect to marital status and family type

For the description of the marital status index cases above 18 were considered. Out of 112 subjects, 69% (n=77) were single and 31% (n=35) were married. Another distribution of subjects was made based on their family type whether Nuclear or Extended. According to that distribution, nuclear family type was dominant contributing 78% (n=230) out of the total 295 cases while the extended family type contributed 22% (n=65) (Fig. 3.6). For marital status, the distribution of gender wise and familial/sporadic was not statistically significant (Table 3.1). For family type, the distribution of gender wise was statistically non-significant but the distribution of familial sporadic was statistically significant (Table 3.1).

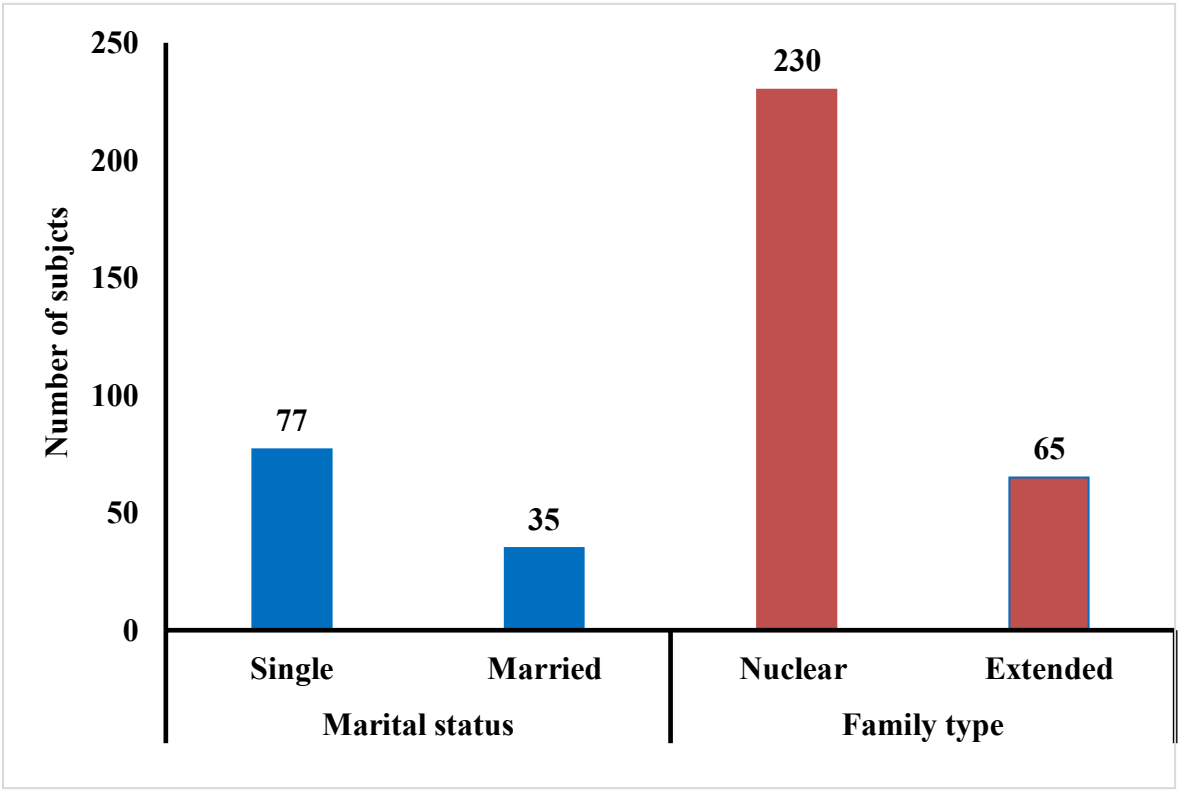

Fig. 3.6. Distribution of subjects based on their marital status and family type

3.1.7 Distribution of subjects based on their economic status

Index cases were divided into 4 groups because of their economic status distribution. As it was a sensitive issue, the families of the subjects self declared about their economic issue. These were Poor, Low, Low-mid and High categories. The highest number of cases belonged to the poor category of economic status with 44% (n=129). The low category covered 38% (n=113), while the low-mid category contributed 17% (n=51) and there were only (n=2) 1% cases from the high economic status category (Fig. 3.7). The distribution of gender wise and familial/sporadic was not statistically significant (Table 3.1).

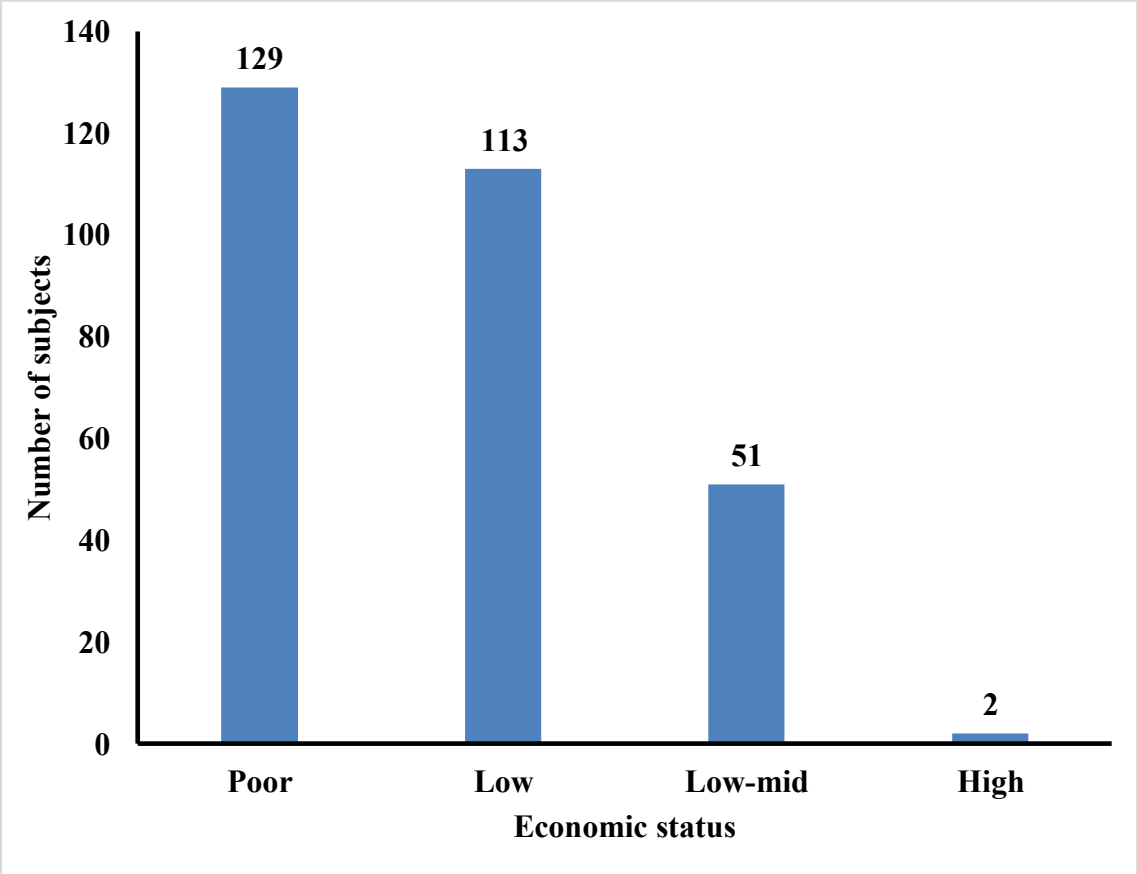

Fig. 3.7. Distribution of subjects based on their economic status

3.1.8 Distribution of the subjects based on their union-councils

The data were collected from 7 different union-councils, Daira Din Pannah, Ahsan Pur, Kot Addu, Pattal, Hinjrai, Haider Ghazi and Drigh. Most of the cases were collected from Daira Din Pannah counting 42% (n=123). Cases observed from Ahsan Pur were 18% (n=52), while Kot Addu accounted for 10% (n=30) cases. The number of cases observed in Pattal was 12% (n=35) whereas in Hinjrai 7% (n=21). In Haider Ghazi, the number of index cases observed was also 7% (n=21). The least number of cases were noted from Drigh and those accounted 4% (n=13) (Fig. 3.8). The distribution of gender wise and familial/sporadic was not statistically significant (Table 3.1).

