# Phenotypic manifestation, Etiology and Associated disorders of Cerebral Palsy: A Cohort study in Pakistan



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# DECLARATION

I hereby declare that I have worked on my thesis "Phenotypic manifestation, etiology and associated disorders of cerebral palsy: a cohort study in Pakistan", independently and the work presented here is original. This thesis has not been submitted in the current or a similar form to any other university.

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# ACKNOWLEDGEMENT

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| Abbreviation | Full Form |
|---|---|
| CP | Cerebral Palsy |
| NIRM | National Institute of Rehabilitation Medicine |
| PakMediNet | Pak Medical Journals Repository |
| NCBI, PubMed | National Centre for Biotechnology Information |
| WHO | World Health Organization |
| ICD version 10 | International Classification of  Disease |
| CPRN | Cerebral Palsy Research Network |
| CDC | Centers for Disease Control and Prevention |
| NPEU | The National Perinatal Epidemiology Unit |
| SCPE | Surveillance of cerebral palsy in Europe |
| MRI | Magnetic Resonance imaging |
| CT scan | Computed Tomography |

## ABSTRACT

Cerebral palsy (CP) is a set of neurological disorder that affects neonates' ability to move, and it is caused by abnormal brain development or injury to the areas of the brain that control movement, balance, and posture. Population-based studies from all around the world found that the prevalence of CP ranged from 1.5 to >4 per 1,000 live births. The overall prevalence recorded in Pakistan was 1.22 per 1000 live births. The majority of research carried out in Pakistan is related to the treatment and management of CP. There is a paucity of comprehensive data in the areas of epidemiology, etiology, maternal factors, and molecular genetic diagnosis which are essential toward the important goal of developing strategies for management and prevention of CP. The aim of this study was to elucidate the phenotypic manifestation, etiology, and associated disorders of CP in a multiethnic population. A cohort study on CP and its biodemographic correlates was conducted and 989 CP patients were recruited from National Institute of Rehabilitation Medicine (NIRM), Islamabad between 2020-2021. Data were collected from parents/guardians of affected children through a structured questionnaire. The questionnaire comprised of 5 sections including demographic detail, phenotypes, clinical variants, family attributes and maternal and risk factors. The data were recorded and maintained in MS-Excel (Office 365), and statistical analyses were done through SPSS (version 20) and GraphPad (Prism; version 5); descriptive statistics was applied and Chi-square test and t-test were employed. From the total of 989 patients recruited, 61% of the patients were male and 39% were female (male-to-female ratio 1.6:1). Majority of the patients (51%) came from Punjab, had rural origin (68%), spoke Punjabi (48%), fall in the age range of 0.1-5 years (42%), belonged to low or low-mid socio-economic status (64%), and extended families (63%). Parental consanguinity was witnessed in 63% cases. The spastic CP had the highest representation (53%), followed by athetoid (29%), ataxic (14%) and mixed types (3.6%). Postnatal, natal and prenatal causes also found higher in spastic CP. Neonatal, maternal, obstetric and gynecological variables were also observed. Various anomalies associated with the CP were observed in which speech impairment was found very high (20%). Treatment given to CP patients and improvement after treatment was also analyzed. This study adds useful and detailed information on various important aspects of CP which could be primer for developing policies regarding the management and prevention of CP.

# CHAPTER 1

# INTRODUCTION

## 1.1. Background

Cerebral palsy (CP) is a set of neurological disorders that affects people's ability to maintain balance, move and posture. CP is defined as "a collection of permanent disorders of posture and movement, that is related to non-progressive problems which occurred in the developing fetal or newborn brain, resulting activity restriction". CP movement abnormalities are frequently accompanied with sensation, cognitive, communication, perception, and behavior issues, musculoskeletal problems and seizures " (Bax et al. 2005). CP is the most prevalent mobility impairment in children (Christensen et al. 2019), and it is caused by injury to the brain areas or abnormal brain development that control posture, movement and balance.

In 1861, William Little described the CP condition for the first time. He defined birth asphyxia as the source of a child's neurological problems. The term "cerebral palsies" was used by William Osler to describe several disorders. The dispute over terminology is still going on, with the phrase "cerebral palsy spectrum disorder" being proposed as a more accurate phrase.

The severity of CP is seen in approximately 40% of children with this condition which are unable to walk independently (Kirby et al. 2011; Christensen, 2019), one-half have cognitive impairment, one-third are nonverbal (Christensen et al. 2019) and one-third have epilepsy (Reid et al. 2016). It might arise at any stage during pregnancy, around delivery, or within the first three years of life (Niemann and Michaelis, 1996). However, in many situations, the root reason is unclear (Blair and Stanley, 1988). Although the tone and postural problems may appear shortly after birth.

Motor disorders in CP are usually followed by sensory, perception, communication, cognitive, and behavior problems, as well as subsequent musculoskeletal issues (Bax et al.

2005; Cronk and Stallin 1997). A paper "CP Children Growth" state that cerebral palsy is a severe disability linked to abnormalities in development, body structure, malnutrition and physical activities. Cerebral palsy children have a distinct body composition as well. According to several studies, brain injury can cause gastrointestinal (GI) disorders. Dysphagia, abnormal eating habits, vomiting, and persistent constipation have all been described in neurologically impaired children (Sinha et al. 2008).

## 1.2. Cerebral palsy prevalence

Studies from all around the world found that the CP prevalence ranged from 1.5 to 4/1,000 live births (Arneson et al. 2009).

During the 1940s, two nonprofit organizations in the United States, United Cerebral Palsy and Easter Seal, began population-based studies to find the incidence of cerebral palsy (Andersen, 1957). The prevalence of cerebral palsy was recorded at 5.9 per 1,000 live births in Schenectady and New York, and 1.8 per 1,000 live births in Minneapolis and Minnesota (Andersen, 1957).

A study on birth prevalence of CP in the United States found that the birth prevalence of CP increased in 1985 from 1.9/1000 in 1-year survivors to 2.2 in 2002, with an overall increase of 1.2% (Van et al. 2016). 58.2% of CP children could walk independently in 2008, hand-held mobility device used by 11.3%, and limited or no walking abilities were found in 30.6% children (Christensen et al. 2019). It was also discovered that in males CP was more common than in females, and the majority of the youngsters (77.4%) were diagnosed with spasticity (Christensen et al. 2019).

The prevalence of CP in the twenty-first century demonstrates that CP prevalence in developed nations was greater in the first decade of the century than in the twentieth. Between 2002 and 2012, CP prevalence estimates increased from 2-3/1,000 live births in

America (Christensen et al. 2019; Arneson et al. 2009), while the survey in 2006 showed a mild decline from 3.5/1000 to 2.9 per 1,000 in 8-year-old children in 2010. However, studies in Australia (Reid et al. 2016), Europe (Glinianaia, et al. 2010), Japan (Touyama et al. 2016), and Canada (Robertson et al. 2017) have shown that the prevalence of CP is decreasing with time, most notably among low birth weight and preterm newborns. Between 1999 and 2017, the number of incidents in China fell from 1.6 to 1.25 cases per 1000 children (He et al. 2017).

## 1.3.  Prevalence of cerebral palsy in Pakistan

According to Pakistan's 1998 National Census, 2.5% of the entire population is disabled. Although the majority of Pakistan's population (more than 60%) lives in rural regions, multiple studies show that the cerebral palsy prevalence in urban areas found greater than in rural ones (Aziz et al. 2017; Iqbal et al. 2019). According to numerous studies, spastic CP is the most prevalent form of the disorder in Pakistan (Akhtar et al. 2017; Iqbal et al. 2019).

Community-based research was conducted in the Swabi district to determine the CP prevalence. Total 278 children were diagnosed with cerebral palsy in the fifty-six (56) union councils, with an average age of 7.6±1.97 years. 69% were male children and 31% were female children, giving a ratio of 2.2:1 (male to female). In comparison to rural regions (8.3%), urban areas had the highest proportion of cases (91.7%). The prevalence was recorded as 1.22/1000 live births (Aziz et al. 2017).

In a study carried out at DHQ Gujranwala, Iqbal et al. (2019) studied 138 CP children; the male patients were 61.4%, outnumbering females 38.4%. Spastic CP was more prevalent 89.9% than athetoid, atonic and mixed CP. The majority of cases (57.2%) were quadriplegic CP, followed by diplegic CP (31.9 %) and hemiplegic CP (10.9%).

Hospital-based research on cerebral palsy in Pakistani children found that 45% were male and 55% were female, with an overall age of 5.6± 2.25 years (Atif Ahmed Khan, 2014). Spastic cerebral palsy (90%) was the most common type of cerebral palsy, with diplegia (33.3%) and quadriplegia (32.4%) being the most common, followed by ataxic/mixed (3.9%), atonic (3.9%) and athetoid CP (2.0%) (Palsi, 2014).

## 1.4(a). Classification

**Spastic cerebral palsy** is the most frequent type and accounts for 70%-75% of all cases (Rana et al. 2017). Body parts are often underdeveloped and rigid, with jerky movements. A child with spastic CP learns to walk with jerks, and his or her legs and feet often bend inside.

**Dyskinetic (Athetoid CP)** accounts for 20% of all cases. The patient exhibits an unusual, involuntary movement that looks to be a mix of fast-moving body tissues, similar to dancing. Slow, uncontrollable movement, cracked or distorted facial expressions that often disappear during sleep. Dystonic patients have a noninvasive, severe muscular condition characterized by prolonged muscle activity and repetition of movement.

**Ataxic CP** occurs in less than 5% of cases. Patients have poor balance and lack communication skills. Legs with a wide range of motion often stumble and fall during travel.

**Mixed CP** is often a mix of spastic and athetoid CP. It is quite usual that 25% of total cases are mixed.

## 1.4(b). Topographical classification

Depending on the body part affected spastic CP is classified as monoplegia, paraplegia, diplegia, hemiplegia, or quadriplegia. In Monoplegia only one part of the body is affected, although the patient can take care of himself (Rana et al. 2017; Sankar et al.

2005). Diplegia is the frequent and prevalent type of spastic cerebral palsy in which two parts of the body are affected (Rana et al. 2017). Both legs are affected in paraplegia and diplegia, and the patient may also have talipes equinovarus. Hemiplegia is a type of spastic cerebral palsy in which one side of the limb is affected more severely than the other. Quadriplegia is a severe type of spastic CP in which the patient's all four limbs are affected. There are few voluntary movements, as well as severe mental retardation. Patients may also experience difficulties swallowing and jerks (Menkes et al. 2000). Patients have difficulty walking with their legs and give a scissors-like appearance when they allow standing.

## 1.5. Symptoms

All types of CP are distinguished by reflexes, abnormal muscle tone, or motor improvement and coordination. Bone and joint deformities and contractures are possible. Spasticity various involuntary movements, balance issues, unsteady gait, and smooth tissue findings consisting typically of reduced muscle mass are the characteristic symptoms. Scissor and toe walking are common among persons who can walk. CP symptomology is quite variable.

CP babies bodies can be both floppy and rigid and usually have an abnormal posture. Birth abnormalities such as spine curvature, a small head sometimes or a small jawbone sometimes manifest along with CP. Symptoms may also appear, or become more severe as an infant grows older. Sometimes no symptoms were displayed by the infants born with CP. CP is often diagnosed when infant reaches the developmental stage of 6/12 - 9/12 and begins to mobilize, asymmetry, or gross motor developmental delay is observed.

## 1.6. Prognosis

Although CP is not a progressive condition, the signs and symptoms might worsen with time. Individuals with this disorder might recover slightly throughout childhood if they

get intensive treatment from specialists. People with CP might develop arthritis at a younger age than the general population due to the pressure exerted on the joints by rigid muscles.

Until the child begins schooling, full mental ability of newborn is usually not recognized. People with CP usually have some type of learning problem; however, it is not related to a person's intelligence or IQ level. Individuals with CP have intellectual levels that range from brilliant to mentally retarded, much like the general population. Experts have stated that it is essential not to underestimate a CP patient's abilities and give them every opportunity to learn (Strauss et al. 2008).

The ability to remain independent with CP depends on the severity of the condition. Some persons require a personal assistant for daily life activities. Others require assistance for certain activities and can live semi-independently. While some can live on their own. However, many people with CP have a normal life expectancy and their survival has been linked to the capacity to self-feed, roll and ambulate (Schejbalová, 2006). Reproductive function are not affected in CP; some CP people have children and have a happy parenting life.

## 1.7. Associated impairments

Mental retardation (MR) occurs in more than 60% of cases of CP (Singhi et al. 2003). According to a study, children with spastic quadriplegia had more intellectual disability than children with spastic hemiplegia. Visual abnormalities such as strabismus, nystagmus, amblyopia, refractive errors and optic atrophy are frequent in CP children. Hearing impairment is also common in children with cerebral palsy. Neonatal meningitis, Low birth weight, severe hypoxic-ischemic and kernicterus cases are associated with CP. Epilepsy, which is correlated with grey and white matter damage, is the most prevalent congenital defect in CP patients (Manlongat et al. 2020). Speech is impaired in CP as a result of bilateral

corticobulbar and oro-motor dysfunctions. Mental retardation and language deficits, both expressive and receptive, are prevalent in CP children. Articulation difficulties and poor speech affect 38% of CP children. There are additional oro-motor issues such as eating difficulty, swallowing abnormalities, and drooling. This can lead to nutritional issues that impair physical growth. Behavioral issues are also well documented. Tactile sensory abnormalities and proprioception are frequent in CP children. Psychiatric disorders such as hyperkinesis, anxiety, inattention, depression, and behavior issues were all observed in children with CP. Brain comorbidities are more prevalent in organ systems adjacent to the brain, such as the eyes and facial clefts, and less common in organ systems far from the brain, such as the kidney and genitalia (Goldsmith et al. 2019). Associated CP comorbidities include hydrocephaly, microcephaly, cleft palate, cleft lip, congenital heart problems, esophageal atresia, congenital eye defects, and congenital hip dislocation (Pharoah et al., 2006). The associated disorders found more disastrous than motor impairment for CP children.

## 1.8.  Causes of cerebral palsy

It is very important to classify the causes based on the period of the brain injury, whether prenatal, perinatal, or postnatal.

### 1.8a. Antenatal

Congenital brain abnormalities, especially cortical development defects, are among the most commonly recognized causes of CP. Children with congenital brain abnormalities have more problems outside of the (CNS) central nervous system (Coorssen et al. 1991), and congenital malformations are significantly linked to cerebral palsy in general (Blair and Stanley, 1993a; Torfs et al. 1990; Croen et al. 2001; Palmer et al. 1995; Nelson and Ellenberg, 1985 and 1986).

Mostly, recognized prenatal causes of CP include maternal infections during the second and first trimesters of pregnancy (toxoplasmosis, cytomegalovirus, rubella) and vascular events (middle cerebral artery blockage). Rare genetic syndromes, Metabolic disorders and maternal toxicity are among the less prevalent causes of CP.

## 1.8b. Perinatal

Obstetric problems such as antepartum hemorrhage, cord prolapse, and obstructed labor may harm the fetus and cause hypoxia. Before CP linked to the acute intrapartum event critical conditions must be met, the criteria include umbilical cord arterial, metabolic acidosis in the fetal scalp, and very early neonatal blood samples (pH< 7.00 and base deficit > 12 mmol/L).

Neonatal encephalopathy is a clinically identified condition of impaired neurological function in the early days of life of newborn infant's, recognized by difficulties in breathing, depression of reflexes and tone, lack of awareness, and, convulsions (Nelson and Leviton, 1991). CP children who have a neonatal encephalopathy history are more likely to show evidence of intrapartum hypoxia (meconium staining of the amniotic fluid) and have a more severe type of CP than those who do not have a history of neonatal encephalopathy (Gaffney et al. 1994).

CP may be caused by severe neonatal infection., severe hypoglycemia, or untreated jaundice.

## 1.8 c. Post-neonatal-acquired cerebral palsy

The majority of cases of post-neonatal acquired cerebral palsy are caused by infection or injury in developed countries. The introduction of new vaccinations should reduce the number of children suffering from meningitis and its related neurological effects. Cerebral palsy can be caused by both accidental events, like as car accidents and near-

drowning experiences, and non-accidental traumas. Other causes include surgery for congenital deformities, prominent life-threatening events, and cerebrovascular accidents. In underdeveloped nations, malaria, meningitis, and septicemia continue to be major causes of CP.

## 1.9. Risk factors role in the genesis of CP

It is important to differentiate between causes, risk factors and associations. It has found that the motor impairment is not caused by a single incident rather sequence of events, in some children with CP. This lead to the "causal pathways," concept which are a series of interconnected events that result in disorder (Stanley et al. 2000). Some of these variables are seen in infants of all gestation, whereas others are only found in preterm or full-term newborns. Multiple pregnancies have some interesting links as well. Risk factors may exist during and before pregnancy, during labor and birth, and in the period immediately following birth.

# 1.9 a. Before pregnancy risk factors

## 1.9(a). Maternal factors

CP is connected with a number of maternal factors including the irregular menstruation, extended intermenstrual intervals, or delayed beginning of menstruation (Torfs et al. 1990). An unusual short or lengthy period between pregnancies has also been recognized as a risk factor for CP (Torfs et al. 1990; Pinto-Martin et al. 1998). Two studies have discovered a link between CP in children of normal birth weight and low socioeconomic status (Dowding and Barry, 1990; Dolk et al. 2001).