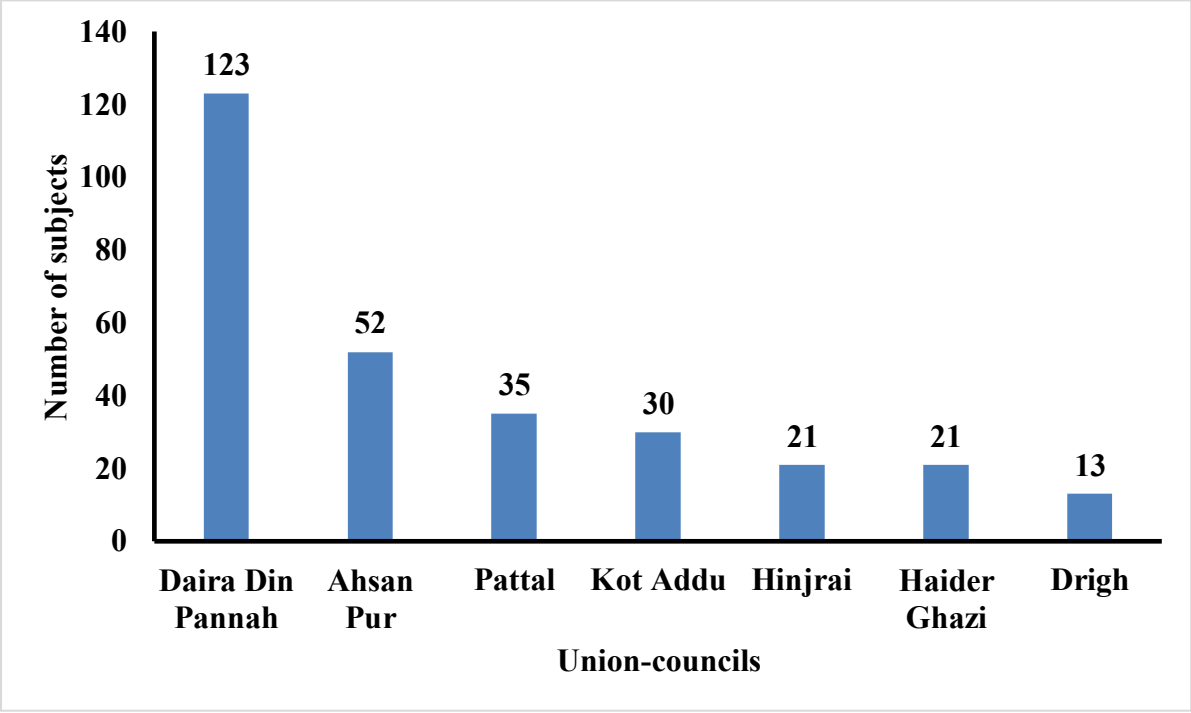

Fig. 3.8. Distribution of index cases based on their union-councils

3.1.9 Distribution of subjects with respect to caste system

The index cases were collected from subjects of many different castes but the most dominant were Mashori and Bhatti with 6.8% (n=20) each. Khokhar contributed 6.4% (n=19) and data collected from Channar caste was 6.1% (n=18) while the Bhutta caste contributed 4.4%. As there were so many castes so, the others category contributed 69.5% (n=205) (Fig. 3.9). The distribution of gender wise was statistically non-significant but the distribution of familial sporadic was statistically significant (Table 3.1).

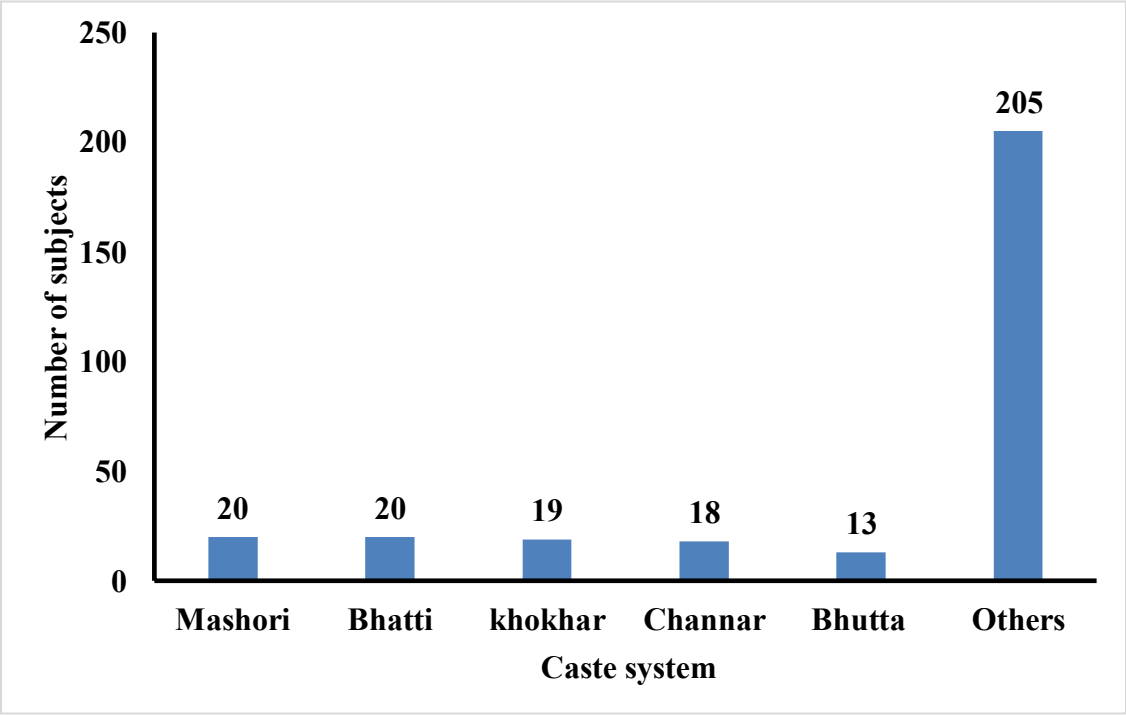

Fig. 3.9 Distribution of subjects with respect to caste system

3.1.10 Distribution of subjects with respect to mother-tongue

The Saraiki was found to be the most spoken language and contributed 98% (n=291) and there was only a fraction of cases speaking other language accounting for only 2% (n=4). That indicated the dominance of the Saraiki language spoken in that area (Fig 3.10). The distribution of gender wise and familial/sporadic was not statistically significant (Table 3.1).

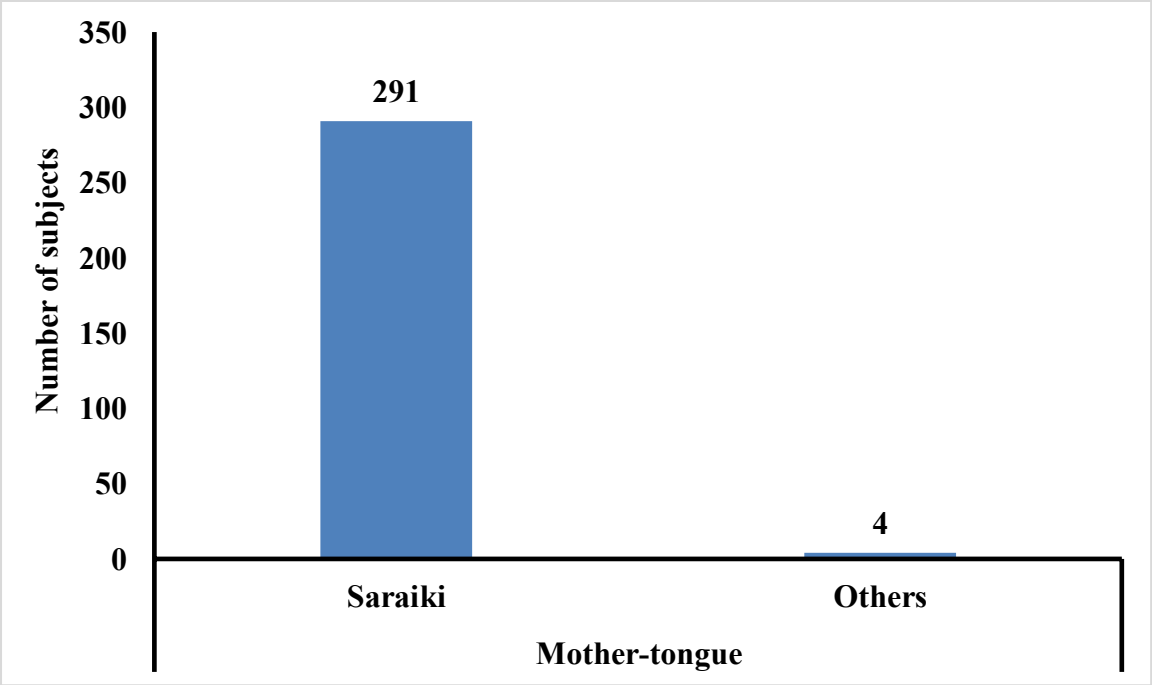

Fig. 3.10. Distribution of subjects based on their mother -tongue

Table 3.1. Demographic distribution of subjects

Demographic variables	Gender		Familial/Sporadic		Total	%
	Male n (%)	Female n (%)	Familial n (%)	Sporadic n (%)		
Origin (n=295)						
Rural	214 (73)	63 (21)	77 (26)	200 (68)	277	94
Urban	16 (5)	2 (1)	4 (1)	14 (5)	18	6
Total	230 (78)	65 (22)	81 (28)	214 (72)	295	
	^{Chi2}=1.33; df=1; P=0.249			**^{Chi2}=0.264; df=1 P=0.608**		
Up to 5	23 (8)	8 (3)	3 (1)	28 (10)	31	10
>5-10	60 (20)	13 (4)	24 (8)	49 (17)	73	25
>10-20	81 (28)	24 (8)	30 (10)	75 (25)	105	36
>20- 30	31 (10)	11 (4)	9 (3)	33 (11)	42	14
>30	35 (12)	9 (3)	15 (5)	29 (10)	44	15
	Chi^2=0.0170; df=1; P=0.896		**Chi^2=27.71; df==4; P=0.0001 Significant**			

Guardian Occupation						
Unemployed	63 (21)	15 (5)	25 (9)	53 (17)	78	26
Farmer	45 (15)	16 (6)	12 (4)	49 (17)	61	21
Labour	72 (25)	19 (6)	31 (10)	60 (20)	91	31
Shopkeeper	34 (12)	9 (3)	8 (3)	35 (12)	43	15
Others	16 (5)	6 (2)	5 (2)	17 (6)	22	7
Total	230 (78)	65 (22)	81 (28)	214 (72)	295	
	Chi^2=1.434; df=1; P=0.838		**Chi^2=6.617; df=4; P=0.157**			
Literacy rate (age <5 not included n=279)						
Literate	33 (12)	5 (1)	15 (5)	23 (8)	38	14
Illiterate	186 (67)	55 (20)	64 (23)	177 (64)	241	86
	Chi^2= 1.816; df==1; P=0.177		**Chi^2=2.698; df=1; P=0.100**			

Level of education (n=38)						
Primary schooling	13 (34)	2 (5)	3 (8)	12 (32)	15	40
Middle schooling	16 (42)	2 (5)	11 (29)	7 (18)	18	47
High schooling	1 (3)	1 (3)	0	2 (5)	2	5
Above	3 (8)	0	1 (3)	2 (5)	3	8
	Chi^2=2.89; df=3; P=0.407		**Chi^2=7.260; df=3; P=0.064**			
Economic status						
Poor	105 (36)	24 (8)	33 (11)	96 (33)	129	44
Low	87 (30)	26 (9)	34 (12)	79 (27)	113	38
Low-mid	37 (12)	14 (5)	13 (4)	38 (13)	51	17
High	1 (0)	1 (0)	1 (0)	1 (0)	2	1
	Chi^2=2.727; df=3; P=0.435		**Chi^2=1.230; df=3; P=0.745**			
Marital status Age =18 or above (n=112)						
Single	59 (53)	18 (16)	19 (17)	58 (52)	77	69
Married	29 (26)	6 (5)	10 (9)	25 (22)	35	31
	Chi^2=0.555; df=1; P=0.4561		**Chi_2=0.190; df=1; P=0.662**			

Family Type						
Nuclear	180 (61)	50 (17)	55 (19)	175 (59)	230	78
Extended	50 (17)	15 (5)	26 (9)	39 (13)	65	22
	Chi^2=0.052; df=1; P=0.818		**Chi^2=6.584; df=1; P=0.0103; Significant**			
Caste system						
Mashori	18 (6)	2 (1)	9 (3)	11 (4)	20	7
Bhatti	15 (5)	5 (2)	10 (3)	10 (3)	20	7
Khokhar	12 (4)	7 (2)	4 (1)	15 (5)	19	6
Channar	16 (5)	2 (1)	2 (1)	16 (6)	18	6
Bhutta	11 (4)	2 (1)	4 (1)	9 (3)	13	4
Others	152 (52)	53 (17)	52 (18)	153 (52)	205	70
	Chi^2=6.419; df=5; P=0.267		**Chi^2=11.52; df=5; P=0.042; Signifiacant**			

Union-council based distribution						
Daira Din Pannah	94 (32)	29 (10)	40 (14)	83 (28)	123	42
Ahsan Pur	43 (15)	9 (3)	17 (6)	35 (12)	52	18
Kot addu	18 (6)	12 (4)	6 (2)	24 (8)	30	10
Pattal	30 (10)	5 (2)	9 (3)	26 (8)	35	12
Hinjrai	17 (6)	4 (1)	6 (2)	15 (5)	21	7
Haider Ghazi	19 (6)	2 (1)	2 (1)	19 (7)	21	7
Drigh	9 (3)	4 (1)	1 (0)	12 (4)	13	4
	Chi^2=10.31; df=6; P=0.112		**Chi^2=9.143; df=6; P=0.165**			
Mother Tongue						
Saraiki	226 (77)	65 (22)	79 (26)	212 (71)	291	99
Others	4 (1)	0	2 (1)	2 (2)	4	1
Total	230	65	81	214	295	
	Chi^2=1.146; df=1; P=0.2844		**Chi^2=1.035; df=1; P=0.3091**			

3.2 Distribution of congenital deformities into major and minor categories

All the index cases were categorized into 6 major groups (Table 3.2). Major and minor categories were formed. Neurological disorders were most common (n=88), followed by neuromuscular defects (n=82), sensorineural/ear defects (n=53), eye/visual impairments (n=28), musculoskeletal defects (n=21), limb defects (n=17) and some cases with less than 3 subjects were combined to be kept under the category of "other defects". The pie chart below (Fig. 3.11) explains the percentage of these major deformities. Minor categories with their classification according to OMIM and ICD-10 databases are figured in the (Table 3.3).

In neurological disorders, the cases with intellectual disability were the most common accounting 94% (n=83) out of total cases. In neuromuscular defects, cerebral palsy was most frequent with 74% (n=61) cases. Leg length discrepancy with 62% (n=13) cases was most frequent in musculoskeletal defects while talipes was 49% (n=8) in case of limb defects. In the sensorineural defects, deaf/mute category was the most common 77% (n=41) and 23% (n=12) were only mute. While the other category contains 1 or 2 cases related to orofacial defects, urinary and blood disorders.

Table 3.2 Major groups of congenital deformities with respect to number of subjects

Anomaly	No. of Subjects (n)	Proportion	Gender (n)		Sporadic/Familial (n)	
			Male	Female	Sporadic	Familial
Neurological disorders	88	0.298	65	23	61	27
Neuromuscular defects	82	0.277	74	8	69	13
Sensorineural/ear defects	53	0.178	42	11	37	16
Eye/visual impairments	28	0.094	19	9	13	15
Limb defects	17	0.057	13	4	8	9
Musculoskeletal defects	21	0.071	12	9	20	1
Others	6	0.02	5	1	6	0
Total	295		230	65	214	81
			Chi^2=15.20; df=6; P=0.0188; Significant		**Chi^2=29.03; df=6; P<0.0001; Significant**	