A study of preterm infants found that having three or more children was a risk (Topp et al. 1997). Mostly studies have found a link between earlier fetal deaths and CP (Powell et al. 1988; Nelson and Ellenberg, 1986). Cerebral palsy is associated with several maternal

medical problems. Intellectual impairment (Nelson and Ellenberg, 1986), thyroid disorders (Nelson and Ellenberg,1986; Blair and Stanley, 1993b), and seizures (Ellenberg and Nelson, 1986), are few examples (Nelson and Ellenberg,1986; Blair and Stanley, 1993b).

## 1.9(b). Sibling and Paternal factors

Sibling and paternal influences are rarely addressed. In people with athetoid/dystonic CP advanced paternal age is more common (Foley and Fletche, 1993). Motor impairment in a sibling has been related to CP in the Collaborative Perinatal Project of the National Institute of Neurological and Communicative Disorders and Stroke (NCPP) (Ellenberg and Nelson, 1986).

## 1.9b. During pregnancy risk factors

In term infants, CP is associated with an increased risk of preeclampsia (Paneth and Collins, 1998), but this connection does not occur in preterm infants (Spinillo et al. 1998a; Murphy et al. 1995). It has been proposed that preeclampsia causes the production of catecholamines in premature newborns, which speeds up fetal maturation (Pettigrew and Amiel-Tison, 1991).

While maternal trauma/injury during pregnancy has been identified as a one of the cause of CP (Gilles et al. 1996). In the NCPP, the rate of CP was higher in children whose mothers received estrogen and thyroid hormone during pregnancy (Ellenberg and Nelson, 1985). Antepartum hemorrhage is found to raise the incidence of CP linked with premature delivery (Stanley et al. 2000).

Two variants have been found to be the heterozygous carriers of venous thrombosis. The most prevalent cause of familial thrombosis is caused by factor V Leiden mutation in

the Factor V gene. Prothrombin is the second gene. The carrier frequency in Caucasian males is more (5.5%) than females (4.8%) (Ridker et al. 1997).

Neonatal stroke or placental thrombosis, may have occurred in the three cases documented, that results in hemiplegia. So, a link between CP and coagulation disorder and markers of autoimmune and inflammatory mediators have been found (Nelson et al. 1998a).

## 1.9(a). Multiple pregnancies

Multiple births are linked with both an increased risk of CP and mortality. Preterm birth, poor intrauterine growth, intrapartum complications, and birth abnormalities are all linked to multiple pregnancies. The survival of only one twin during the monochorionic twin pregnancy is recognized as a major risk factor for developing CP. During gestation death of one twin may damage the survivor's brain development (Cooke and Pharaoh, 1997).

## 1.9c. During labor-risk factors

Major causes of perinatal asphyxia include; prolonged or traumatic delivery (cephalopelvic disproportion/abnormal presentation), prolapsed cord, maternal shock, substantial intrapartum hemorrhage, and a large baby with shoulder dystocia (Stanley et al. 2000). Other observed associations with cerebral palsy include emergency caesarian delivery and the extended second stage of labor (Powell et al. 1988), abnormal fetal position and preterm placental separation (Torfs et al. 1990). In term infants, intrauterine infection, particularly chorioamnionitis, during labor and in the latter stages of pregnancy is a substantial risk factor for CP (Nelson and Willoughby, 2000; Murphy et al 1995; Walstab et al. 2002; Polivka et al. 1997). Furthermore, infants were more likely to be hypotensive, have newborn convulsions and have a clinically diagnose of hypoxic-ischemic encephalopathy when born from infected women (Nelson and Grether, 1997).

The presence of meconium-stained fluid (Walstab et al. 2002; Spinillo et al. 1998b), of all gestations infants prolonged rupture of the membranes (Ellenberg and Nelson, 1985), tight nuchal cord and preterm newborns (Grether and Nelson, 1998b) are other associations with CP.

Magnesium sulfate, which is used to treat severe preeclampsia, may protect against the development of CP in premature infants (Schendel et al. 1996; Grether and Nelson, 1995). Several multicenter randomized studies are now underway.

## 1.9d. At birth- risk factors

High-tech diagnostic methods and neonatal intensive care facilities has increased the survival of premature infants, some of whom develop CP later in life. Fertility techniques have also increased the number of premature births. The risk of CP increases with decreasing birth weight (Murphy et al. 1995; Hagberg et al. 1993; Torfs et al. 1990; Stanley and Watson, 1992). The risk of cerebral palsy increases with prolonged gestation and decreasing birth age (Stanley et al 2000). Especially, in moderately premature babies poor intrauterine growth increases the risk of cerebral palsy (Hagberg and Uvebrant, 1992; Stanley and Blair, 1990). In premature babies subsequent brain injury caused by complications such as intraventricular hemorrhage and the increasing number of low birth weight infants with CP might be linked to their survival. Low placental weight and low Apgar scores (Torfs et al. 1990) are strongly associated with CP (Van de Riet et al. 1999).

## 1.9e. Risk factors in the newborn period

CP is related to sepsis (Stanley and Blair, 1993a), respiratory diseases, and neonatal seizures (Torfs et al 1990; Powell et al. 1988). Hypotension, prolonged ventilation, patent ductus arteriosus, hyponatremia, blood transfusion, pneumothorax, complete parenteral nutrition, parenchymal damage with substantial ventricular dilation and seizures are all

documented risk factors in premature infants in cerebral ultrasound (Murphy et al. 1997). Neonatal seizures are strongly linked with the risk of cerebral palsy (Torfs et al. 1990; Murphy et al. 1997).

## 1.1o. Diagnosis

Cerebral palsy is most commonly diagnosed during pregnancy, although it can also occur during labor or immediately after birth. Unusual posture, irregular muscle tone, and slow motor development are the most common initial signs of the diagnosis of CP. In the past, cerebral palsy was mostly diagnosed clinically, based on the observation of symptoms for example delays in completing motor milestones and changes in muscle tone. The clinical diagnosis of CP be confirmed by imaging MRI and cranial ultrasonography.

The testing technique is based on clinical imaging, family history, symptom development patterns, and other factors that determine the probability of diagnosis. Laboratory/brain testing include ultrasound, MRI and CT scan are effective diagnostic tools. Associated impairments such as visual and hearing impairment, cognitive dysfunction, seizures, and touch or pain perception can help in the clinical assessment and determine the diagnosis.

Since the 1970s, clinical gait analysis has been used to investigate children with cerebral palsy (Hoffer and Perry, 1983). For clinical gait analysis there are several technical solutions available that help in the measurement of joint kinematics. 3D passive-marker systems with infrared cameras, bi-planar video observation, inertial sensors and 3D active-marker systems with light-emitting diodes are among them. For CP diagnosis, clinical prediction models and neuroimaging are employed, when patients are under the age of two years. Further research is required in it.

## 1.11. Treatments

Although, there is no as such treatment for CP, but a variety of therapies/treatments can help a person with the disorder function and live more efficiently. However, children with CP have a better chance of overcoming developmental problems if treatment begins early. Cerebral palsy is treated with a variety of treatments, including physical therapy, speech therapy, medication, and surgery.

### 1.11(a). Physical Therapy

Several recent studies had been conducted to determine the efficacy of resistive exercise (Andersson et al. 2003; Dodd, Taylor and Damiano, 2002). One research used the pendulum test to detect the stretch reflex and discovered that CP children immediately following strengthening exercises did not have greater spasticity of the quadriceps femoris muscle. This study also shows that resistive exercise may be beneficial in muscle strengthening when muscular weakness causes dysfunction. A research study (Dodd, Taylor, and Damiano, 2002) discovered that training can help people with cerebral palsy increase their strength and perhaps improve their motor function.

### 1.11(b). Surgical treatments

Muscle imbalance induced by spasticity can result in hip and knee dislocation. Hip dislocation is common in CP children, with up to 59% of them experiencing it (Hodgkinson et al. 2001). Surgical treatments include non-invasive abduction bracing, pelvic osteotomies, proximal femoral resection and soft-tissue releases. Proximal femoral varus-producing osteotomy with a combination of suitable soft tissue is a most popular surgical technique.

### 1.11(c). Medications

For the treatment of equine spasticity several studies supported the use of botulinum toxin type A (Houltram et al. 2001), but a literature review (Ade-Hall and Moore, 2000) found no solid evidence to refute or support its use for the treatment of leg spasticity in CP children. Injections had very long lasting effects and were preferred by patients, similarly Botulinum toxin type A injections were equally successful as serial casting (Houltram et al. 2001). According to research, intrathecal baclofen has been used to treat spastic and dystonic cerebral palsy. However, there is no evidence in the data to support its use in reducing spasticity in the lower limbs, and the benefits in the upper extremities are uncertain. Caffeine is a popular treatment for apnoea in neonatal intensive care units (Schmidt et al., 2006).

### 1.11(d). Electrical Stimulation

Cerebral palsy can also be treated with electrical stimulation. Several research has been conducted to document its effects. One research (Wright and Granat, 2000) showed it to be a vey effective therapy for upper limb dysfunction in Paediatrics; however, in other studies (Dali et al. 2002) no significant clinical effects found when applied to lower limb dysfunction.

## 1.12. Prevention and care

Preventive strategies for cerebral palsy include efforts to minimize prematurity, such as cervical sutures to avoid preterm delivery in mothers with cervical incompetence (Alfirevic et al. 2012) and the use of tocolytic medications to prevent the onset of labor (van Vliet et al. 2014; Vogel et al. 2014). According to one study, utilizing Magnesium sulfate can reduce the chance of CP when a woman is at risk of preterm birth. When given before 34 weeks of gestation, prenatal steroids are also useful in preventing cerebral palsy (Sotiriadis et al. 2015). They frequently exhibit depressed symptoms (Van Der Slot et al.,

2012). Therefore, parents have the responsibility to make them morally and mentally strong and provide an environment where they feel comfortable.

## 1.13. Literature Review

A survey of studies carried out on cerebral palsy in Pakistan highlights the year, place of research, study duration, sample size, study design, study domain, and treatment methods. After a thorough literature review on cerebral palsy, it was evident that there were few studies published that covered the etiological, risk, impact on caregivers, treatment and management (Table 1.1). The etiology of cerebral palsy concerning gender and clinical types has not been reported.

**Table 1.1: Literature Review Table**

| Sr. No. | Reference | Publish Article/Paper | Institute | Design | Duration | Sample size (M/F ratio) | Study domain | Management Plan |
|---|---|---|---|---|---|---|---|---|
| 1. | Babar M, Ahmad S, 2001 | Rehabilitation Management with Ambulation Dysfunction of Diplegic CP child | Children's Hospital, Lahore | Descriptive study | 2000 - 2001 | 50 ----- | Thr./Mng. # (Upper and Lower Limb Physical Therapy) | Physical therapy and bracing |
| 2. | Nazir et al. 2003 | Etiology and types of CP | Allied Hospital, Faisalabad | Prospective study | 1998 - 2000 | 160 ----- | Clinical types/risk factor | |
| 3. | Dai et al. 2006 | The management of Cerebral Palsy: low or high dose- Botulinum toxin type A | Karachi | Review article | ------- | ------- | Thr./Mng. # (Management) | Botulinum toxin type-A |
| 4. | Nazir et al. 2006 | Relationship of etiology of cerebral palsy with the types | Allied Hospital, Faisalabd | Descriptive case study | 2002-2004 | 120 ----- | Clinical types/risk factor | |
| 5. | Khalique et al.2006 | Multivariate analysis of the metals in selected CP patients hair | Rehabilitation centers, Islamabad | Experimental study | 2004 | 95 | Risk factors (Metals in hair) | |
| 6. | Ahmed et al. 2008 | Cases related to neurology admitted into a general pediatrics ward. | Civil Hospital, Karachi | cohort study | 2006 | 67 | Association (Brain) | |
| 7. | Ibrahim et al.2010 | Treatment of infantile spasms by using vigabatrin & ACTH | AKUH, Karachi | Descriptive study | 2006-2008 | 56 | Thr./Mng. # (Management) | Vigabatrin and ACTH |
| 8. | Nabila et al. 2011 | Sensory Abilities recognition in CP Children | BMSI, JPMC, Karachi | Randomized controlled trial | 2010-2011. | 60 ----- | Thr./Mng. # (Management) | Gabapentin and Carbamazepine |
| 9. | Soomro et al. 2011 | Cognitive-behavioral Therapy effectiveness in mothers of CP Children mothers | Karachi | Experimental study | 2011 | 24 ------ | Impact on caregivers (Maternal health) | Cognitive-behavioral Therapy |
| 10. | Saeed et al. 2011 | Epilepsy frequency in children with CP | Children Hospital, Lahore | Retrospective analysis | 2007-2009 | 300 ------ | Association (Epilepsy) | |
| 11. | Ahmed et al. 2011 | Equinovarus deformity treatment through surgery in CP children | Jamshoro. | | ------- | 20 ----- | Thr./Mng. # (Surgery) | Treatment of equinovarus deformity |

| 12. | Fatima et al. 2013 | Cerebral palsy relation with maternal health | IPM&R, DUHS, Karachi | Observational study | ------- | 65 ----- | Impact on caregivers (Maternal health) | |
|-----|------|------|------|------|------|------|------|------|
| 13. | Nabila et al. 2013 | Obstetrics Determinants of CP from birth to five years child | Institute of Physical Medicine and Rehabilitation, Karachi | Cross-sectional study | 2007-2010 | 300 ----- | Risk factors | |
| 14. | Akhter et al. 2013 | Talipis Equinovarus surgical treatment in Children with CP and Poliomyelitis | PIMS | Retrospective study | 2008-2011 | 23 (70%/30%) | Thr./Mng. # (Surgery) | Surgical correction of TEV |
| 15. | Ibrahim et al.2013 | Prevalence of childhood disability Sind, Pakistan. | Sindh | Cross-Sectional study | 2013 | 176 364 (51%/ 49%) | Epidem # | |
| 16. | Bangash et al. 2014 | Risk factors and clinical types of cerebral palsy | Karachi | Cross-sectional study | 2010-2011 | 20 ------ | Epidem. # / Clinical types/risk factors | |
| 17. | Khan et al.2014 | CP in Pakistani Children- A Hospital Survey | AFIRM, Rawalpindi | Case Report | 2011-2013 | 102 (45%/ 55%) | Epidem # / Risk factors | |
| 18. | Afzal et al. 2014 | Perinatal adverse events association with the CP | Children's Hospital &the Institute of Child Health, Multan. | Cross-sectional study | 2010-2012 | 178 ------ | Epidem. # /risk factors | |
| 19. | Iram et al. 2014 | Non-invasive interventions treatment for controlling drooling | PSRD, Lahore | Experimental study | 2014 | 15 ----- | Thr./Mng. # (Mouth Therapy) | Non-invasive interventions for drooling |
| 20. | Pervez et al. 2014 | Kinesiologic taping therapy treatment for controlling drooling in CP children | Islamabad | Experimental study | 2014 | 30 ------ | Thr./Mng. # (Mouth Physical Therapy) | Kinesiologic taping therapy in drooling management |
| 21. | Khan et al. 2016 | Treadmill training vs overground gait training in spastic CP children | Karachi | Randomized Control Trail | 2016 | 28 ----- | Thr./Mng. # (Lower Limb Physical Therapy) | Treadmill training with overground gait training |
| 22. | Ali et al. 2016 | Birth venue effect on CP children | Lady Reading | Observational study | 2013 | 82 ----- | Clinical association | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Hospital, Peshawar | | | | | |
| 23. | Shoukat et al. 2016 | Effectiveness of Modified Constraint Induced Movement Therapy in Hemiplegic CP children | Pakistan Railway Hospital, Rawalpindi. | ------- | 2016 | 18 ----- | Thr./Mng. # (Upper and Lower Limb Physical Therapy) | Modified Constraint Induced Movement Therapy |
| 24. | Hira et al. 2016 | Bimanual therapy vs Constraint induced movement therapy in Upper limb in children with hemiplegic CP. | Islamabad | Randomized control trial | 2016 | 20 ----- | Thr./Mng. # (Upper Limb Physical Therapy) | Constraint induced movement therapy vs bimanual therapy in Upper motor function |
| 25. | Khan et al. 2016 | Bimanual Intensive Therapy effectiveness in Spastic CP children | Lahore. | Experimental study | 2014-2015 | 30 ----- | Thr./Mng. # (Upper Limb Physical Therapy) | Hand-Arm Bimanual Intensive Therapy |
| 26. | Ryu et al.2016 | Horseback riding and aquatic movement therapies in patients with CP | South Korea | Experimental study | 2016 | 32 (56%/44 %) | Thr./Mng. # (Aquatic and Therapeutic Physical Therapy) | Aquatic movement and horseback riding therapy |
| 27. | Kumar et al. 2016 | Severity of Depression in CP Children mothers | Civil Hospital , DUHS Karachi | Cross Sectional study | 2013 | 81 ----- | Knowledge and aptitude(Maternal health) | |
| 28. | Liaqat et al. 2016 | Universal Exercise Unit Therapy effectiveness in Spastic And Athetoid CP children | Lahore | Experimental design | 2016 | 23 ----- | Thr./Mng. # (Upper and Lower Limb Physical Therapy) | Universal Exercise Unit Therapy |
| 29. | Shaheen et al. 2016 | Stretching exercises role in the management of constipation in spastic CP | IIRS | Experimental Study | 2016 | 30 ----- | Thr./Mng. # (Gastrointestinal Physical Therapy) | Stretching exercises |
| 30. | Shafique et al. 2017 | Neurological findings prevalence in CP children | Lahore | Descriptive study | ------- | 104 (54%/46 %) | Clinical association (Brain) | |

# Epidem.=Epidemiology; Thr./mng.= therapy and management

## 1.14. Study gap

During the literature review of cerebral palsy, the following study gaps were evident:

- An epidemiological study with respect to clinical types is rarely reported.