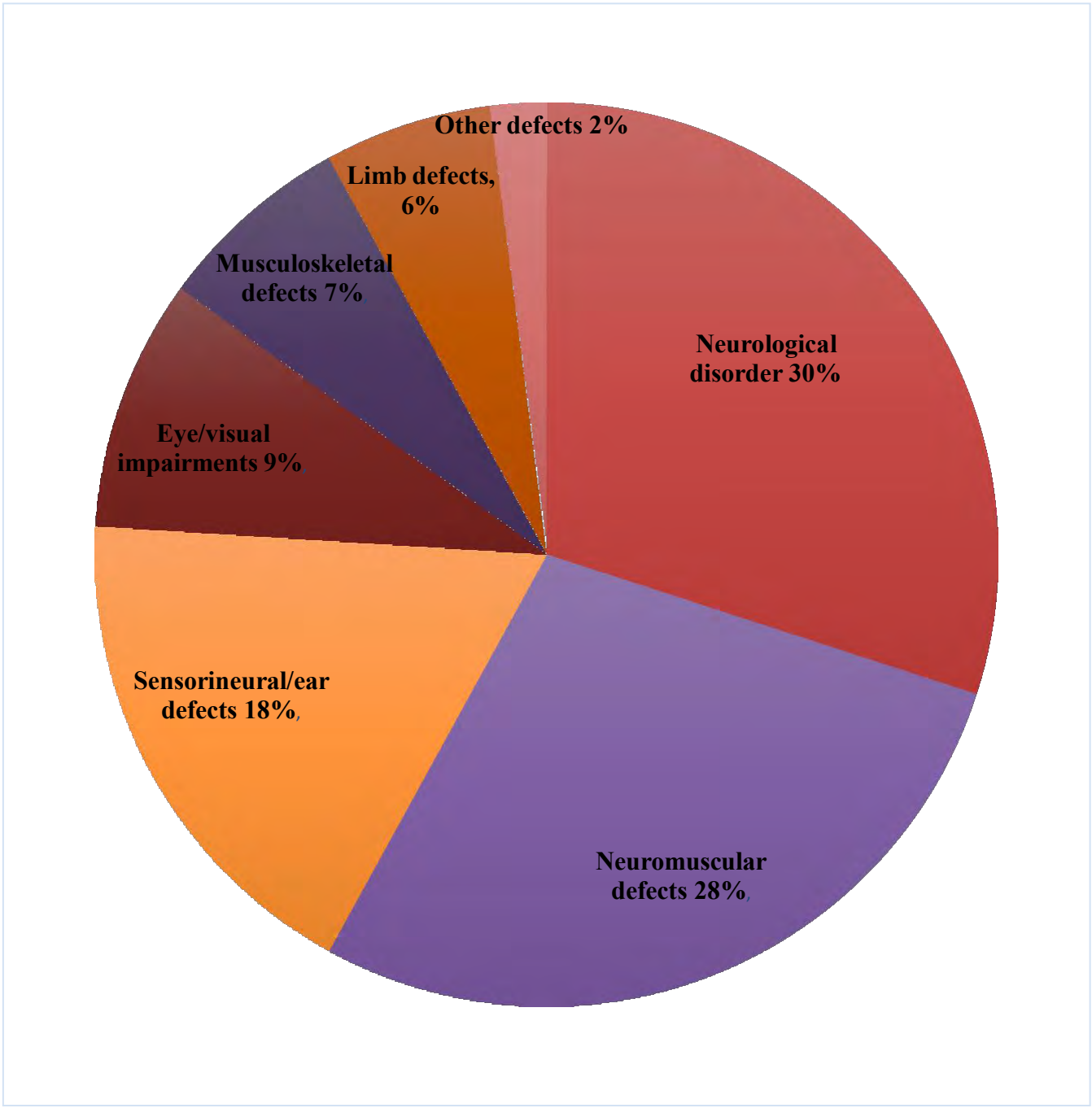

Fig 3.11. Major categories of congenital deformities

Table 3.3 Minor categories of congenital deformities

Anomaly (major/minor)	No. of cases	Proportion	OMIM	ICD-10
Neurological disorders	**88**			
Intellectual disability	83	0.281	300419	F 70
			300298	F 71
			300253	F 72
Epilepsy	4	0.013	607208	G 40
Other	1	0.003		
Neuromuscular defects	**82**			
Cerebral palsy	61	0.206	605388	G 80.9
Leg hypotonia	16	0.054		
Muscular dystrophy	5	0.016	310200	G 71.0
			253600	
Sensorineural /ear defects	**53**			
Deaf/Mute	41	0.138	304400	Q 18
Only mute	12	0.03		
Eye/visual impairment	**28**			
Blind	20	0.067		
Myopia	5	0.016		
Night blindness	2	0.006	310500	H 53.60
Squint eye	2	0.006	185100	Q 10

Musculoskeletal defects	**21**	**Proportion**	**OMIM**	**ICD-10**
Leg length discrepancy	13	0.044		
Dwarfism	2	0.006		
Scoliosis	2	0.006	181800	M 41.9
Pectus carinatum	3	0.01		
Knock knees	1	0.003		
Limb defects	**17**			
Club foot	8	0.027	119800	Q 66.8
Amputation	3	0.01	217100	Q 73.8
Overriding toes	2	0.006		
Polydactyly	1	0.003		
Synopolydactyly	1	0.003		
Bifid thumb	1	0.003		
Floppy hands	1	0.003		
Other defects	**6**			
Cleft lip	3	0.01	119530	Q 36.9
Albinism	1	0.003	300500	E 70.3
Anemia	1	0.003		
Urethral fistula	1	0.003	314390	N 36.0
Total	**295**			

3.3 Distribution of subjects with respect to genetic attributes

3.3.1 Distribution of deformities with reference to gender

There was a total number of 295 cases where male cases were 230 making 78% while there were only 22% females (n=65). In all the categories of congenital deformities observed, male cases were more frequent. In neurological disorders, 74% (n=65) were male and 26% (n=23) were female cases. In the case of neuromuscular defects, male cases were quite dominant and contributed 90% (n=74) whereas female cases were only 10% (n=8). Male cases were also higher in sensorineural/ear defects and counted 79% (n=42) while female cases were only 21% (n=11). In eye/visual impairments, male cases contributed 68% (n=19) whereas 32% (n=9) were female members. In musculoskeletal defects, male numbers were slightly higher 57% (n=12) as compared to 43% (n=9) females. In the limb defects, similarly, female cases were less in numbers with 24% (n=4) and male cases were dominant with 76% (n=13) cases. In the other defects category, 83% (n=5) were male members whereas 17% were female cases. (Table 3.2) and (Fig. 3.12) explain all the details). The distribution of gender wise was not statistically significant (Table 3.4).

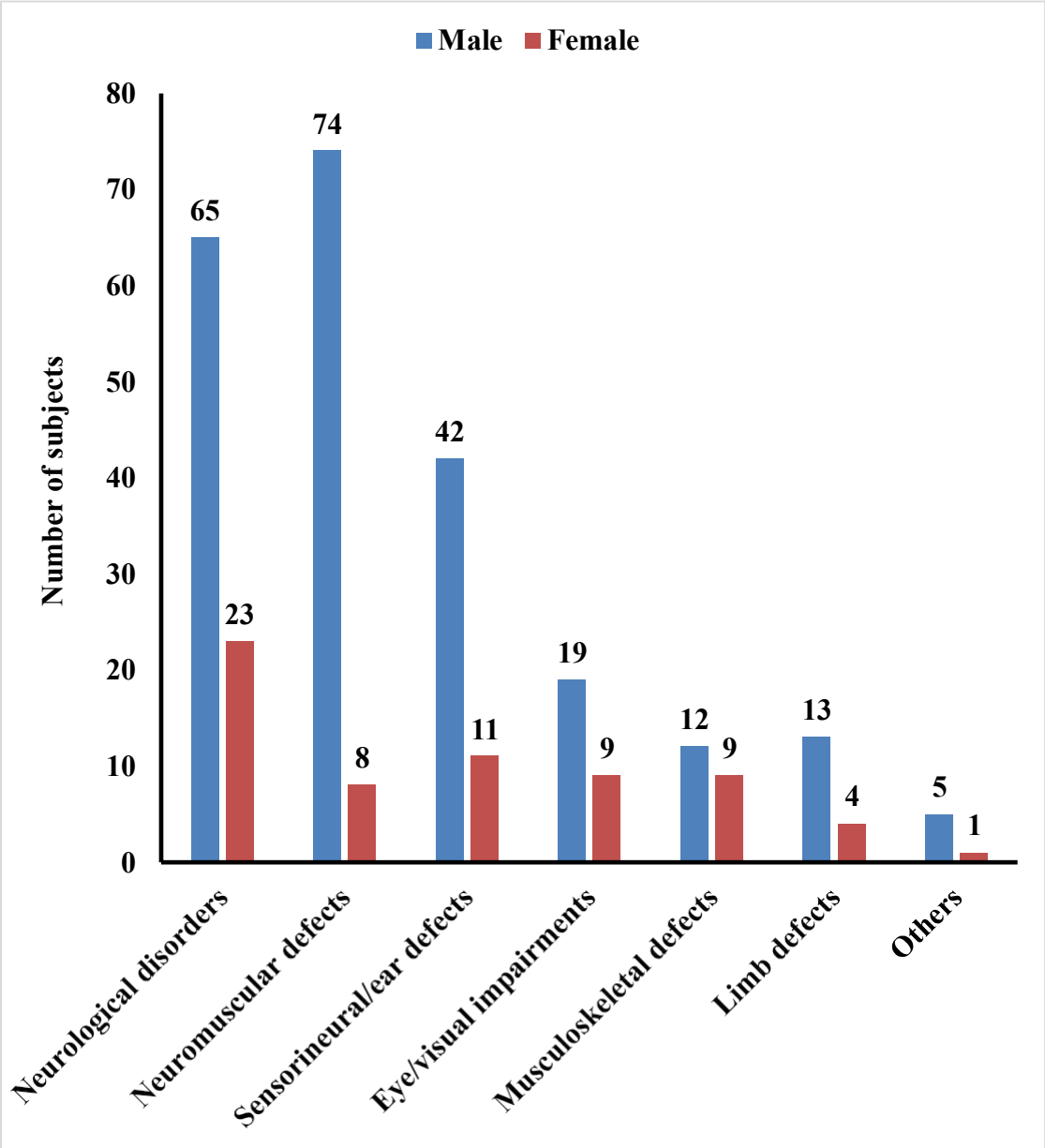

Fig 3.12. Distribution of deformities with reference to gender

3.3.2 Distribution of deformities with respect to familial/sporadic nature

The total number of sporadic cases was 214 contributing 72% (n=214) whereas familial cases were 81 making 28% of the total 295 cases. In neurological disorders, sporadic cases were dominant contributing 69% (n=61) whereas familial cases contributed 31% (n=27). Sporadic cases outnumbered those of neuromuscular defects with 84% (n=69) while familial cases were 16% (n=27). In sensorineural defects, similarly, sporadic cases were frequent with 70% (n=37) whereas 30% (n=16) were familial. In eye/visual impairments, familial cases were slightly higher contributing 54% (n=15) whereas sporadic cases were slightly less making 46% (n=13). In musculoskeletal defects, there was only 1 familial case and contributed only 5% and the rest were sporadic cases making 95% (n=200) cases. Familial cases in case of limb defects were slightly higher making 53% (n=9) cases while sporadic cases contributed 47% (n=8). In the other defects category, all the cases were sporadic (n=6) and there was no familial case reported. Due to null values the statistical test was not applicable (Table 3.4).

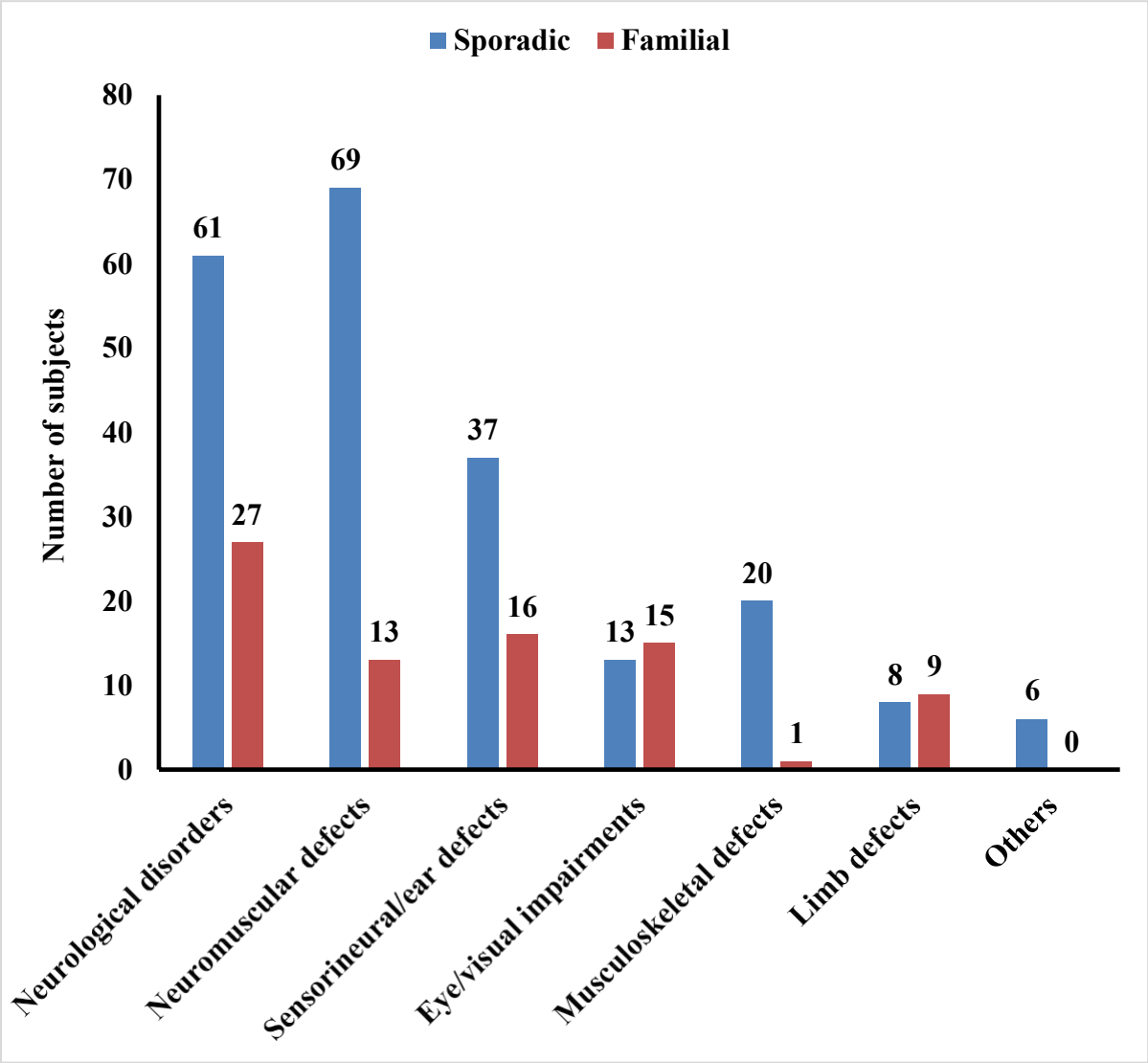

Fig 3.13. Distribution of deformities with respect to familial/sporadic nature

Table 3.4 Distribution of deformities with respect to familial/sporadic nature

Congenital anomaly type	No. of subjects	Sporadic*			Familial**		
		Male	Female	Both	Male	Female	Both
Neurological disorders	88	43	18	61	22	5	27
Neuromuscular defects	82	61	8	69	13	0	13
Sensorineural defects	53	30	7	37	12	4	16
Eye/visual impairments	28	10	3	13	9	6	15
Limb defects	17	5	3	8	8	1	9
Musculoskeletal defects	21	11	9	20	1	0	1
Other defects	6	5	1	6	0	0	0
Total	295	165	49	214	65	16	81

***Chi2=8.136;**

df=6; (for sporadic cases)

P=0.228

****Due to null values chi square was not applicable (for familial cases)**

3.3.3 Distribution of parity order in sporadic cases

Parity order was analyzed to establish any link between the parity and the types of deformities observed. Out of total of 214 sporadic cases, the highest number of subjects were recorded from the 1st order subject with 60 cases with 28% contribution. After that 2nd parity contributed to 22% of cases with (n=47), followed by 3rd with (n=42) and 19.6% cases, 4th with (Table 3.5) with a detailed description is present below. The distribution of subjects for parity order was not statisticaly significant (Table 3.5).

Table 3.5 Parity order in sporadic cases (n=214)

Congenital anomaly type	**No of subjects**	**Parity order in sporadic cases (n=214)**				
		1st	**2nd**	**3rd**	**4th**	**>4th**
Neurological disorders	61	16	16	15	8	6
Neuromuscular defects	69	20	14	12	14	9
Sensorineural defects	37	13	5	6	6	7
Eye/visual impairments	13	4	3	2	3	1
Limb defects	8	3	3	0	2	0
Musculoskeletal defects	20	3	6	4	2	5
Other defects	6	1	0	3	0	2
Total	**214**	**60**	**47**	**42**	**35**	**30**
Chi^2=22.29; df=24; P=0.561						

3.3.4 Distribution of number of normal sibs in sporadic cases

Subjects with more than 4 normal sibs were the highest in number with 36% cases (n=76). Subjects with 4 normal sibs were (n=41) with 19% cases. There were 18% (n=39) cases reported with 3 normal sibs while the number of people with 2 normal sibs were 28, contributing to 13% of the total sporadic cases. The least number of cases (n=9) with 4% contribution was noted from subjects with no normal sibs whereas subjects with only 1 sib contributed to 10% (n=21) cases (Table 3.6). . The distribution of subjects for number of normal sibs was not statisticaly significant (Table 3.6).

Table 3.6 Distribution of number of normal sibs for sporadic cases (n=214)

Congenital anomaly type	**Number of normal sibs for sporadic cases (n=214)**					
	0	**1**	**2**	**3**	**4**	**>4**
Neurological disorders	1	4	10	14	11	21
Neuromuscular defects	4	3	9	9	17	27
Sensorineural defects	2	7	5	5	6	12
Eye/visual impairments	1	1	3	3	1	4
Limb defects	1	3	0	3	0	1
Musculoskeletal defects	0	2	0	4	6	8
Other defects	0	1	1	1	0	3
Total	**9**	**21**	**28**	**39**	**41**	**76**
Chi^2=34.25; df=24; P=0.270						

3.3.5 Distribution of disease segregating generations for familial cases

To describe the number of generations affected in the familial cases the data was analyzed to know any link between the deformity type and the number of generations it was affecting. Out of total 81 familial cases, 67% (n=54) were found with only 1 generation affected whereas 33% (n=27) cases were found with 2 generations affected. . The distribution of subjects for generation with disease was not statisticaly significant (Table 3.7).

Table 3.7 Distribution of generations with disease in familial cases (n=81)

Congenital anomaly type	Number of cases	Generations with disease	
		1	2
Neurological disorders	27	18	9
Neuromuscular defects	13	10	3
Sensorineural/ear defects	16	10	6
Eye/visual impairments	15	10	5
Limb defects	9	5	4
Musculoskeletal defects	1	1	0
Total	**81**	**54**	**27**
	Chi^2=1.740; df=5; P=0.561		

3.3.6 Distribution of affected sibship in familial cases

The numbers of affected sibships along with different categories of congenital deformities in the familial cases were considered in this section. The data was analyzed and there were 3 categories; 1 sibship affected, 2 sibships affected and more than 2 sibships affected. The highest number of cases were found in the category of 2 sibships affected where 52% (n=42) cases had 2 affected sibships. 44% (n=36) cases were found with only one sibship affected. Only 4% (n=3) cases were found with more than 2 sibships affected. . The distribution of subjects for affected sibship was not statisticaly significant (Table 3.8).

Table 3.8 Distribution of number of affected sibships in familial cases (n=81)

Congenital anomaly type	**Affected sibship for familial cases**		
	1	**2**	**>2**
Neurological disorders	10	15	2
Neuromuscular defects	7	6	0
Eye/visual impairments	7	7	1
Musculoskeletal defects	0	1	0
Limb defects	4	5	0
Total	**36**	**42**	**3**
Chi^2=3.405; df=8; P=0.906			

3.3.7 Distribution of affected family members in familial cases

In familial cases, affected family members were divided into 4 categories; with two affected family members, with 3-4 affected family members, with 5-6 affected family members and with more than 6 affected family members. There were 74% (n=60) cases when only two family members were affected. There were also 20% (n=16) cases when 3-4 subjects were affected. Only 2% (n=20) cases were found when 5-6 cases were affected, and 4% (n=3) cases were having more than 6 affected subjects in the family. The distribution of subjects for affected family members was not statisticaly significant (Table 3.9).