- Treatment plans have been reported however, studies highlighting the risk factors including genetic and environmental concerning clinical types are rarely found in Pakistan.

- True incidence and prevalence studies for cerebral palsy in Pakistan are rarely reported.

- Differences in the **Antenatal,** Neonatal **and post-neonatal** complications as an etiology were not well studied in Pakistan.

- No research conducted regarding the genetic underpinning of CP and various aspects like its familial/sporadic nature, syndromic/non-syndromic occurrences, mutation profile, and genetic heterogeneity remains unexplored.

- Impact of consanguinity on CP is not well studied in Pakistan.

- Preventive strategies for cerebral palsy in Pakistan should be implemented.

## 1.15. Aims and objectives

### 1.15(a). Aims

Understanding the phenotypic manifestation, etiology, and associated disorders of cerebral palsy in our population concerning gender and clinical types.

### 1.15(b). Objectives

Following were the objectives of the present study;

- Finding relative proportion of CP clinical types in the study population.

- Finding sociodemographic attributes that might increase the risk of CP.

- Finding frequency distribution of CP concerning sex ratio.

- Finding the prenatal, genetic, and environmental attributes and their contribution to the etiology of CP.

- Finding various associated anomalies with CP.

- Observing treatment and management plan in terms of each clinical CP type.

# CHAPTER 2

# METHODOLOGY

## 2.1. Ethical and Consent Approval

This study was launched after receiving official permission from the Executive Director, National Institute of Rehabilitation Medicine (NIRM), Islamabad and ethical approval from the Ethical Review Committee of Quaid-i-Azam University. The patients' or guardians' consents were obtained before data collection. Information was not obtained from patients whose guardians refused to provide consent or whose information was incomplete.

## 2.2. Study subjects and data collection site

This was a hospital-based study carried out at NIRM. The National Institute of Rehabilitation Medicine (NIRM) in Islamabad is one of the largest rehabilitation centers for disabled and handicapped people. The influx of patients is not only from Punjab but also from Khyber Pakhtunkhwa, Azad Jammu and Kashmir, FATA and war-affected areas. Despite limited resources and manpower, this institute serves patients from all across Pakistan with expert physicians, surgeons, and skilled medical personnel. The institute has around 200 beds, four minor and major operation theaters, and a four-bed intensive care unit (ICU). The outpatient section is available at NIRM for regular treatment and diagnostics. On a daily basis, this institute provides medical services to around 900 patients. This institute provides preference-based and free medical services to disabled persons such as diagnosis, admission, surgery, post-surgery nutrition guidance, and rehabilitation. Artificial devices, such as hearing devices and orthotics, are provided free of cost. It is a tertiary care center including diagnosis through radiology, ultrasonography, CT scan, MRI and mobile X-ray units. Patients get a higher degree of professional therapies such as physiotherapy, speech therapies, and so on from properly qualified and trained physiotherapists, speech therapists, etc. A higher level of professional therapies such as physiotherapy, speech therapies, etc. are provided to the patients with professionally qualified and trained physiotherapists and

speech therapists. The majority of patients visiting NIRM originate from the lower socioeconomic class. Patients entitled to government services and federal employees are also treated at this facility.

## 2.3. Study Design and Sampling Method and Duration

A cohort study on CP and its biodemographic correlates was conducted through an epidemiologically based study design across Pakistan on 989 subjects. The study was performed on children with CP at NIRM, Islamabad in Pakistan between 2020-2021. Multiple sources of information were used, including records of patients who visited a rehabilitation center.

## 2.4. Recruitment of Patients

Subjects with CP or parents/attendants of children with CP irrespective of their age, gender and ethnicity were recruited for the present study. Clinically confirmed cases were collected after proper diagnosis and identification from the physicians, physiotherapists and speech therapists.

## 2.5. Identification and classification of cerebral palsy

The Swedish and European (SCPE) classifications were used to classify the CP subtypes (Hagberg et al. 1975; Hagberg et al. 1984; Hagberg, 1989). The SCPE, initially includes 3 spastic syndromes: spastic quadriplegia, spastic diplegia and spastic hemiplegia. Spastic quadriplegia is a severe complete motor impairment affecting all four limbs, with the lower limbs affected to at least the same extent as the upper ones. In spastic diplegic CP group the lower limbs are more affected than the upper limbs. Ataxic types include simple ataxia and ataxic diplegia (Hagberg et al. 1972). Dystonia, athetosis, choreo-athetosis, and

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a fourth category, choreo-athetosis plus dystonia, are the dyskinetic subgroup (which is not included in this study).

The SCPE network introduced a new CP subtype classification in 2000. The spastic subtypes in the SCPE classification tree are; unilateral spastic CP (USCP) and bilateral spastic CP (BSCP). According to the SCPE classification, hypokinesia is distinguished by dystonic CP, whereas choreo-athetosis is distinguished by hyperkinesia is distinguished by choreo-athetosis, a tendency to reduce muscle tone. These subtype classifications include a mixed (SCPE) or non-classifiable(SCPE) category for exceptional cases.

Motor disability is also classified as mild, moderate, and severe. The degree of limitation of daily functions and activities could be used to determine severity: in severe CP there is significant limitations or prevents daily functions and activities; in moderate there is some limitations and performing daily activities with help of an aid, and in mild there is no limitations in daily activities (Wu et al. 2011).

## 2.6. Questionnaire Designing

After a thorough literature review, the proforma was designed by observing the risk factors that were analyzed in the literature. The proforma comprised of following sections:

**Sociodemographic parameters** included age, gender, province, caste-system, language, rural/urban origin, economic status, marital status and literacy.

**Parental parameters** included maternal and paternal age, maternal education and occupation.

**Genetic parameters** included consanguinity, familial/sporadic nature, family history such as generation affected, sibship with disorder and number of affected in the family.

**Clinical parameters** included clinical types, associations and treatments.

**Birth parameters** included gestation period, birth weight, mode and place of delivery.

**Pregnancy record** included pregnancy complications, trauma during pregnancy, pregnancy number, maternal malnutrition, high fever during pregnancy and maternal morbidity.

**Environmental exposure** included jaundice, meningitis, head injury, microcephaly, hydrocephalous.

**Treatments** included drugs and therapies given, starting of the treatment, and improvement due to it.

### 2.6.1. Proforma Filling

Following the routine checkup by a specialized doctor, the patients were asked to participate in the study by briefly explaining the aim and purpose of this study. Generally, the patients originating from urban areas and those who were educated were highly helpful and provided detailed information. Few parents, however, were hesitant to provide the information because they were concerned about the confidentiality of their personal information; such incomplete proforma were not included in the analyses. Clarification of the goal of collecting this data and its use for research purposes only, without any access or identification of a subject established their trust. Family history was recorded with the help of pedigree construction.

## 2.7. Exclusion and Inclusion criteria

The inclusion criteria included the patients with a confirmed diagnosis of "CP" by a specialist and their families accepted to participate in the study. All children were assessed by a CP clinician, who included three senior physicians, physiotherapists, and speech

therapists with good clinical experience, and particular training in the CP children evaluation. Cerebral palsy phenotypes associated with other disorders like mental retardation, epilepsy, and limb anomalies were included in this study. While all cases in which the major presentation was Talipes, Duchene Muscular dystrophy, Polio, Arthrogryposis, and Limb amputation, while cerebral palsy occurred as a minor disorder, were not included.

## 2.8. Data Analysis

Proformas were carefully assembled and data entry and storage were carried out with the help of MS-Excel (Office 365). For data analysis, the data were cleaned for inconsistencies, preparing contingency tables (crosstabulation) for bivariate analysis and then applying Chi-square test (P<0.05 is significant) to find out a significant difference between dependent and independent variables and multivariate regression analysis was also done.

Excel and SPSS (version 20) were used for preparing cross tables and graphs. Prism GraphPad (version 5) was also used to apply Chi-square test.

Multivariate regression analysis was also performed. The dependent variable gender and clinical types were taken as dichotomous, while the parental factors, sociodemographic factors, maternal factors, clinical factors were considered as independent variables. For multiple regression analysis a stepwise logistic regression was performed and only the significant variables were retained in the final model. Initially socio-demographic and epidemiology variables were included. Secondly, parental demographic variables were included. Thirdly, clinical parameters were included. Fourthly, neonatal, maternal, obstetric and gynecological problems were included. In the fifth model, treatments were included. Finally, all parameters were incorporated, and combination of variables were found to have a significant association.

## 2.9. Databases Visited for Study

During the study period for the literature survey, different databases were visited such as PakMediNet, NCBI, Pub Med, and Google Scholar, thus to select the topic, finding study gaps and designing the proforma.

## Databases visited

**Table 2.1: Databases Visited**

| Data Base | Explanation | Purpose | URL |
|---|---|---|---|
| PakMediNet | Pak Medical Journals Repository | Literature research/ Paper retrieval | https://www.pakmedinet.com/ |
| NCBI, PubMed | National Centre for Biotechnology Information | Literature research/ Paper retrieval | https://www.ncbi.nlm.nih.gov/ |
| Google Scholar | Google Scholar | Literature research/ Paper retrieval | https://scholar.google.com/ |
| WHO | World Health Organization | Maintains Data/deal Congenital anomalies | https://www.who.int/news-room/factsheets/detail/congenital-anomalies |
| ICD version 10 | International Classification of Disease | Classification | https://www.who.int/classifications/icd/icd/icdonlineversions/en/ |

| | | | |
|---|---|---|---|
| CPRN | Cerebral Palsy Research Network | Research and monitor trend in CP | https://cprn.org/ |
| CDC | Centers for Disease Control and Prevention | Collects American People health data | https://www.cdc.gov/ncbddd/cp/data.html |
| NPEU | The National Perinatal Epidemiology Unit | Statistical/ epidemiology research on newborn | https://www.npeu.ox.ac.uk/ |
| Cerebral Palsy Alliance | Cerebral Palsy Alliance | Genomic database for CP | https://cerebralpalsy.org.au/ |
| SCPE | Surveillance of cerebral palsy in Europe | Research and monitor trend in CP | https://eu-rd-platform.jrc.ec.europa.eu/scpe_en |

# CHAPTER 3

# RESULTS

From February 2021 to August 2021, the study was conducted through hospital-based surveillance of CP children at the National Institute of Rehabilitation Medicine (NIRM), Islamabad, Pakistan. More than one thousand subjects were recruited out of those 989 fulfilled the inclusion criteria and provided complete information. The results have been divided into five different sections.

- Demographic attributes of the patients included province, origin, occupation, literacy, socio-economic status and parental consanguinity, etc. In all of these representations, males (61%) were higher than females (39%).

- Cerebral palsy was classified according to motor impairment, severity levels and parental consanguinity. It was observed that spastic CP was found higher in number (53%) than the remaining types. Postnatal natal and prenatal causes also found higher in spastic CP.

- Neonatal, maternal, obstetric and gynecological problems were also discussed. Various anomalies associated with the CP were observed in which speech impairment was found very high (20%).

- Treatment given to CP patients and improvement after treatment was also analyzed.

## 3.1 : Demographic attributes of index subjects

### 3.1.1. Distribution of index subjects based on province

Out of 989 subjects, half of the patients originated from Punjab (51%), followed by KPK (30%), Azad Jammu and Kashmir (12%), and Islamabad (5%). The remaining 2% of patients belong to the province of Sindh, Chitral and FATA areas (Fig. 3.1.1). The representation of males in these provinces was seen to be higher than females (1.5:1). However, no significant association was observed when data were distributed with respect to gender and province (Table 3.1a).



**Fig. 3.1.1: Distribution of index subjects based on province**

### 3.1.2. Distribution of index subjects with respect to rural/urban origin

An estimated 68% of subjects originated from rural areas and the remaining 32% were from urban areas (Fig. 3.1.2). The representation of male subjects was found to be higher in rural areas than in urban areas. However, no significant association was observed when data were distributed with respect to gender and origin (Table 3.1a).



**Fig. 3.1.2: Distribution of index subjects based on rural/urban origin.**

### 3.1.3. Distribution of index subjects based on mother tongue

Among the 989 index subjects, most of the patients had Punjabi ethnicity (48%), followed by Pashto (15.7%), Hindko (15%), and Kashmiri/Pahari (7%). The representation of other languages such as Khowar (6%) and Urdu (5%) were comparatively low in numbers (Fig. 3.1.3). The representation of males was higher in all these provinces than in index females. However, no significant association was observed when data were distributed with respect to mother tongue and gender (Table 3.1a).
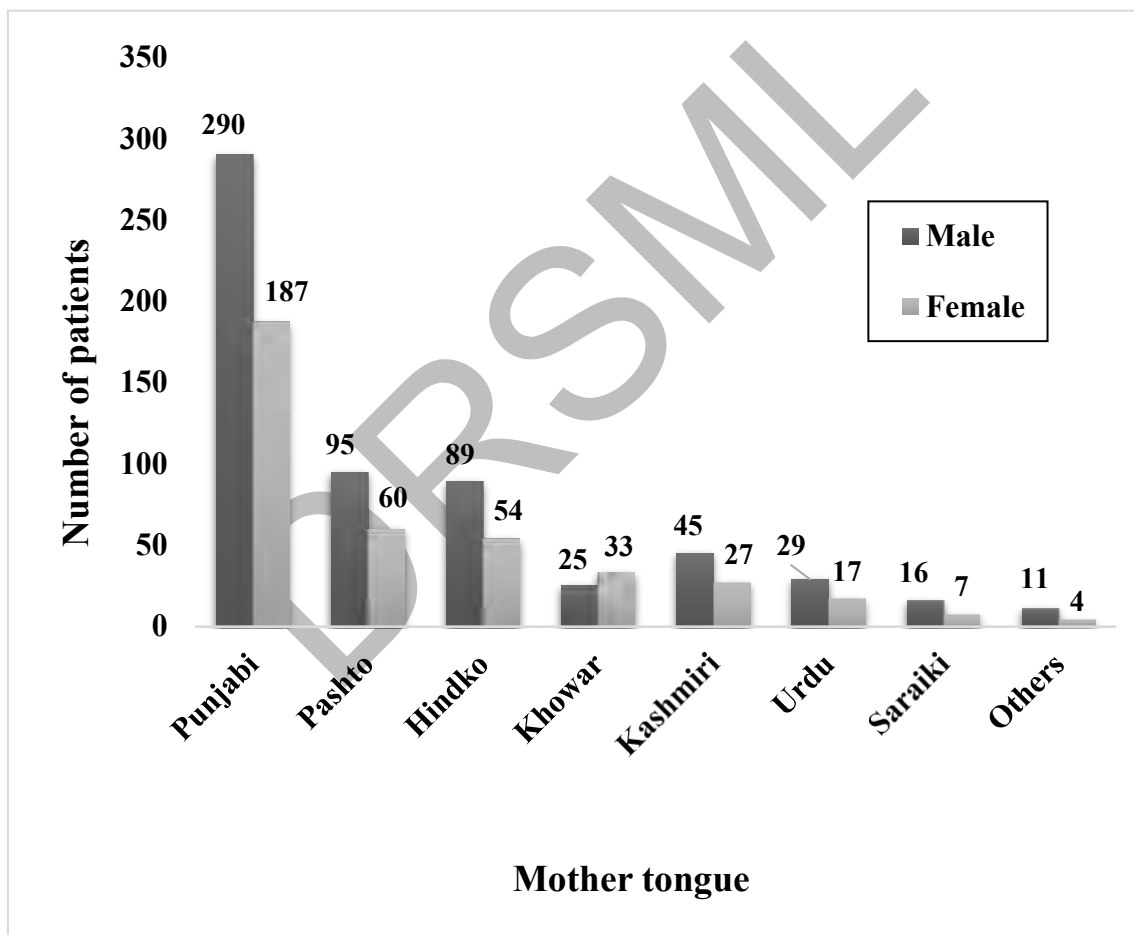


**Fig. 3.1.3: Distribution of index subjects based on mother tongue.**

### 3.1.4. Distribution of index subjects based on age intervals

Five age categories were established. The highest representation of subjects (42%) was in the age category 0.1-5 years followed by the age category up to $\geq$5.1-9 (22%), $\geq$9.1-19 (24.2%), $\geq$19.1-29 (7%) and $\geq$29.1 years (5%) (Fig. 3.1.4). Representation of males was higher in all age groups. However, no significant association was observed when data were distributed with respect to gender and age (Table 3.1a).
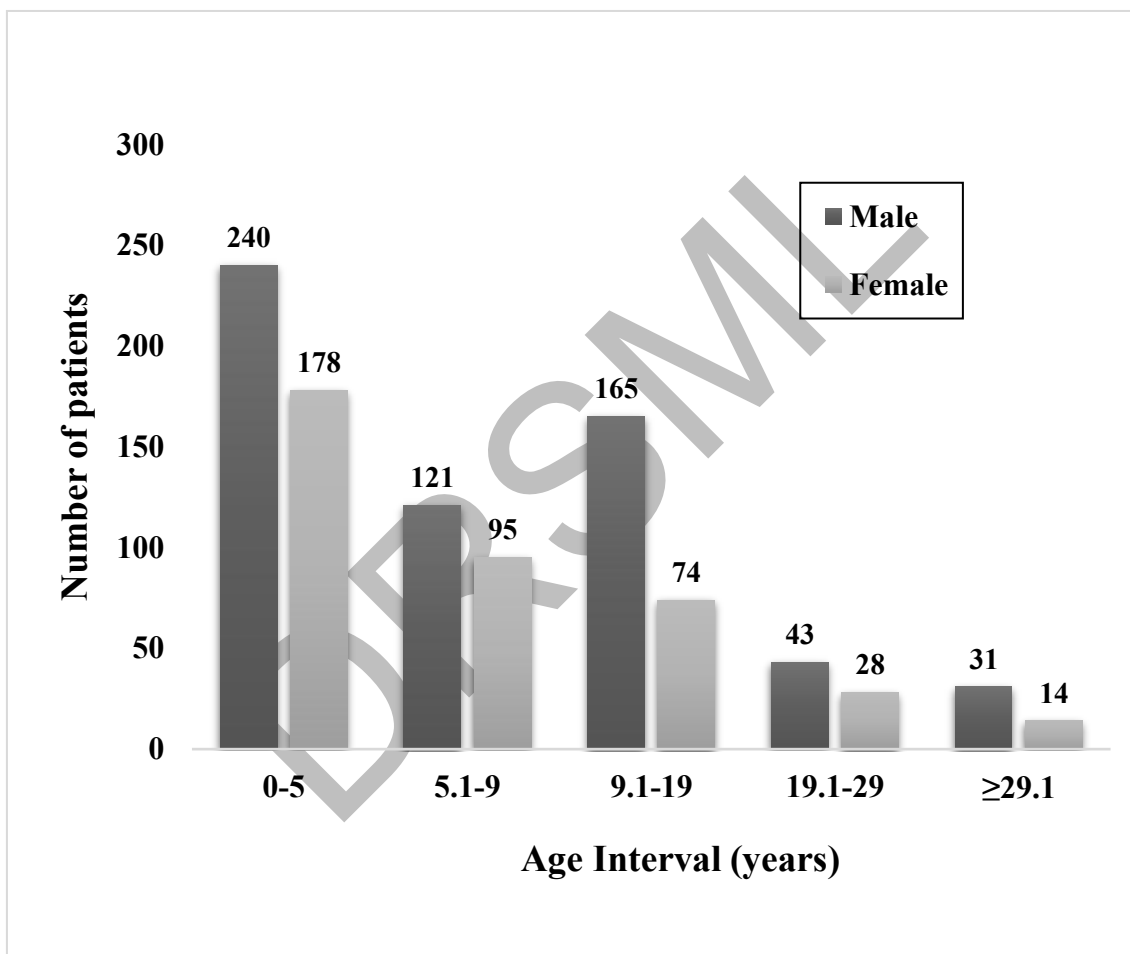


**Fig. 3.1.4: Distribution of index subjects based on age intervals.**

**Table 3.1a: Demographic distribution of index subjects and odds of affected males compared to the affected females**

| Demographic variables | Gender | | Total No. | Percentage | OR[#] |
|---|---|---|---|---|---|
| | Male | Female | | | |
| **Province** | | | | | |
| Punjab | 311 | 189 | 500 | 50.6 | 1.09 |
| Khyber Pakhtunkhwa | 166 | 126 | 292 | 29.5 | Ref. |
| Azad Jammu Kashmir | 72 | 51 | 123 | 12.4 | 1.03 |
| Islamabad | 35 | 18 | 53 | 5.4 | 1.16 |
| Others | 16 | 5 | 21 | 2.1 | 1.34 |
| **Sum** | **600** | **389** | **989** | **100.0** | |
| $\chi^2$ test | $\chi^2$=5.27;        df=4; p=0.261 | | | | |
| **Origin** | | | | | |
| Rural | 401 | 273 | 674 | 68.1 | Ref. |
| Urban | 199 | 116 | 315 | 31.9 | 1.06 |
| $\chi^2$ test | $\chi^2$=1.22;        df=1; p=0.269 | | | | |
| **Mother tongue** | | | | | |
| Punjabi | 290 | 187 | 477 | 48.2 | 1.41 |
| Pashto | 95 | 60 | 155 | 15.7 | 1.42 |
| Hindko | 89 | 54 | 143 | 14.5 | 1.44 |
| Kashmiri/Pahari | 45 | 27 | 72 | 7.3 | 1.45 |
| Khowar | 25 | 33 | 58 | 5.9 | Ref. |
| Urdu | 29 | 17 | 46 | 4.7 | 1.46 |
| Others | 27 | 11 | 38 | 3.8 | 1.65 |
| $\chi^2$ test | $\chi^2$=9.06;        df=6; p=0.1424 | | | | |
| **Age range (years)** | | | | | |
| 0.1-5 | 240 | 178 | 418 | 42.3 | Ref. |
| ≥5.1-9 | 121 | 95 | 216 | 21.8 | 0.98 |
| ≥9.1-19 | 165 | 74 | 239 | 24.2 | 1.20 |
| ≥19.1-29 | 43 | 28 | 71 | 7.2 | 1.05 |
| ≥29.1 | 31 | 14 | 45 | 4.6 | 1.20 |
| $\chi^2$ test | $\chi^2$=12.10; df=4; p=0.017; * | | | | |

#, OR=Odd ratio

### 3.1.5. Distribution of index subjects based on occupational status

Out of 989 subjects, the majority of the subjects (age≥5 years) were unemployed (81%) as compared to employed (19%) (Fig. 3.1.5). Employment and unemployment number was found higher in males than females. However, no significant association was observed when data were distributed with respect to gender and occupation (Table 3.1b).



**Fig. 3.1.5: Distribution of index subjects based on occupation status.**

### 3.1.6. Distribution of index subjects based on literacy level

Among the 989 subjects, most of the subjects were illiterate (79%) with no formal education as compared to literate (21%) (Fig. 3.1.6). Literacy was observed to be higher in males than females. But, no significant association was observed when data were distributed with respect to gender and literacy (Table 3.1b).
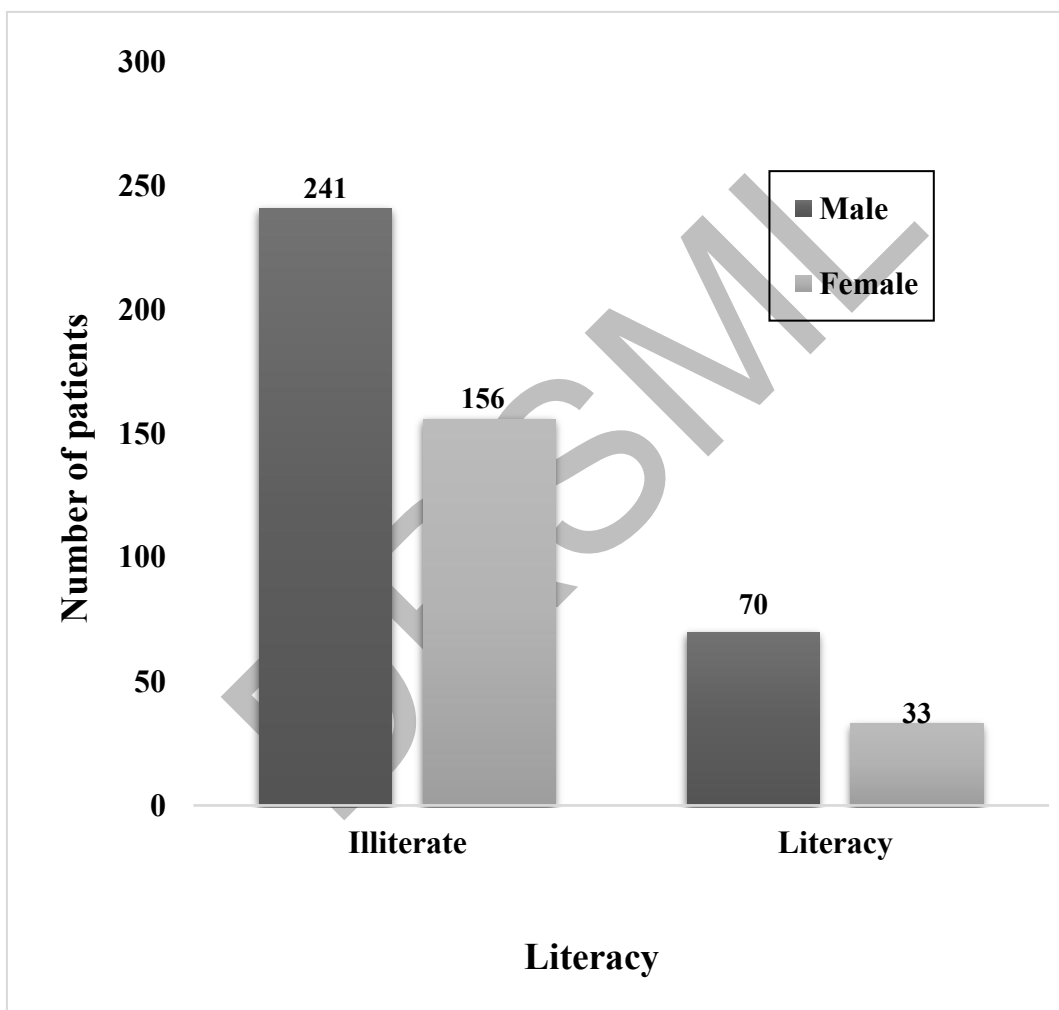


**Fig. 3.1.6: Distribution of index subjects based on literacy level.**

### 3.1.7. Distribution of index subjects based on socio-economic status

Socio-economic status is divided into four categories, based on the definitions of the Pakistan Demographic Health Survey. In most of the cases, patients belong to low-mid economic status (34%) followed by mid (32%), low (30%), and high-mid (3%) categories (Fig. 3.1.7). Representation of males than females was higher in all categories. However, no significant association was observed when data were distributed with respect to gender and economic status (Table 3.1b).
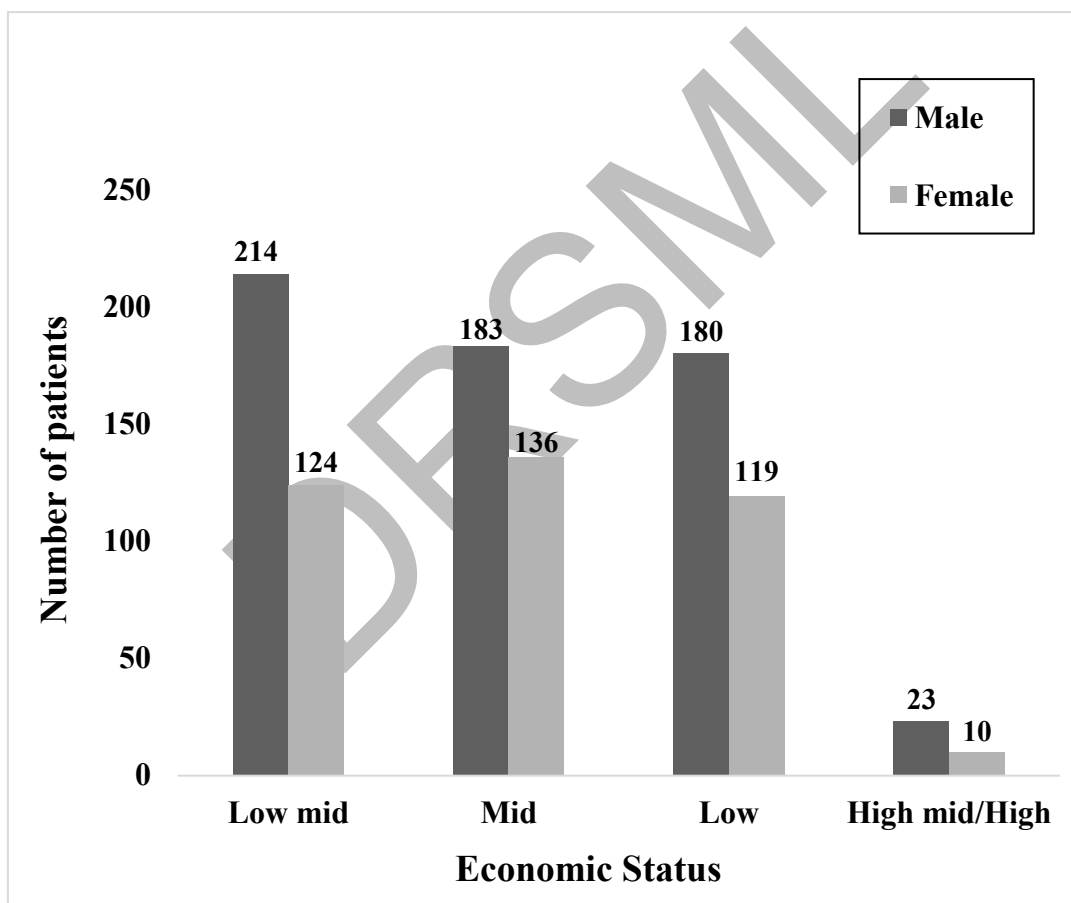


**Fig. 3.1.7: Distribution of index subjects based on socio-economic status.**

## 3.1.8. Distribution of index subjects based on marital status

In cerebral palsy, most of the subjects (age≥15 years) were severely affected hence, the majority of the patients were single (93%) as compared to married (7%) (Fig. 3.1.8). No significant association was observed when data were distributed with respect to gender and marital status (Table 3.1b).
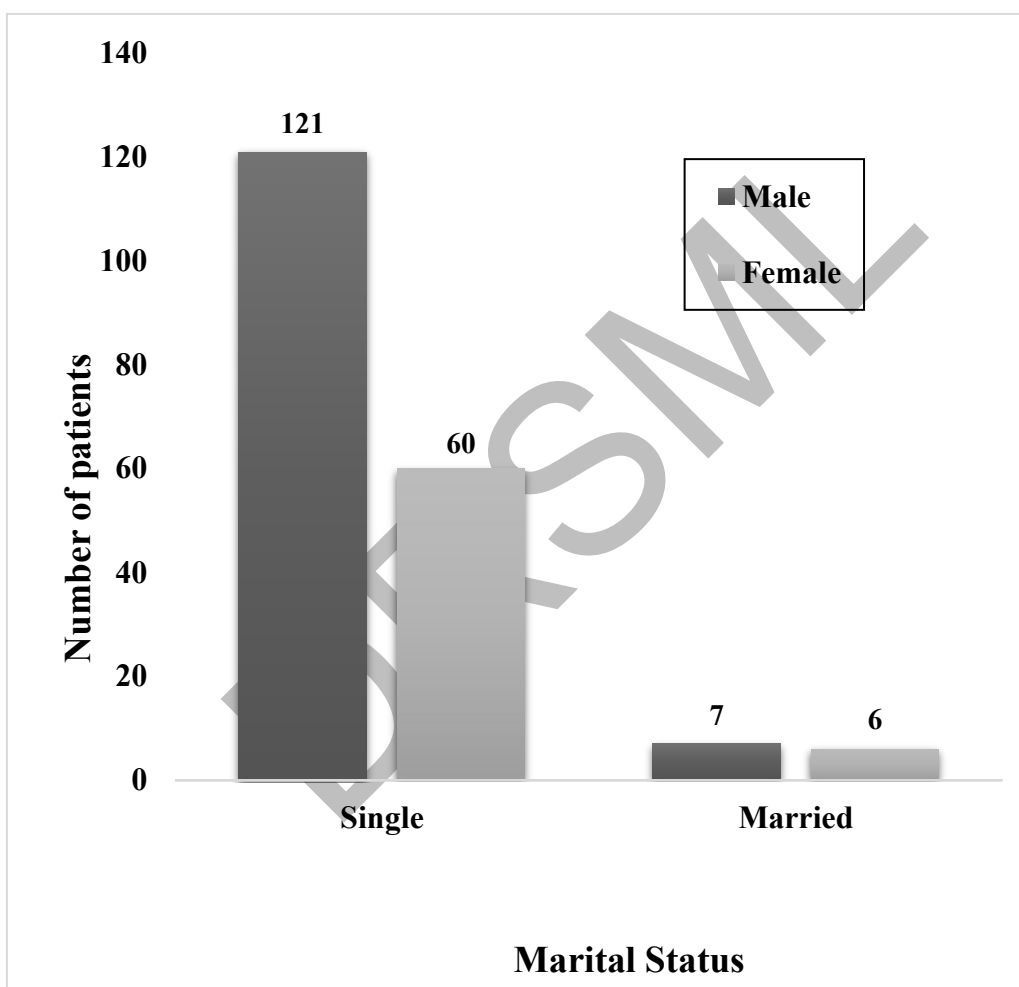