Table 3.9 Distribution of affected family members in the familial cases (n=81)

Congenital anomaly type	**Number of cases**	**2**	**3-4**	**5-6**	**>6**
Neurological disorders	27	21	5	0	1
Neuromuscular defects	13	9	4	0	0
Sensorineural defects	16	10	5	0	1
Eye/visual impairments	15	11	1	2	1
Musculoskeletal defects	9	1	0	0	0
Limb defects	1	8	1	0	0
Total	**81**	**60**	**16**	**2**	**3**
Chi^2=14.75; df=15; P=0.4692					

3.4 Classification of neurological disorders

In this study, neurological disorders contribute 30% of the total disorders. Neurological disorders are further classified in three minor anomaly types: intellectual disability, epilepsy and one other category. But intellectual disability contributed to 94 % of overall neurological disorders.

3.4.1 Classification of intellectual disability

Intellectual disability was further classified into 4 categories: mild, moderate, severe and profound type. The data was further analyzed with gender, familial/sporadic nature and isolated/syndromic nature. Out of total 83 cases of intellectual disability, 49% (n=42) cases were of the severe type whereas 35% (n=29) cases belonged to the moderate category. Around 10% (n=8) of subjects were in the profound category while only 6% of cases contributed from the mild type of intellectual disability. There were 72% (n=60) males affected with an intellectual disability whereas 28% (n=23) cases were of females with this disability. Around 68% (n=56) cases of intellectual disability were of sporadic nature whereas 32% of cases belonged to the familial category. There were 66% (n=55) cases syndromic in nature while 34% (n=28) cases were isolated in nature (Table 3.10). The distribution of gender wise, familial/sporadic snd isolated/syndromic was not statistically significant (Table 3.10).

Table 3.10 Distribution of subjects of intellectual disability based on gender, familial/sporadic and isolated/syndromic nature

Intellectual disability	Gender		Familial/Sporadic		Isolated/Syndromic		Total
	Male	Female	Familial	Sporadic	Isolated	Syndromic	
Mild	5	0	2	3	2	3	5
Moderate	18	11	6	23	9	20	29
Severe	30	11	15	26	11	30	41
Profound	7	1	4	4	6	2	8
Total	**60**	**23**	**27**	**56**	28	55	83
	Chi^2=4.369; df=3; P=0.224		**Chi^2=3.399; df=3; P=0.334**		**Chi^2=7.151; df=3; P=0.067**		

3.5 Classification of neuromuscular defects

Neuromuscular defects contributed 28 % of the total congenital deformities. They were further subdivided into 3 minor categories, CP, leg hypotonia and muscular dystrophy. There was a 74% (n=61) contribution CP cases out of the total neuromuscular defects whereas leg hypotonia contributed 20% (n=16) of the neuromuscular defects. Muscular dystrophy contributed 6% (n=5) of the subjects.

3.5.1 Classification of neuromuscular defects based on gender and familial/sporadic nature

In cerebral palsy, there were 90% (n=55) male subjects and there were only 9.8% (n=6) female subjects. The sporadic cases were contributing 82% (n=50) while familial cases only contributed 18% (n=11). In leg hypotonia, the male category was dominant with 88% (n=14) cases whereas there were only 12% (n=2) female subjects. Around 94% (n=15) cases of this category were sporadic in nature whereas only 6% (n=1) subject was familial. All 100% (n=5) cases in muscular dystrophy were of male subjects and there was no female subject. There were 80% (n=4) sporadic cases, and 20% (n=1) case was familial (Table 3.11). The distribution for gender wise and familial/sporadic was not statistically significant (Table 3.11).

Table 3.11 Classification of neuromuscular defects based on gender and familial/sporadic nature

Neuromuscular	Gender		Familial/Sporadic		Total	%
	Male	Female	Familial	Sporadic		
Cerebral palsy	55	6	11	50	61	74.4
Leg hypotonia	14	2	1	15	16	19.5
Muscular dystrophy	5	0	1	4	5	6.1
Total	74	8	13	69	82	100
	Chi^2=0.677; df=2; P=0.712		**Chi^2=1.388; df=2; P=0.4996**			

3.6 Parental parameters

3.6.1 Parental consanguinity

To find out the marriage types among the parents of index cases, data was analyzed, and it indicated that there were 69% (n=204) cases when consanguineous marriage type was found whereas non-consanguineous marriages were found in only 30% (n=91) cases (Fig. 3.14). When different categories of congenital deformities were taken along the parental marriage types, the consanguineous marriage type was dominant (Table 3.12). The distribution of subjects for parental marriage type was not statistically significant (Table 3.12).

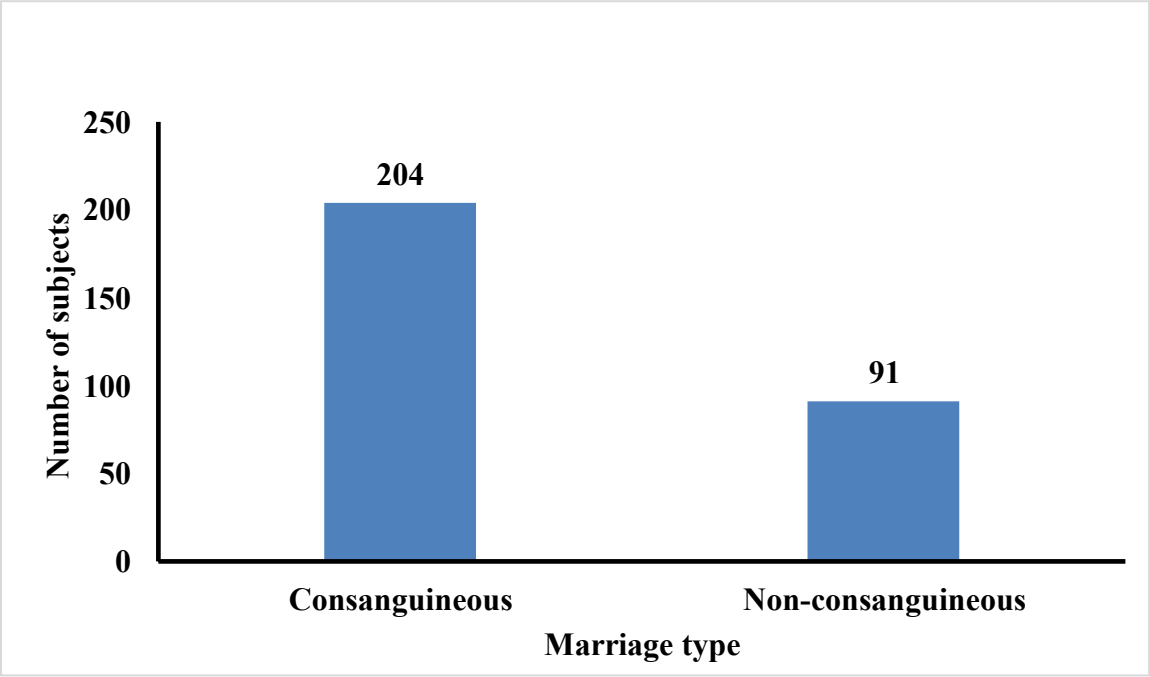

Fig. 3.14. Distribution of marriage types between parents of index subjects

Table 3.12 Distribution of deformities with respect to parental marriage types

	Parental marriage types		
Congenital anomaly type	**Consanguineous**	**Non-consanguineous**	**Total**
Neurological disorders	57	31	88
Neuromuscular defects	59	23	82
Sensorineural/ear defects	36	17	53
Eye/visual impairments	23	5	28
Musculoskeletal defects	15	6	21
Limb defects	9	8	17
Other defects	5	1	6
Total	**204**	**91**	**295**
	Chi^2=6.056; df=6; P=0.417		

3.6.2 Distribution of parental marriage types with respect to gender and familial/sporadic nature

Consanguineous marriage type was dominant in males as there were (n=160) consanguineous males as compared to the (n=70) non-consanguineous males. In females, consanguineous marriage type was dominant with (n=44) cases as compared to (n=21) non-consanguineous females. Sporadic consanguineous cases (n=145) were more frequent as compared to sporadic non-consanguineous cases (n=69). Familial consanguineous cases were also more frequent with (n=59) as compared to familial non-consanguineous cases (n=22). The distribution of parentral marriage types based on gender wise and familial/sporadic was not statistically significant.

Table 3.13 Distribution of parental marriage types with respect to gender and familial/sporadic nature

	Parental marriage types			
Variable	**Consanguineous**	**Non-consanguineous**	**Total**	
Male	160	70	**230**	
Female	44	21	**65**	
	Chi^2=0.083; df=1; P=0.772			
Familial	59	22	**81**	
Sporadic	145	69	**204**	
	Chi^2=0.711; df=1; P=0.398			

3.6.3 Parental age at birth of index subjects

For each anomaly type, average paternal and maternal age was calculated and data indicated that it was found highest in 'other defects' category i.e. 32.5 and 30.16 years, respectively. In neurological disorders, the average paternal age was 30.54 years whereas the average maternal age was 28.69 years (Table 3.14) below explains the details about each anomaly type.