**Fig. 3.1.8: Distribution of index subjects based on marital status.**

### 3.1.9. Distribution of index subjects based on family type

The majority of the patients belonged to extended family types making 63% of the total subjects. Only 37% belonged to nuclear family type (Fig. 3.1.9). Representation of males were higher in each family type. However, no significant association was observed when data were distributed with respect to gender and family type (Table 3.1b).
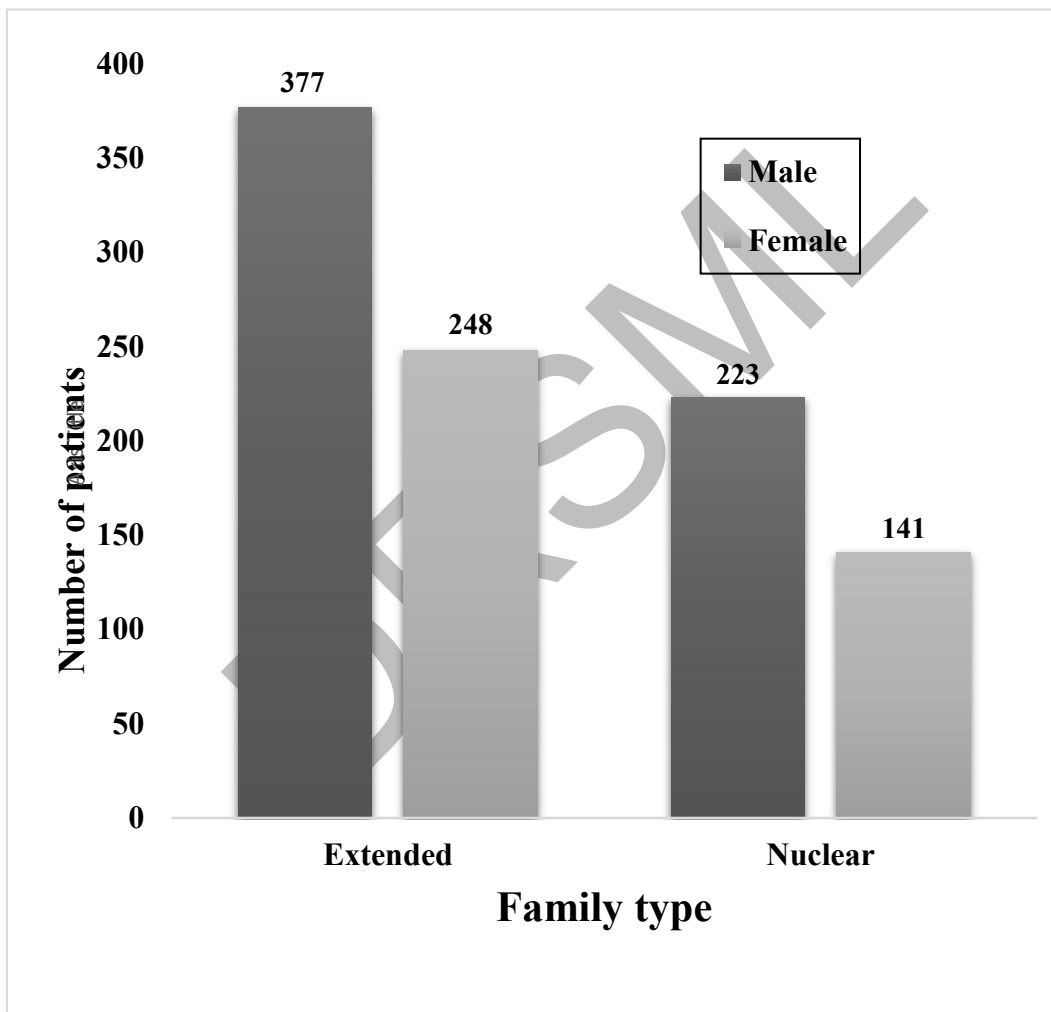


**Fig. 3.1.9: Distribution of index subjects based on the family type.**

### 3.1.10.  Distribution of index subjects based on religion

The graph shown below explains that 99% of patients were followers of Islam, while 1% of patients had Christianity as their religion (Fig. 3.1.10). The number of males was higher in each religion. However, no significant association was observed when data were distributed with respect to gender and religion (Table 3.1b).
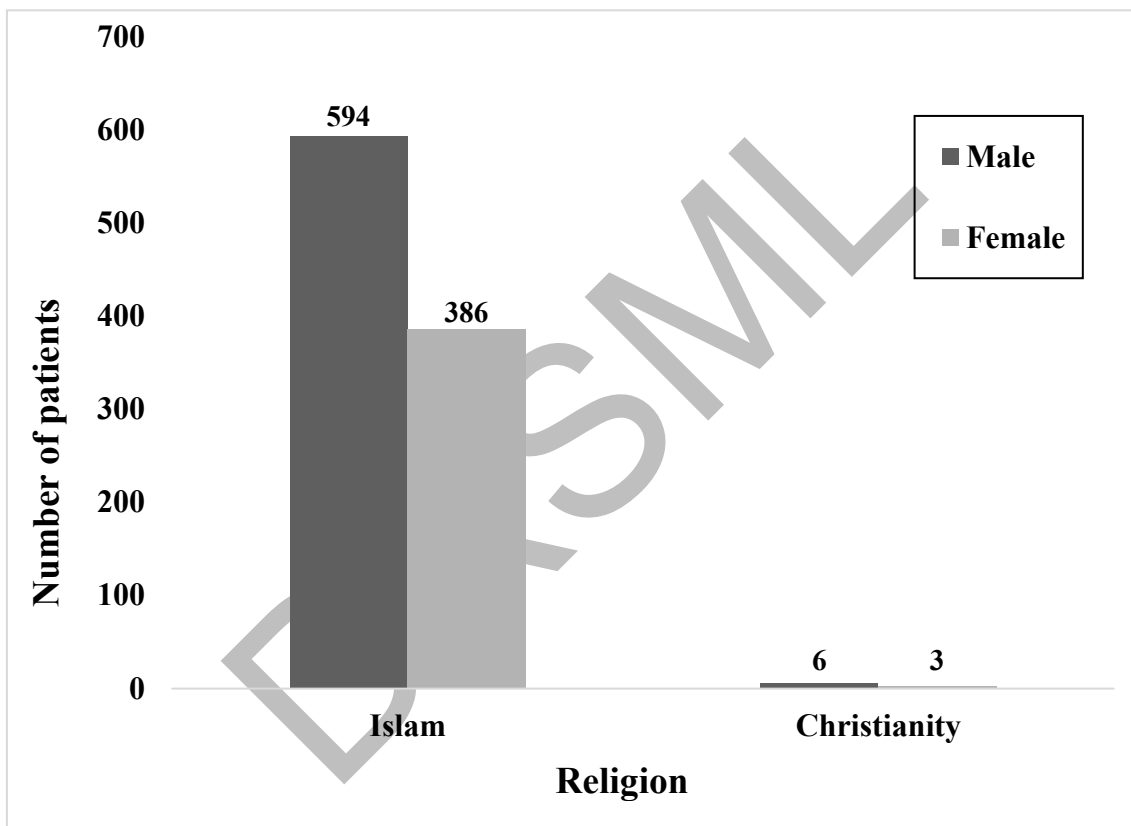


**Fig. 3.1.10: Distribution of index subjects based on religion.**

### 3.1.11.  Distribution of index subjects based on parental consanguinity

Out of 989, 63% of patients had parental consanguinity (Fig. 3.1.11). This indicates that parental consanguinity had a strong impact on CP children. Parental consanguinity was found higher among male subjects parents than female subjects. However, no significant association was observed when data were distributed with respect to gender and parental consanguinity (Table 3.1b).
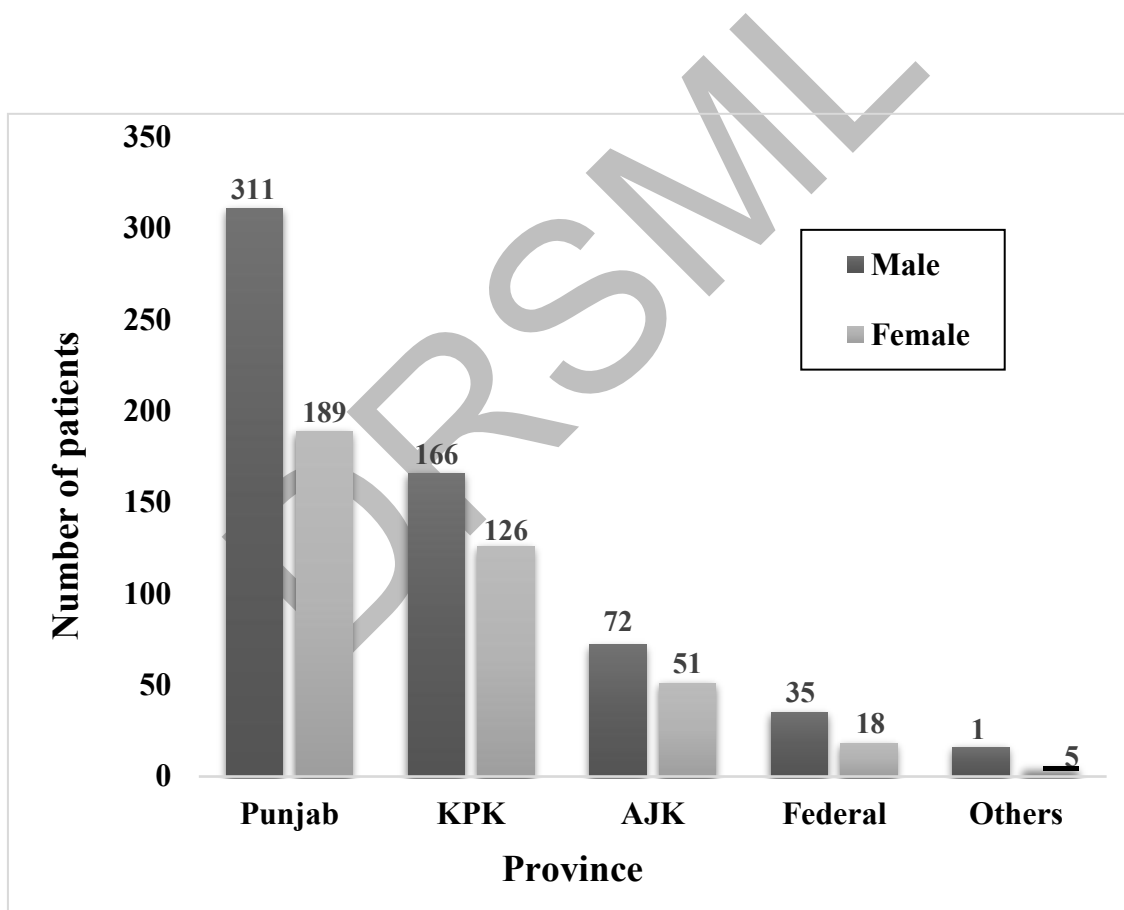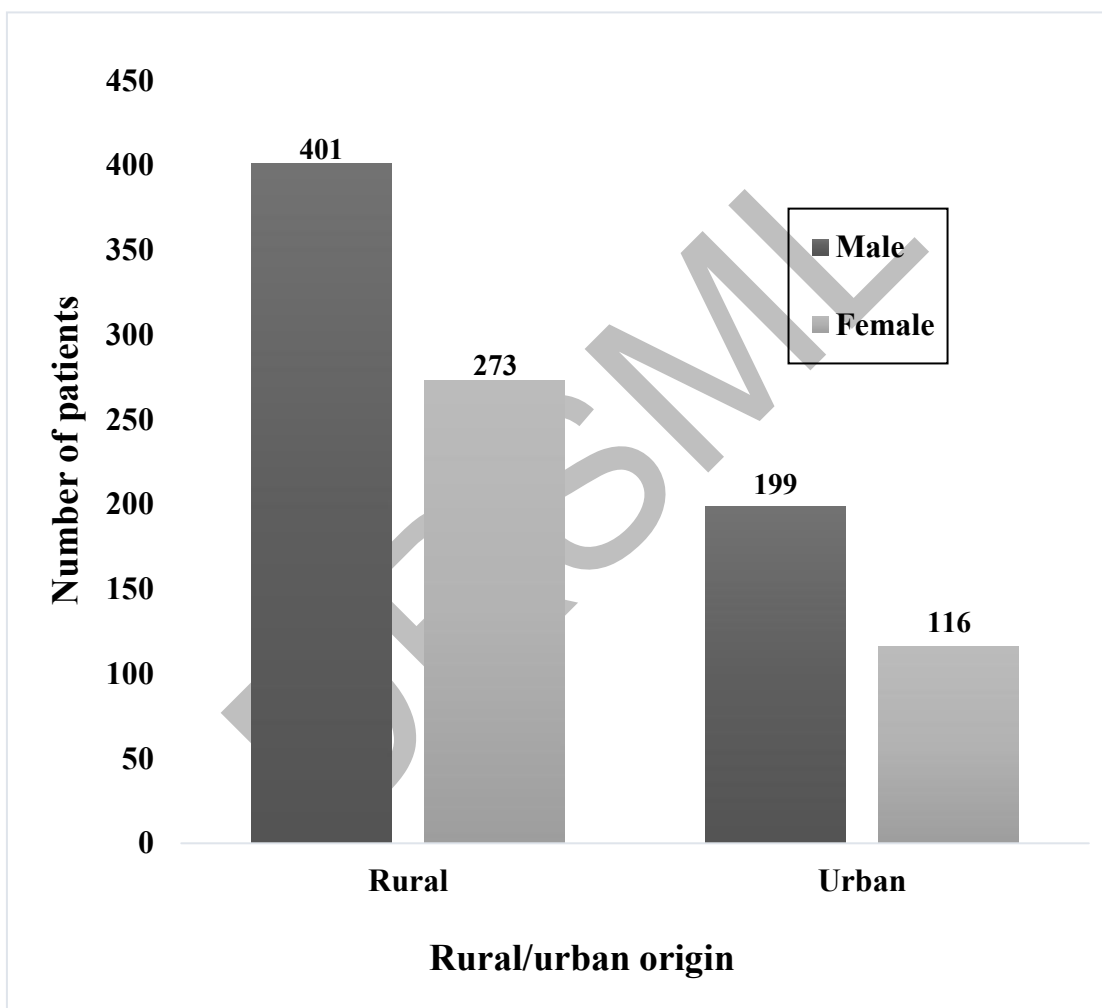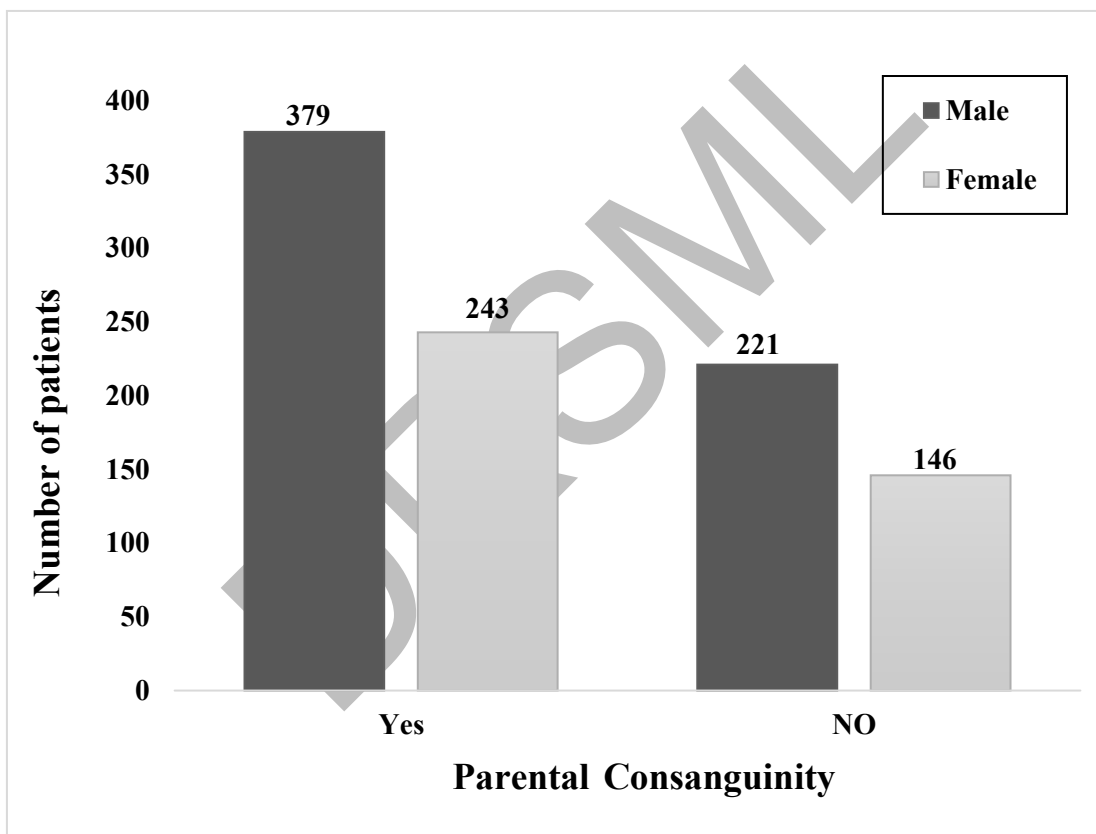


**Fig. 3.1.11: Distribution of index subjects based on parental consanguinity.**

**Table 3.1b: Socio-economic and household attributes of index subjects and Odds of affected males compared to the affected females**

| Variables | Gender | | Total No. | Percentage | OR# |
|---|---|---|---|---|---|
| | **Male** | **Female** | | | |
| **Occupation (age≥15 years; n=117)** | | | | | |
| Unemployed | 57 | 38 | 95 | 81.2 | Ref. |
| Employed | 21 | 1 | 22 | 18.8 | 1.59 |
| $\chi^2$ test | $\chi^2$=10.10; df=1; p=0.0015; ** | | | | |
| **Literacy age (age≥5 years; n=500)** | | | | | |
| Illiterate (no formal education) | 241 | 156 | 397 | 79.4 | Ref. |
| Literate | 70 | 33 | 103 | 20.6 | 1.12 |
| $\chi^2$ test | $\chi^2$=1.83; df=1; p=0.176 | | | | |
| **Literacy level (n=103)** | | | | | |
| Primary schooling | 40 | 25 | 65 | 63.1 | Ref. |
| Middle schooling | 16 | 2 | 18 | 17.5 | 1.44 |
| High schooling | 9 | 4 | 13 | 12.6 | 1.12 |
| Graduation and higher | 5 | 2 | 7 | 6.8 | 1.16 |
| $\chi^2$ test | $\chi^2$=1.83; df=1; p=0.176 | | | | |
| **Socio-economic status (n=989)** | | | | | |
| Low | 180 | 119 | 299 | 30.2 | 1.05 |
| Low mid | 214 | 124 | 338 | 34.2 | 1.10 |
| Mid | 183 | 136 | 319 | 32.3 | Ref. |
| High mid/High | 23 | 10 | 33 | 3.3 | 1.21 |
| $\chi^2$ test | $\chi^2$=3.60; df=3; p=0.308 | | | | |
| **Marital status (age≥15 years; n=194)** | | | | | |
| Single | 121 | 60 | 181 | 93.3 | Ref. |
| Married | 7 | 6 | 13 | 6.7 | 0.81 |
| Sum | 128 | 66 | 194 | | |
| $\chi^2$ test | $\chi^2$=0.91; df=1; p=0.339 | | | | |

| **Family type (n=989)** | | | | | |
|---|---|---|---|---|---|
| Extended | 377 | 248 | 625 | 63.2 | Ref. |
| Nuclear | 223 | 141 | 364 | 36.8 | 1.02 |
| $\chi^2$ test | $\chi^2$=0.086;      df=1; p=0.770 | | | | |
| **Religion** | | | | | |
| Islam | 594 | 386 | 980 | 99.1 | |
| Christianity | 6 | 3 | 9 | 0.9 | |
| $\chi^2$ test | $\chi^2$=0.14;      df=1; p=0.711 | | | | |
| **Parental consanguinity** | | | | | |
| Yes | 379 | 243 | 622 | 62.9 | 1.01 |
| No | 221 | 146 | 367 | 37.1 | Ref. |
| $\chi^2$ test | $\chi^2$=0.05;      df=1; p=0.824 | | | | |

#, OR= odd ratio

## 3.2 : Clinical manifestations of cerebral palsy in various classification schemes

### 3.2.1. Classification of index subjects based on clinical types

Out of 989, the majority of patients were represented with spastic CP (53%), followed by athetoid CP (29%), ataxic CP (14%) and mixed CP (4%) (Fig. 3.2.1). Representation of males was higher in types than females. But, no significant association was observed when data were distributed with respect to gender and clinical types of CP (Table 3.2a).



**Fig. 3.2.1: Classification of index subjects based on clinical types.**

### 3.2.2. Classification of index subjects based on topographical distribution

According to topography, the majority of the patients were presented with quadriplegia (30%), followed by paraplegia (19%), diplegia (18%), left hemiplegia (13%), right hemiplegia (12%), monoplegia (6%) and triplegia (2%) (Fig. 3.2.2). The number of males was high in all topographical types than females. However, no significant association was observed when data were distributed with respect to gender and topographical types (Table 3.2a).



**Fig. 3.2.2: Classification of index subjects based on topographical distribution.**

### 3.2.3. Classification of index subjects based on dyskinetic/athetoid type

In athetoid, the majority of cases (56%) were dystonic followed by athetosis (43%) and choreo-athetosis (1%) (Fig 3.2.3). The number of males were higher in dystonic and athetosis while the number of females was higher in choreo-athetosis. No significant association was found between gender and dyskinetic (Table 3.2a).
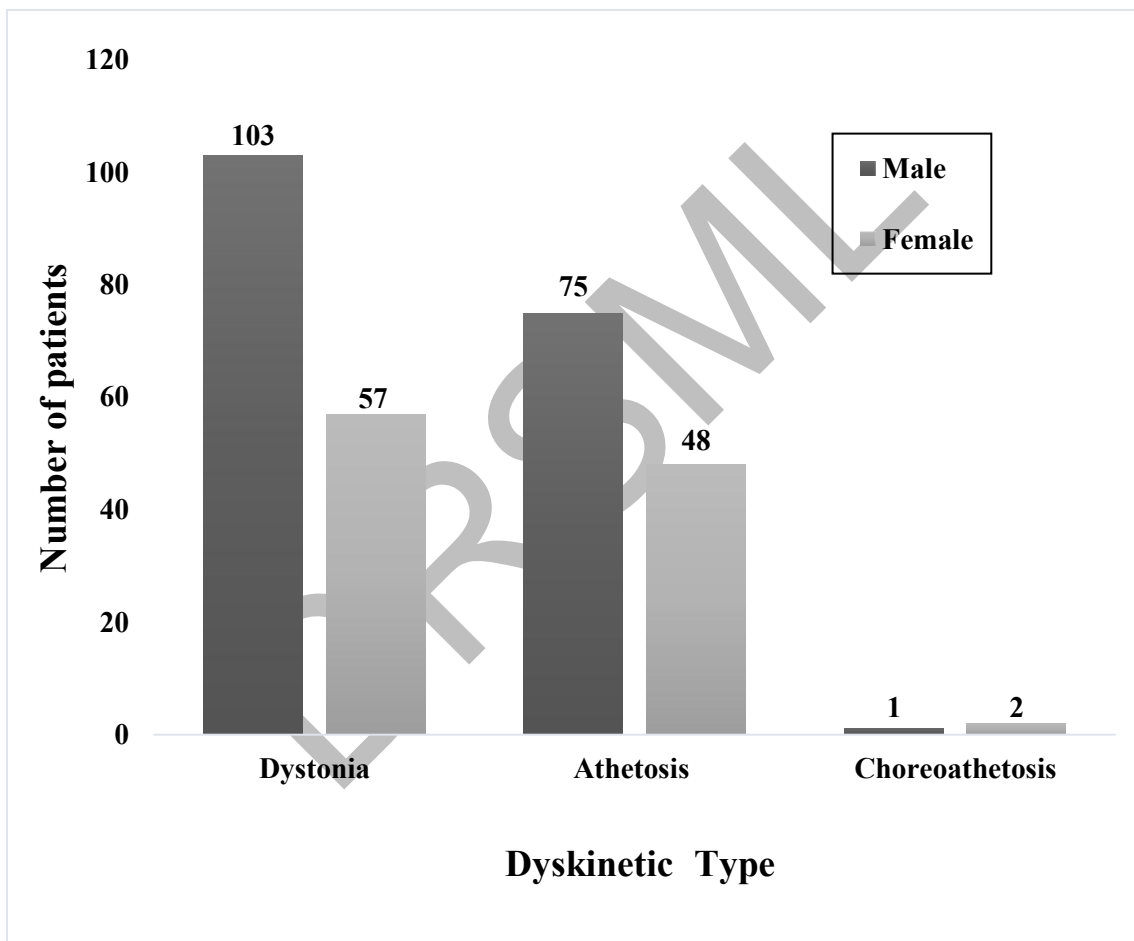


**Fig. 3.2.3: Classification of index subjects based on dyskinetic types.**

## 3.2.4. Classification of index subjects based on the severity level

With respect to their severity, severely affected cases were 62% followed by moderate 20% and mild 18% (Fig. 3.2.4). The number of males was found higher in severe, moderate and mild cases than in females. But, no significant association was observed when data were distributed with respect to gender and severity levels (Table 3.2a).
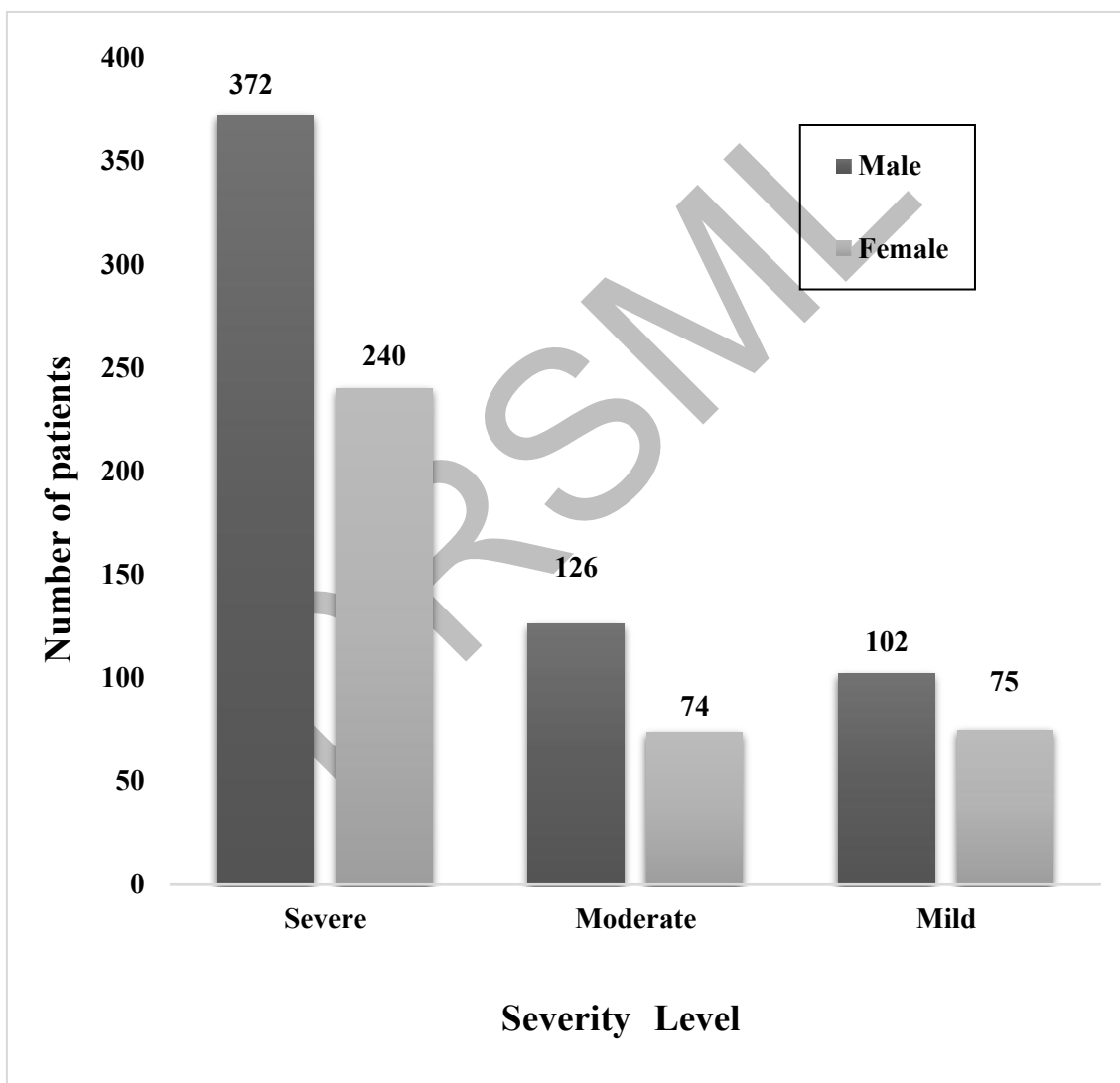


**Fig. 3.2.4: Classification of index subjects based on severity level.**

## 3.2.5. Classification of index subjects based on SCPE scheme

According to the SCPE classification bilateral cases were 69% and unilateral 31% (Fig. 3.2.5). The bilateral and unilateral number was found higher in males than females. However, no significant association was observed when data were distributed with respect to gender and SCPE classification (Table 3.2a).
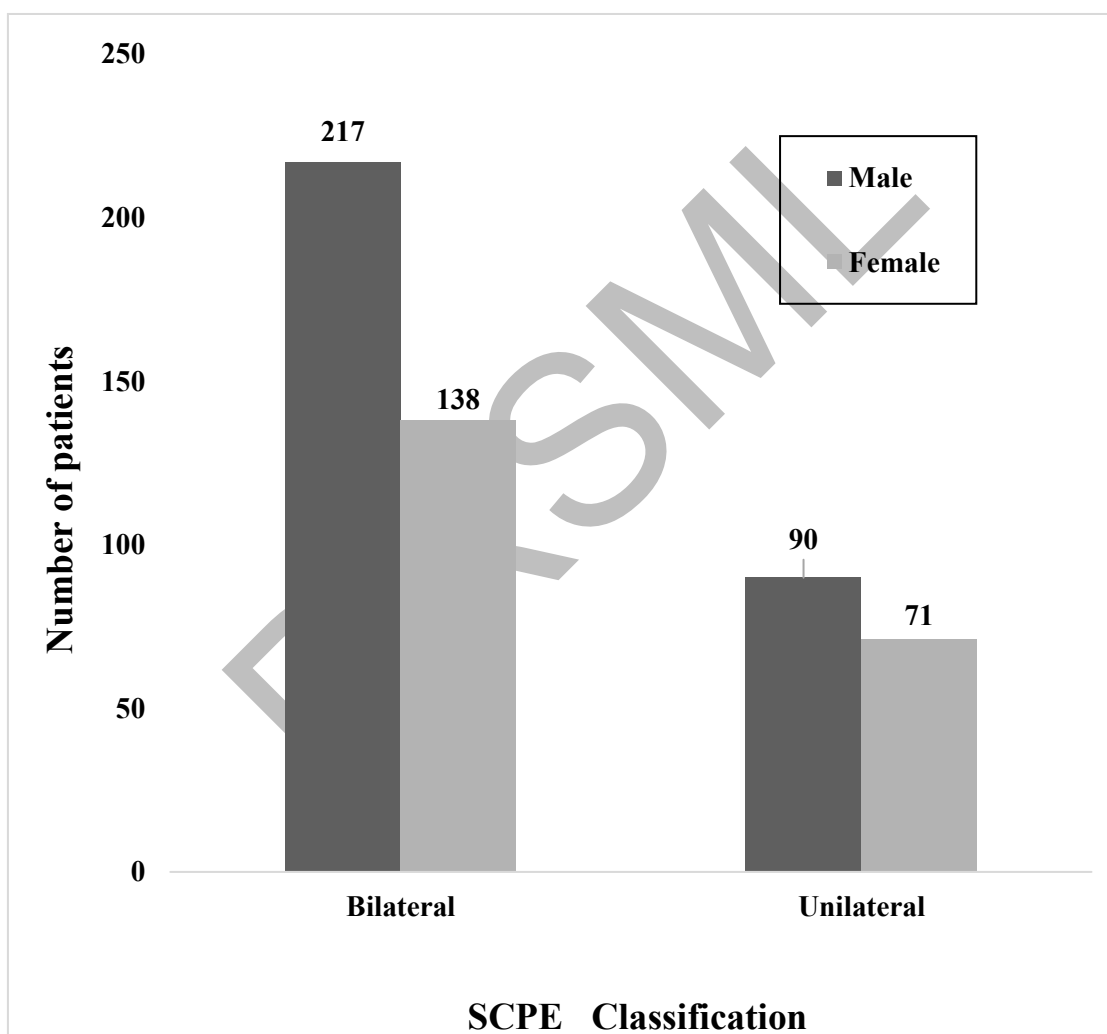