Table 3.14 Average parental age at birth of index subjects

			Average Parental age at birth	
Congenital anomaly type		**Number of cases**	**Paternal age (years)**	**Maternal age (years)**
Neurological disorders		88	30.54	28.69
Neuromuscular defects		82	29.62	28.63
Sensorineural/ear defects		53	31.54	29.64
Eye/visual impairments		28	28.89	27.71
Musculoskeletal defects		21	32.09	29.42
Limb defects		17	28.11	26.05
Other defects		6	32.5	30.16
Average			**30.47**	**28.61**

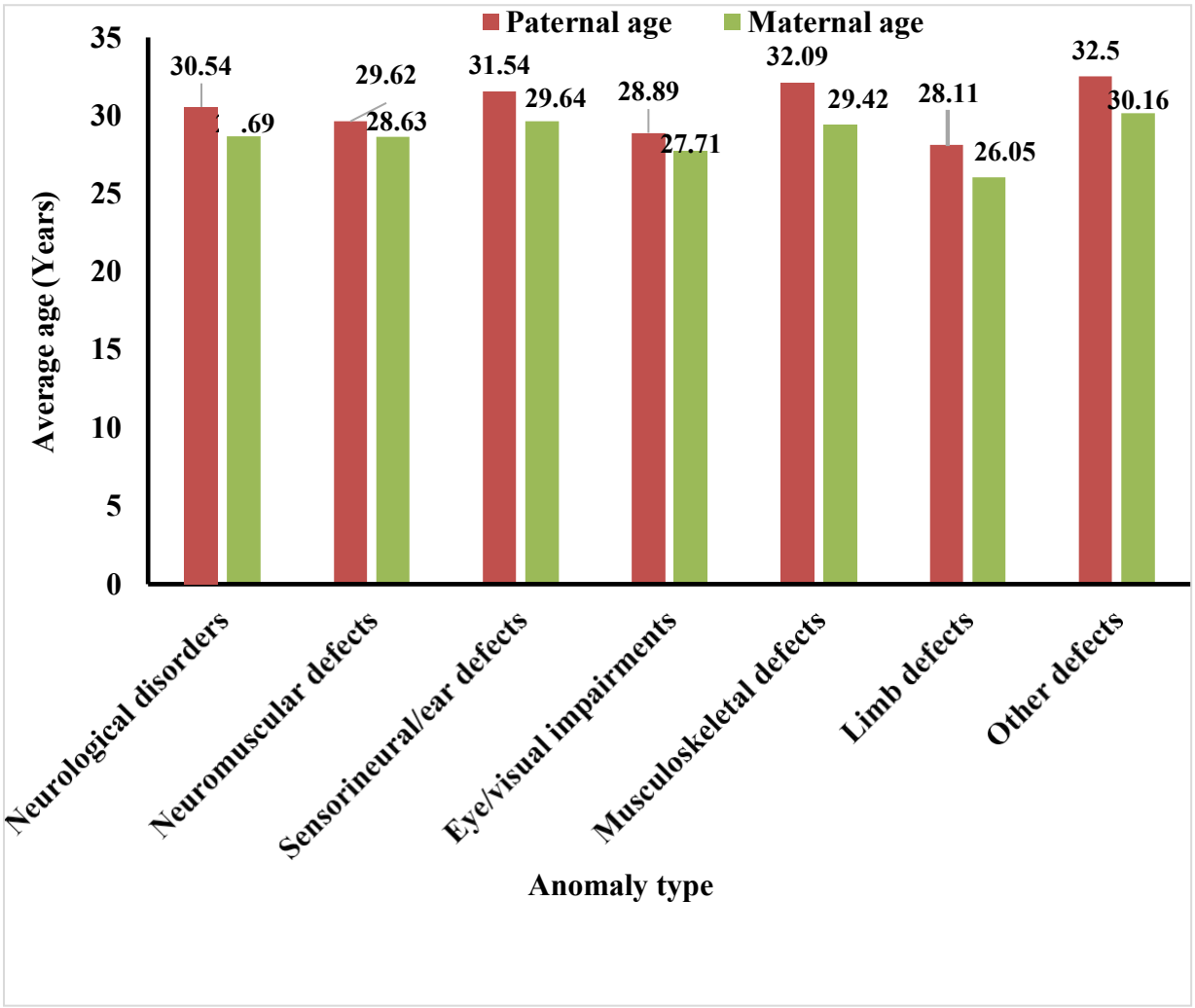

Fig. 3.15. Average parental age at birth of index subjects

3.7 Representative pedigrees

Pedigrees for all the index subjects were drawn for all congenital deformities. Here are few pedigrees mentioned below for the represention of index subjects. Pedigree 1 is describing the family of intellectual disabiity, showing segregation of phenotype in 2 generations. In Pedigree 2, a family of bind people have been shown, with disease affecting the same generation.

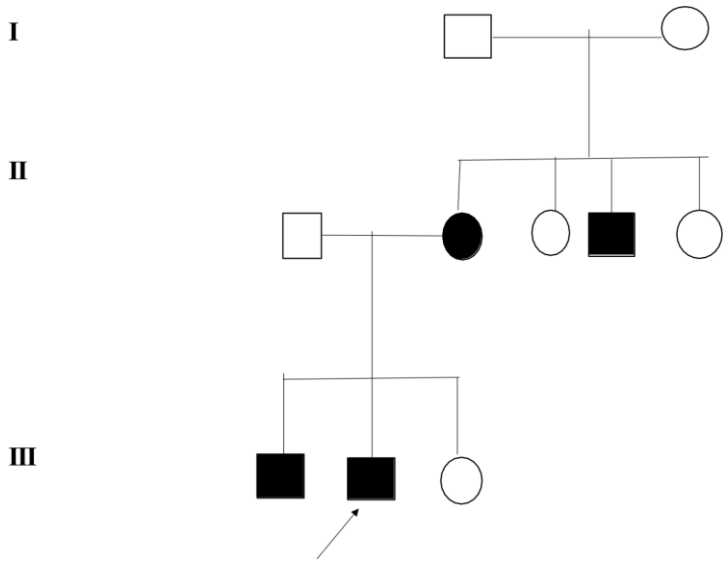

Fig. 3.16. Pedigree of a family of intellectual disability segregating the trait in two generations with arrow pointing index subjects

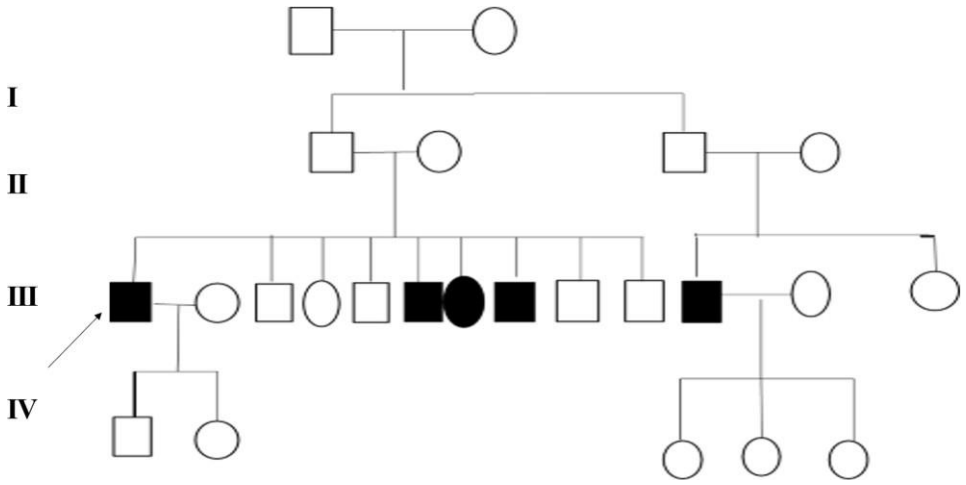

Fig.3.17 Pedigree of a family of bindness segregating in the same generation with arrow pointing index subject

3.8 Representative phenotypes

During the field work photos from the index subjects were taken. Here are the few index subjects shown below expressing different disease phenotypes.

Fig. 3.18 A. Leg length discrepancy; B. Clubfoot; C. Leg hypotonia; D. polydactyly

Individuals bearing genetic defects face hardships in their routine life activities, and there is always a requirement for their special care. Most of the time, they are considered an economic burden on society and struggle to achieve their basic rights. They are always deprived of their social rights. Genetic deformities have been a concern for geneticists and a major worry for pregnant women. Genetic defects are always difficult to manage because they necessitate lifelong attention and care, as well as extensive therapies.

The purpose of studying genetic deformities is to establish baseline rates, identify changes over time, and find out the actual cause of disease. Understanding the pattern and prevalence of congenital deformities would help us determine the needs of the health care system and estimate any possible incidence or incidence rate for that particular disease.

In the present study, a total of 295 index subjects were ascertained. In the Kot Addu district, this survey is being undertaken for the first time. The research region is in Pakistan's Southern Punjab. This data was gathered from the rural parts of the district Kot Addu and indicates a high prevalence of teratogenic exposure, inadequate maternal care, lack of family planning, maternal diseases, late and early marriages, and poor socioeconomic conditions. The families and society at large suffer economically, socially, and mentally as a result of the health care system's inability to handle and support the subject/families afflicted by certain congenital and genetic deformities. Proper documentation of births and congenital deformities is deficient in the said area due to the poor infrastructure of health facilities and staff. Congenital

deformities account for 6–9% of prenatal deaths in Pakistan (Korejo et al., 2007).