**Fig. 3.2.5: Classification of index subjects based on SCPE scheme.**

### 3.2.6. Classification of index subjects based on congenital/acquired cases

In the majority of the patients 98%, of the anomaly is congenital in nature and 2% of cases had late-onset/acquired (Fig. 3.2.6). Representation of males was found higher in both congenital and acquired CP cases. However, no significant association was observed when data were distributed with respect to gender and congenital/acquired cases (Table 3.2a).
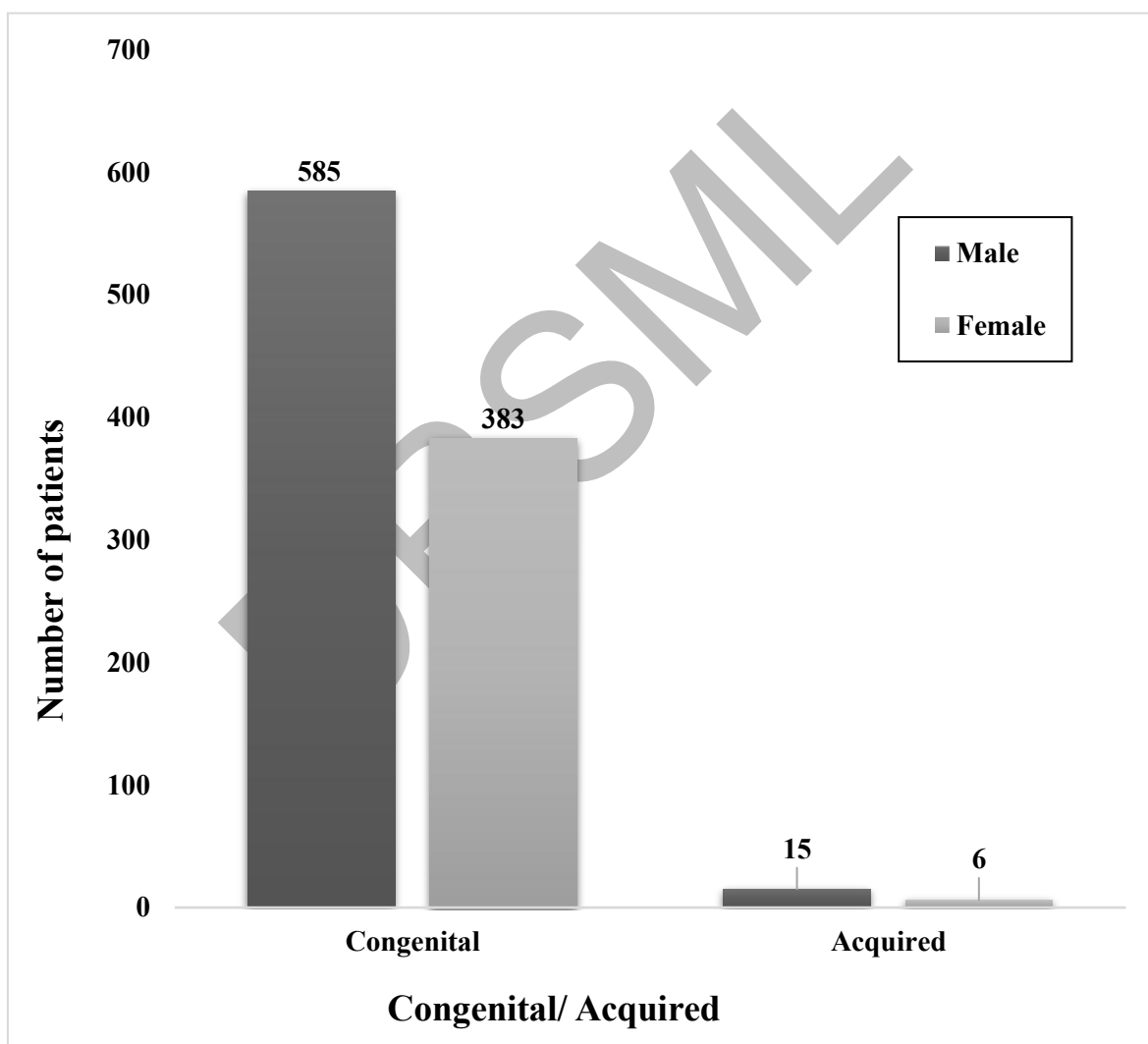


**Fig. 3.2.6: Classification of index subjects based on congenital/acquired cases.**

**Table 3.2a: Clinical manifestations of CP in various classification schemes and odds of affected males compared to affected females**

| Clinical variables | Gender | | Total | Percentage | Proportion | 95% CI# | OR# |
|---|---|---|---|---|---|---|---|
| | Male | Female | | | | | |
| **Cerebral palsy types** | | | | | | | |
| Spastic CP | 314 | 212 | 526 | 53.2 | 0.532 | 0.501-0.563 | 1.05 |
| Athetoid CP | 179 | 107 | 286 | 28.9 | 0.289 | 0.261-0.317 | 1.10 |
| Ataxic CP | 80 | 61 | 141 | 14.3 | 0.143 | 0.121-0.164 | Ref. |
| Mixed CP | 27 | 9 | 36 | 3.6 | 0.036 | 0.025-0.048 | 1.32 |
| Sum | 600 | 389 | 989 | 100.0 | | | |
| $\chi^2$ test | $\chi^2$=4.66; df=3; p=0.198 | | | | | | |
| **Topographical distribution** | | | | | | | |
| Quadriplegia | 101 | 59 | 160 | 30.4 | 0.304 | 0.265-0.343 | 1.19 |
| Paraplegia | 60 | 39 | 99 | 18.8 | 0.188 | 0.155-0.222 | 1.14 |
| Diplegia | 56 | 40 | 96 | 18.3 | 0.183 | 0.149-0.216 | 1.10 |
| Left hemiplegia | 38 | 28 | 66 | 12.5 | 0.125 | 0.097-0.154 | 1.08 |
| Right hemiplegia | 33 | 29 | 62 | 11.8 | 0.118 | 0.090-0.145 | Ref. |
| Monoplegia | 19 | 14 | 33 | 6.3 | 0.063 | 0.042-0.083 | 1.08 |
| Triplegia | 7 | 3 | 10 | 1.9 | 0.019 | 0.007-0.031 | 1.32 |
| $\chi^2$ test | $\chi^2$=2.60; df=6; p=0.858 | | | | | | |
| **Dyskinetic/Athetoid types (n=286)** | | | | | | | |
| Dystonic | 103 | 57 | 160 | 55.9 | 0.559 | 0.502-0.617 | 1.93 |
| Athetosis | 75 | 48 | 123 | 43.0 | 0.430 | 0.373-0.487 | 1.83 |
| Choreoathetosis | 1 | 2 | 3 | 1.0 | 0.010 | -0.001-0.022 | Ref. |
| $\chi^2$ test | $\chi^2$=1.45; df=2; p=0.484 | | | | | | |

| Severity level | | | | | | | |
|---|---|---|---|---|---|---|---|
| Severe | 372 | 240 | 612 | 61.9 | 0.619 | 0.589-0.649 | 1.05 |
| Moderate | 126 | 74 | 200 | 20.2 | 0.202 | 0.177-0.227 | 1.09 |
| Mild | 102 | 75 | 177 | 17.9 | 0.179 | 0.155-0.203 | Ref. |
| $\chi^2$ test | $\chi^2$=1.15; df=2; p=0.564 | | | | | | |
| **SCPE classification** | | | | | | | |
| Bilateral | 217 | 138 | 355 | 68.8 | 0.688 | 0.648-0.728 | 1.09 |
| Unilateral | 90 | 71 | 161 | 31.2 | 0.312 | 0.272-0.352 | Ref. |
| $\chi^2$ test | $\chi^2$=1.26; df=1; p=0.263 | | | | | | |
| **Congenital/acquired** | | | | | | | |
| Congenital | 585 | 383 | 968 | 97.88 | 0.979 | 0.970-0.988 | Ref. |
| Late onset/acquired | 15 | 6 | 21 | 2.123 | 0.021 | 0.012-0.030 | 1.18 |
| $\chi^2$ test | $\chi^2$=1.04; df=1; p=0.308 | | | | | | |

#, OR=odd ratio, 95% CI= 95% confidence interval

### 3.2.7. Classification of index subjects based on the severity in clinical types

With respect to their severity levels, athetoid CP, mixed CP and ataxic CP types were presented with the severe phenotype (93%, 92% and 74% respectively) compare to moderate (5%, 6%, 17%) and mild (2%, 3%, 9%) phenotype. Spastic CP in which 40% had severe phenotype while 30% were moderate and 30% were mild (Fig. 3.2.7). A significant association was found between severity levels and cerebral palsy types. Severity levels were higher in males in each type. However, no significant association was observed when data were distributed with respect to gender and CP types (Table 3.2b and 3.2c).
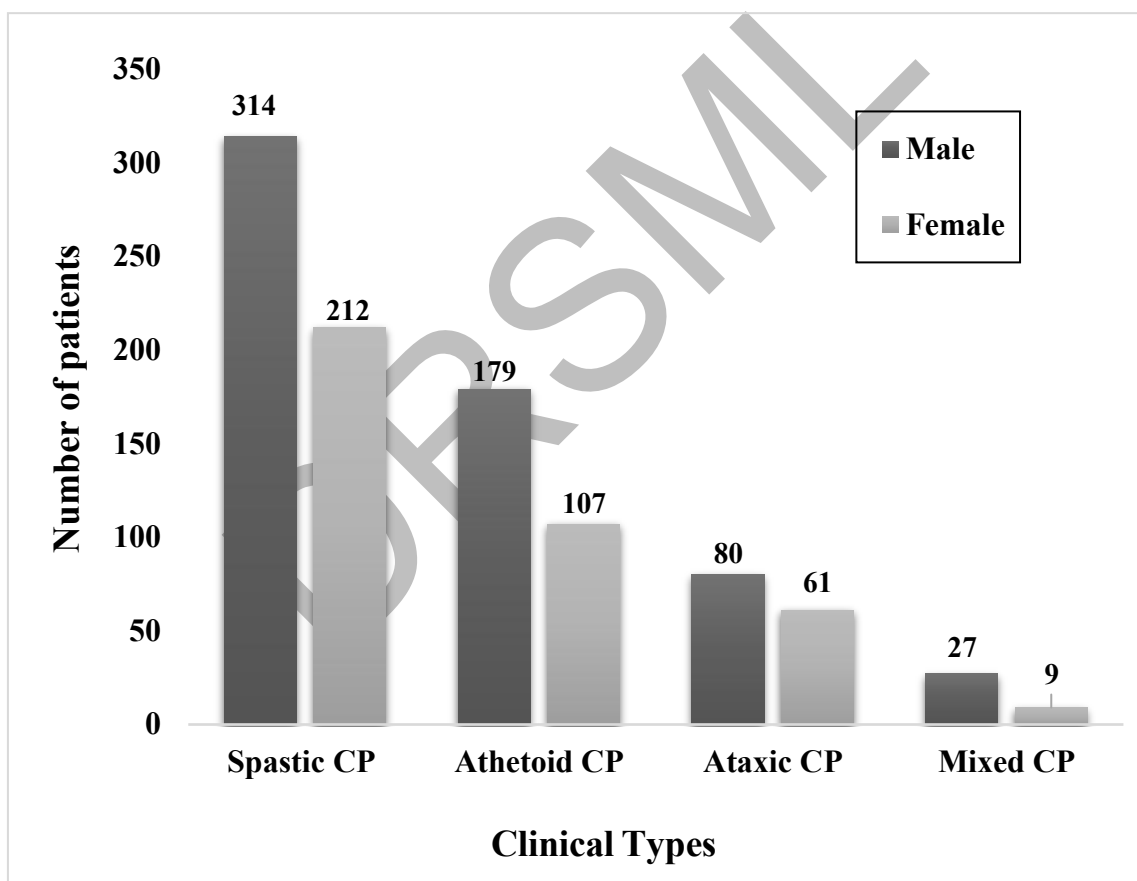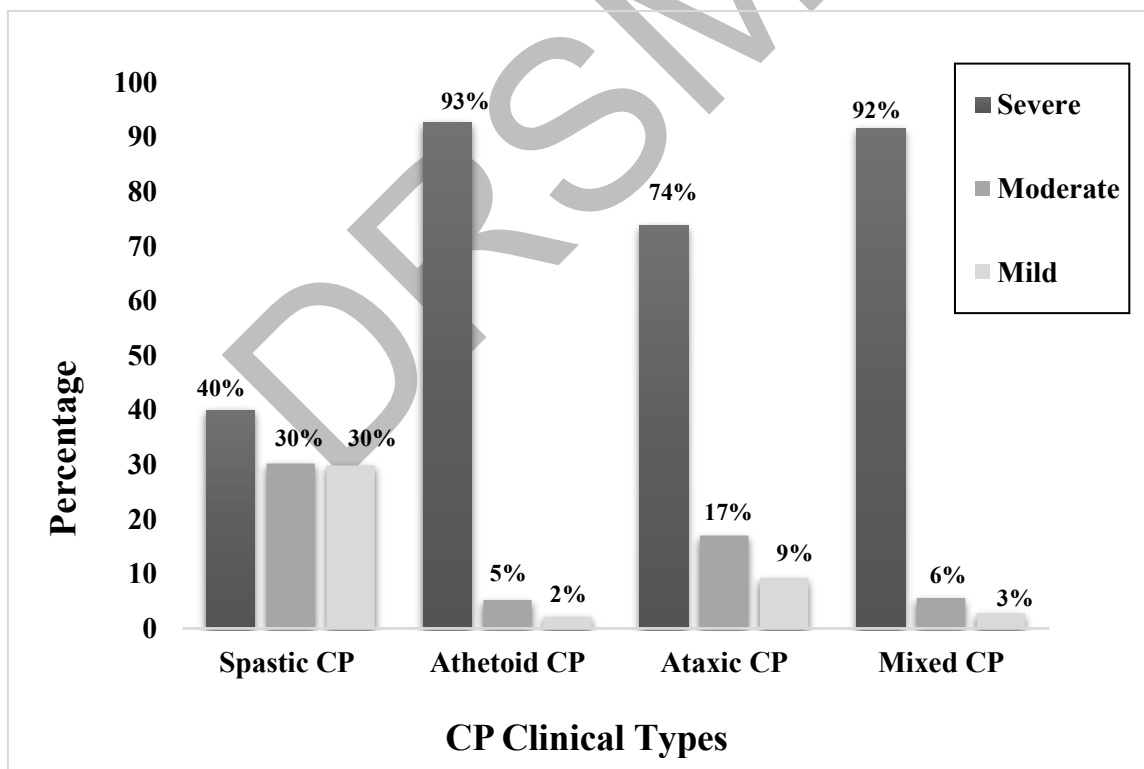


**Fig. 3.2.7: Classification of index subjects based on severity in clinical types.**

## 3.2.8. Classification of index subjects based on severity in topographical types

According to the topographical distribution, severity was very high in quadriplegia (21%). Moderate cases found high in paraplegia i-e 10%. While mild cases were seen high in diplegia (9%), left hemiplegia (7%), right hemiplegia (6%) and monoplegia (5%) than severe and moderate cases (Fig. 3.2.8). A significant association was found between severity level and topographical types. Severity was found higher in males in each type. However, no significant association was observed when data were distributed with respect to gender and topographical distribution (Table 3.2b and 3.2c).
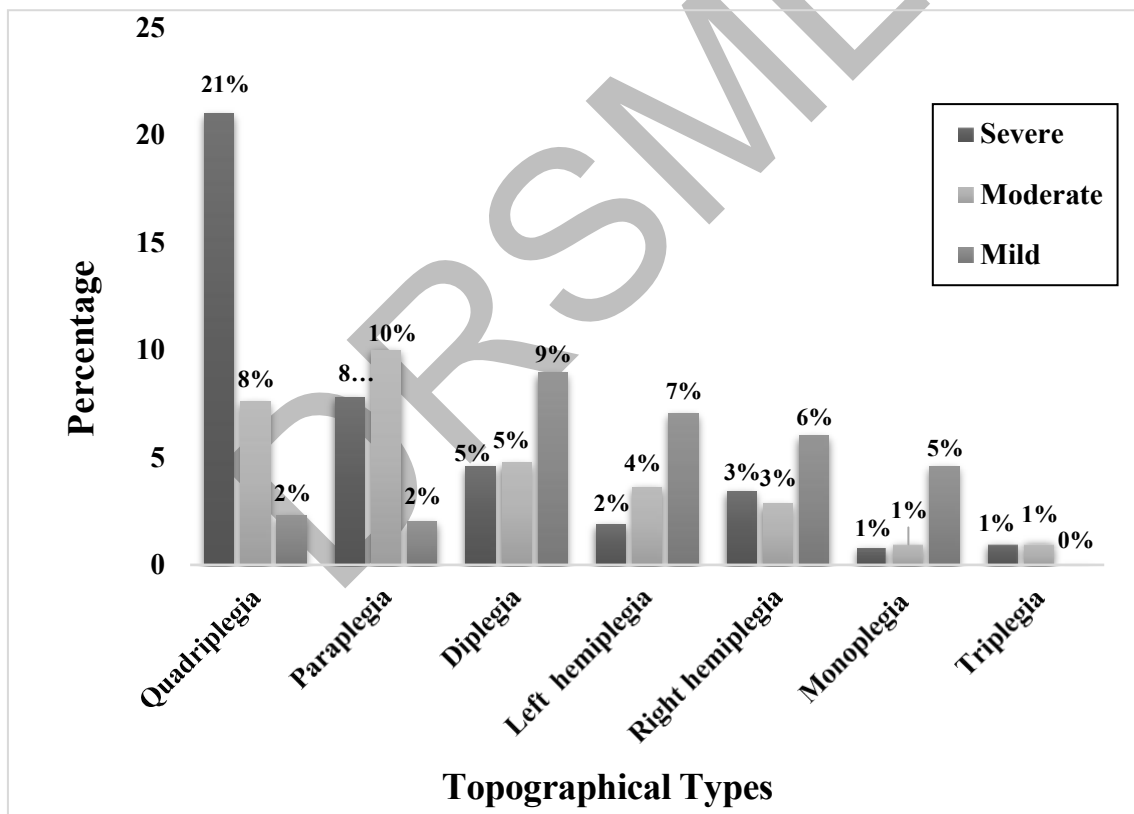