Males were affected in greater numbers than females; 78% of males were affected, while 22% of females were affected. Significantly, the study discovered a lower number of affected index female patients. A study conducted by (Ochoga et al., 2018) found that male subjects (60%) outnumbered female subjects (40%) in terms of congenital deformities. Our findings are similar to those of (Baruah et al., 2019), who conducted research in Assam, India, and discovered that the proportion of affected males (58%) was significantly higher than the percentage of affected females (48%). In a study conducted in Assam, India, (Hemonta et al., 2010), the ratio of affected males was 66% higher than females 34%. This finding followed the current study, in which males outnumbered females.

The lower female representation in this study may be due to Pakistani society's specific socio-cultural norms, such as girls' shyness and guardians' conventional restrictions on the information they provide. In some cases, acquiring family approval for research was difficult because guardians were not always available at home. The current study also sought to examine the link between congenital deformities and demographic factors (such as age, language, caste, origin, residence, education, and consanguinity).

The results showed that most deformities were neurological disorders (30%), followed by neuromuscular defects (28%), sensorineural/ear defects (18%), eye/visual impairments (9%), musculoskeletal defects (7%), limb defects (6%), and other accounted (2%). Our findings were comparable to those of (Bhatti et al., 2019), who found that neurological disorders (31%) were the second-highest after limb defects

(46%). The study carried out by (Zahra et al., 2017) also reported that neurological disorders (34%) were the most common. The present study is also in line with the study conducted by (Bibi et al., 2022), In their cohort, neurological disorders were observed to be the most prevalent (41%), followed by limb defects (25%) and musculoskeletal defects (9%).

The most prevalent deformities were neurological disorders 30% (n=88). Neurological disorders were further classified into 3 minor categories. Among the neurological disorders intellectual disability was in majority 94% (n=83), followed by epilepsy 4% (n=4), and others (2%). The present study is consistent with the study conducted by (Taye et al., 2019) who reported maximum subjects of neurological disorders. The present study findings are also in conjunction with the result of (Zahra et al., 2017) and (Amin et al., 2018) who also reported maximum subjects of neurological disorders.

Based on phenotype, internet databases, local doctors, and information supplied by the family guardian, the highest number of patients with neurological disorders were diagnosed. Studies have revealed a high frequency of severe mental impairment in Pakistan and India, with rates ranging from 12 to 24 per 1000 persons (Sharma et al., 2015). In the present study severe type of intellectual disability 49% (n=42) exceeds both the moderate 35% (n=29) whereas 10% (n=8) were in profound category and mild type 6% (n=4), our findings agree with those of a previous population-based study conducted by (Stromme et al., 2000), who found that cases of severe mental retardation were dominant as compared to those of mild and moderate mental retardation by (42%) to (33%) respectively. The distribution of inherited and

congenital defects varies in different regions and ethnic groups, according to a periodic evaluation of the literature. Deformities and discrepancies may be impacted by social, economic, ethnic, and ecological factors as well as the consanguinity rate. The type of sample analyzed and the diagnosis made could be potential explanations for variations.

The high prevalence of intellectual disability in the present study area may be due to the deficiency of micronutrients like iodine and folic acid, according to (Penchaszadeh et al., 2002), Every day, pregnant women should use iodized salt and ingest 400 micrograms of folic acid. Extreme weather circumstances, a deficient healthcare system, ignorance of congenital defects, the topography of the region, and socioeconomic conditions are the possible causes of different congenital defects.

Neuromuscular defects were the second most common congenital and inherited malformations in the current study. The results of the current study are in line with those of (Bhatti et al., 2019), whose findings also show a significant number of neuromuscular defects. The neuromuscular defects were further classified into three minor groups. Among the neuromuscular deformities, CP patients were most prominent at 74% (n=61), followed by leg hypotonia 20% (n=16) and muscular dystrophy. CP is a non-progressive motor disorder, and individuals with it may experience a range of issues, including intellectual disabilities, seizure disorders, squint eyes, and walking difficulties (Jan et al., 2006). With the assistance of the resident physician and other medical experts, the majority of the CP patients in the current study were categorised.

Sensorineural defects are the third most common category in the current study, accounting for (n=53) cases. Durkin et al. (2000) discovered deaf mutism in 70% of patients (n = 76: 30 women: 46 men) from 10 hospitals in Bangladesh, while cerebral palsy was found in 12%, mental retardation was found in 11%, blindness was found in 4%, and syndactyly was found in 2%. In the current study, 18% of people were deaf-mute. This study, unlike the others mentioned above, is conducted door-door, but still results are consistent with (Durkin et al. 2000). The current study's findings are slightly higher than those of (Glueria et al., 2017), who found (13%) of sensorineural/ear defects. A previous study (Bhatti et al., 2019) also reported sensorineural/ear, which is consistent with the current study.

The index 295 subjects were analayzed based on their familial/sporadic nature and the sporadic cases dominated with 72% (n=214) cases and familial cases were 28% (n==81). The current study is in line with the results of (Ullah et al., 2015), who found the highest number of sporadic (n=120) and familial (n=33) cases. This study is consistent with the findings of (Zahra et al., 2017), who also reported the highest number of sporadic cases.

The current study has the highest number of sporadic cases due to a lack of essential nutrients such as iodine and folic acid, which play an important role in preventing pregnancy complications and mental growth. Because the current study area is rural, there is a lack of awareness about the importance of supplement (iodine and folic acid) usage. The second factor is thermal radiation; the study area is near a

few thermal stations and is also rich in industries, including Pakistan's largest oil refinery (Pak Arab Oil Refinery). As a result, there is a risk of air pollution, which can result in novel mutations. The third factor is the region's socio-cultural norms, which make people reluctant to disclose personal information such as consanguinity, pedigree information, consanguinity, and number of family members.

The current study was also examined in terms of isolated and syndromic nature. The majority of families/index subjects (n=170) fall into the isolated category, while (n=125) fall into the syndromic category. The majority of syndromic cases reported in neurological disorders were isolated cases (n=59) and (n=29) were syndromic. The male guardian of the family have provided the most isolated cases in the current study, as the male parent of the family is mostly unaware of the index subjects' behaviour and other defects in the body. The study conducted by (Najamabdi et al., 2011), reported the maximum number of isolated (n=37) cases and only (n=4) syndromic cases which contrast the finding of the present where the syndromic cases were maximum (n=59) and isolated cases were (n=29.

In the current study, congenital and hereditary deformities in index subjects were analysed based on age group; deformities were more prevalent in the age group 11-20 years 27% (n=81), with a smaller number of index subjects falling in the age group 1-5 years 7.8% (n=23). The current study findings are consistent with those of a previous study conducted by (Taye et al., 2019), in which the majority of the subjects with congenital deformities were aged up to 17 years. Bhatti et al., (2019) is also consistent with the current study findings, which show that the majority of subjects

are between the age of 9 and 19 years. According to (Zahra et al., 2017), the majority of patients with deformities fall into the 10–19 age range, which is consistent with the current findings that the majority of index subjects fall into this age range, 11-20 years.

The 295 subjects were also examined in terms of the socioeconomic condition of the families; the majority of the subjects (44%) self-identified as poor, followed by low (38%), low-mid (17%), and only one family in the high group. In contrast to the findings of the current survey, which found that the majority of families fall into the poor group, a study conducted by (Taye et al., 2019) found that the majority of 74 family (49%) belong into the middle-income family category, followed by low-income families (43%).

It was found that those with poor socioeconomic level were more prone to experience genetic diseases. Numerous factors contributed to the high prevalence of congenital deformities among the poor, including poor maternal health, malnutrition, a lack of access to basic medical care, including medications and drugs, pollution, and poverty. The prevalence of psychological and mental illnesses like intellectual disability, and behavioural disorders is higher in the impoverished. Because of their circumstances, poor people are frequently anxious, and this stress is regularly passed down through their generations. According to the study's statistical analysis, neurological illnesses were more frequently reported in the poor.

Based on parity, the 214 sporadic subjects with congenital and inherited

deformities were studied. First parity was present in a total of (28%) people, followed by second (22%) and third (20%) parities. Our findings are in line with those of (Mahela, 2016), who indicated that the first parity (31%) and second parity (18%) had the highest prevalence rates, respectively.

The 81 selected familial subjects had their generation with disease analyzed as well. The deformities segregating in 2 generations were (34%) whereas the majority of cases were (66%) in the 1 generation. The findings of the current study are in line with those of (Zahra et al., 2017), which found the highest number of diseases segregating in 1 generation.

In the present study, consanguinity was found higher as compared to the non-consanguineous marriages among the parents of recruited subjects. Consanguinity was noted in (69%) cases whereas the non-consanguineous marriages were (31%) and the results are in line with (Zahra et al., 2017), they also noted high consanguinity. It is because of the fact that people tend to focus on close marriages and prefer to marry in their close relatives. Present study is also in accordance with the (Bibi et al., 2022), who also noted 66% consanguinity.

So, overall there were different causes of congenital deformities; poor economic background, poor health conditions, thermal radiations, alterations in gene, high consanguineous marriages, lack of health facilities, nutritional deficiencies in pregnant mothers.

The findings are showing the high trends of neurological disordres and neuromuscular defects and high consanguineous marriages.

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