**Fig. 3.2.8: Classification of index subjects based on severity in topographical types**

## 3.2.9. Classification of index subjects based on the severity in dyskinetic types

In athetoid CP, severity was observed to be high in dystonic (56%), followed by athetosis (36%), choreoathetosis (1%) as compared to moderate and mild cases (Fig. 3.2.9). A significant association was found between severity levels and dyskinetic types. Severity was found higher in females in dystonia and choreoathetosis cases while in athetosis was found higher in males. Thus, a significant association was observed when data were distributed with respect to gender and dyskinetic types (Table 3.2b and 3.2c).
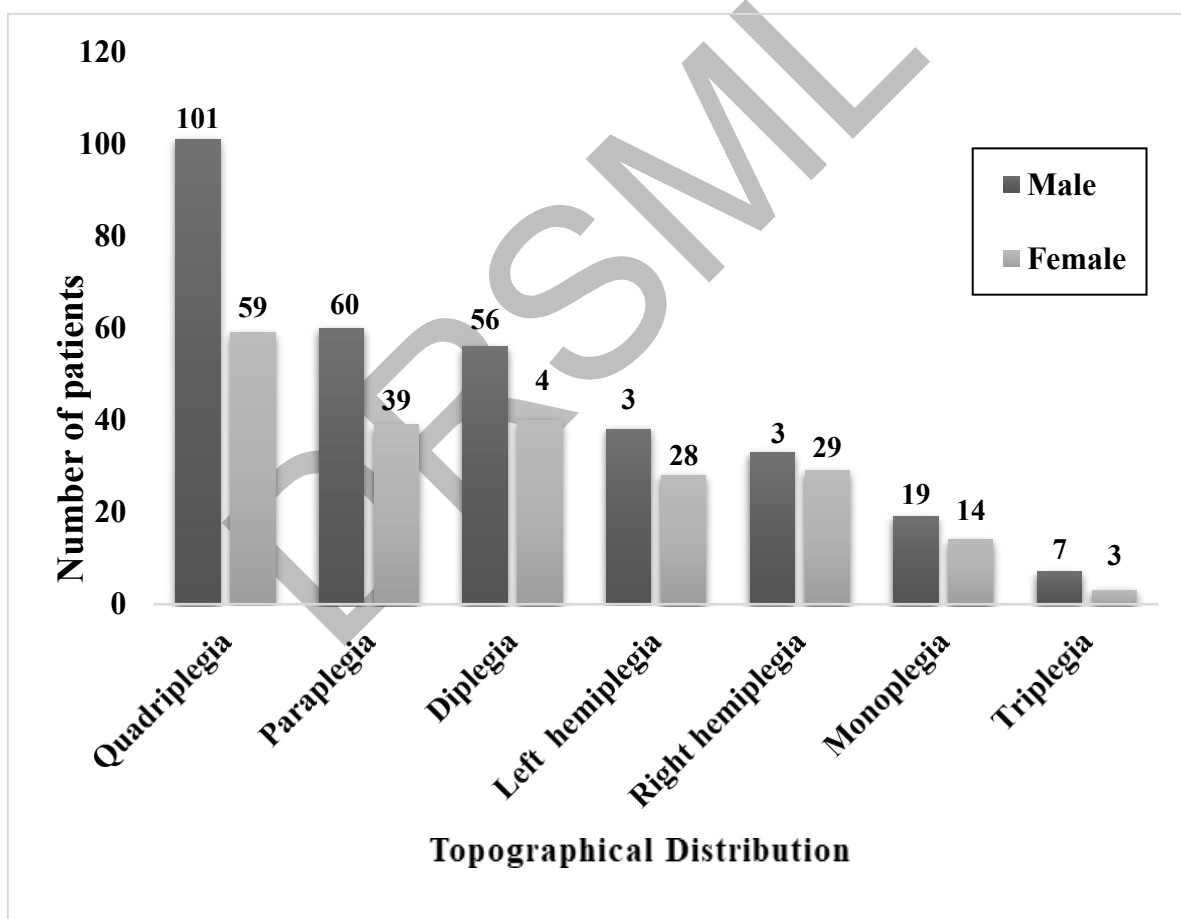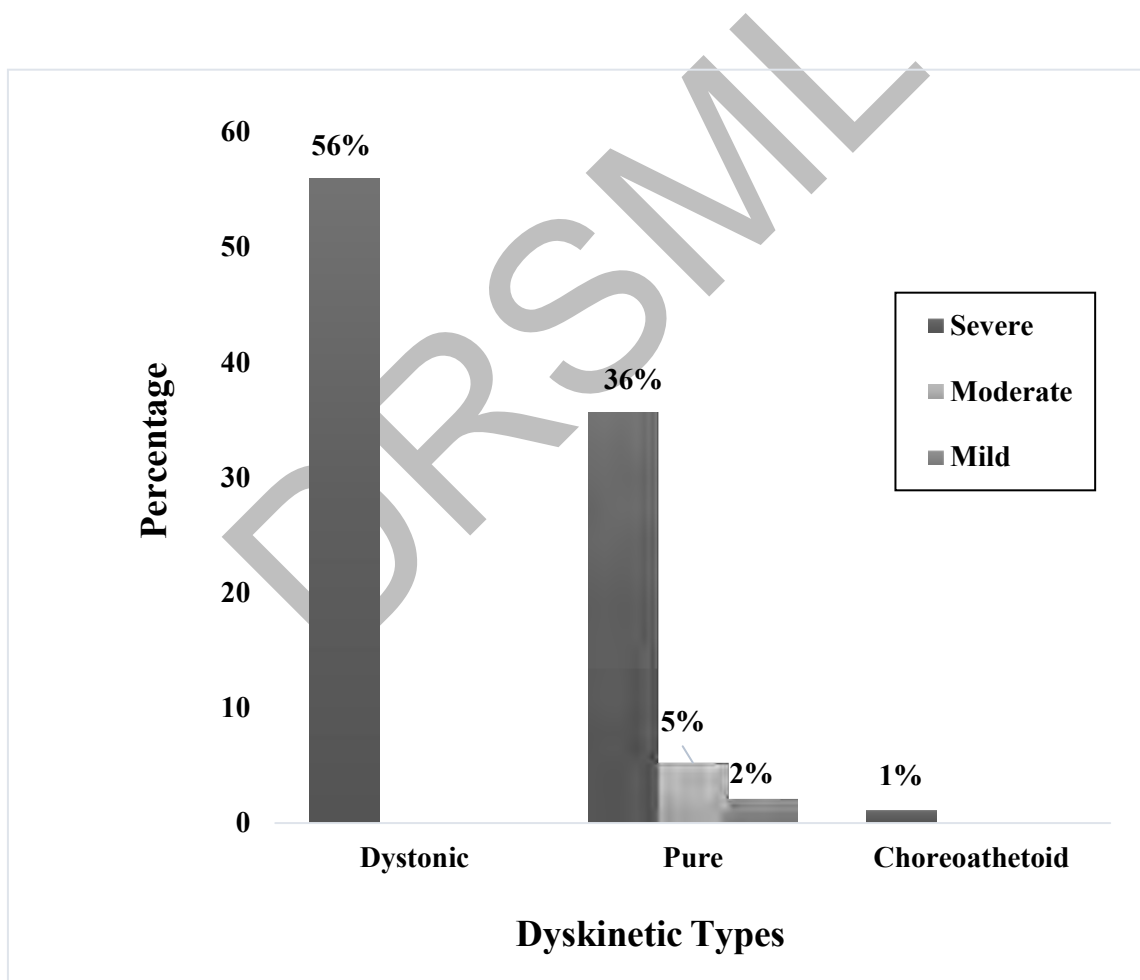


**Fig. 3.2.9: Classification of index subjects based on severity in dyskinetic types**

**Table 3.2b: Classification of index subjects based on severity in CP.**

| Severity of motor impairment | | | |
|---|---|---|---|
| Clinical types | Severe | Moderate | Mild | Grand Total |
| Spastic CP | 210 | 159 | 157 | 526 |
| Athetoid CP | 265 | 15 | 6 | 286 |
| Ataxic CP | 104 | 24 | 13 | 141 |
| Mixed CP | 33 | 2 | 1 | 36 |
| Grand Total | 612 | 200 | 177 | 989 |
| χ2 test | χ2=247.8; df=6; P<0.0001; *** | | | |
| Topographical Distribution | | | | |
| Quadriplegia | 108 | 40 | 12 | 160 |
| Paraplegia | 41 | 50 | 8 | 99 |
| Diplegia | 24 | 25 | 47 | 96 |
| Left  hemiplegia | 10 | 19 | 37 | 66 |
| Right hemiplegia | 18 | 15 | 29 | 62 |
| Monoplegia | 4 | 5 | 24 | 33 |
| Triplegia | 5 | 5 | 0 | 10 |
| χ2 test | χ2=173.2; df=12; P<0.0001; *** | | | |
| Dyskinetic/Athetoid types (n=286) | | | | |
| Dystonic | 160 | 0 | 0 | 160 |
| Athetosis | 102 | 15 | 6 | 123 |
| Choreoathetosis | 3 | 0 | 0 | 3 |
| χ2 test | χ2=30.03; df=4; P<0.0001; *** | | | |

*** = highly significant

**Table 3.2c: Classification of index subjects based on severity in CP.**

| Severity of motor impairment | Severe | | Moderate | | Mild | | Total |
|---|---|---|---|---|---|---|---|
| | Male | Female | Male | Female | Male | Female | |
| **Clinical types** | | | | | | | |
| Spastic CP | 125 | 85 | 100 | 59 | 89 | 68 | 526 |
| Athetoid CP | 164 | 101 | 11 | 4 | 4 | 2 | 286 |
| Ataxic CP | 57 | 47 | 15 | 9 | 8 | 5 | 141 |
| Mixed CP | 26 | 7 | 0 | 2 | 1 | 0 | 36 |
| Grand Total | 372 | 240 | 126 | 74 | 102 | 75 | 989 |
| $\chi^2$ test | $\chi^2$=6.321; df=3; P=0.0970 | | $\chi^2$=4.096; df=3; P=0.2513 | | $\chi^2$=1.074; df=3; P=0.7833 | | |
| **Topographical Distribution(n=526)** | | | | | | | |
| Quadriplegia | 66 | 42 | 27 | 13 | 8 | 4 | 160 |
| Paraplegia | 24 | 17 | 34 | 16 | 2 | 6 | 99 |
| Diplegia | 15 | 9 | 12 | 13 | 29 | 18 | 96 |
| Left Hemiplegia | 5 | 5 | 13 | 6 | 20 | 17 | 66 |
| Right Hemiplegia | 8 | 10 | 8 | 7 | 17 | 12 | 62 |
| Monoplegia | 3 | 1 | 3 | 2 | 13 | 11 | 33 |
| Triplegia | 4 | 1 | 3 | 2 | 0 | 0 | 10 |
| $\chi^2$ test | $\chi^2$=3.561; df=6; P=0.7359 | | $\chi^2$=4.171; df=6; P=0.6536 | | $\chi^2$=0.03081; df=1; P=0.8607 | | |
| **Dyskinetic/Athetoid (n=286)** | | | | | | | |
| Dystonic | 57 | 103 | 0 | 0 | 0 | 0 | 160 |
| Athetosis | 60 | 42 | 11 | 4 | 4 | 2 | 123 |
| Choreoathetosis | 1 | 2 | 0 | 0 | 0 | 0 | 3 |
| $\chi^2$ test | $\chi^2$="13.73; df=2; P=0.0010; ** | | $\chi^2$= ; df= 1; P<0.0001; *** | | $\chi^2$= ; df=1; P<0.0001; *** | | |

** or *** = highly significant

## 3.2.10. Classification of index subjects based on parental consanguinity in cerebral palsy clinical types

Parental consanguinity was found to be high among all types of cerebral palsy such as spastic CP and ataxic CP (63%), athetoid CP (62%) and mixed CP (69%) as compared to non-consanguineous marriages (Fig. 3.2.10). However, no significant association was observed when data were distributed with respect to parental consanguinity and clinical types (Table 3.2d).
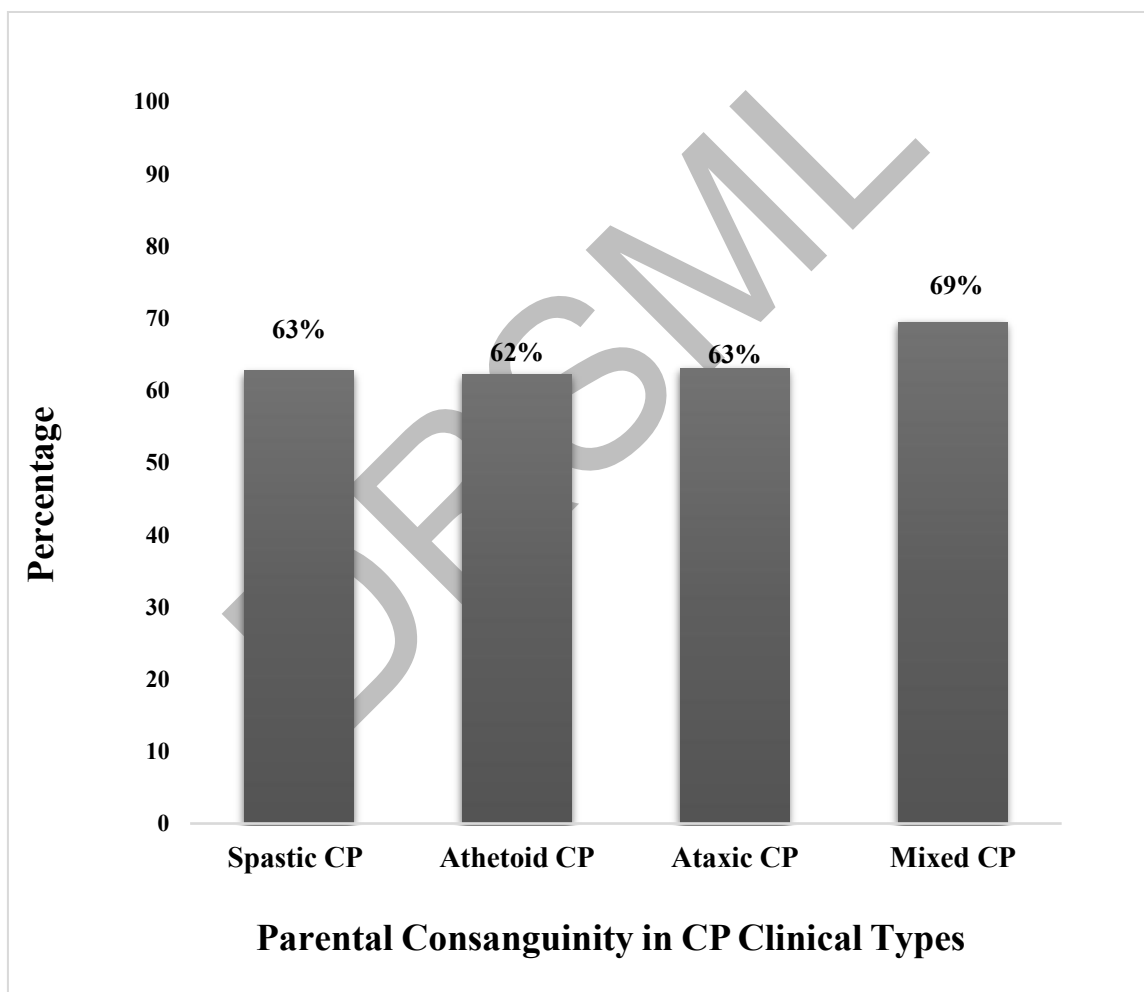


**Fig. 3.2.10: Classification of index subjects based on parental consanguinity in CP clinical types.**

## 3.2.11. Classification of index subjects based on parental consanguinity in topographical types

Parental consanguinity was found very high in left hemiplegia (70%), followed by quadriplegia (69%), diplegia (64%), triplegia (60%), paraplegia (57%), right hemiplegia (55%) and monoplegia (52%) as compared to non-consanguineous marriages (Fig. 3.2.11). But, no significant association was observed when data were distributed with respect to parental consanguinity and topographical distribution types (Table 3.2d).
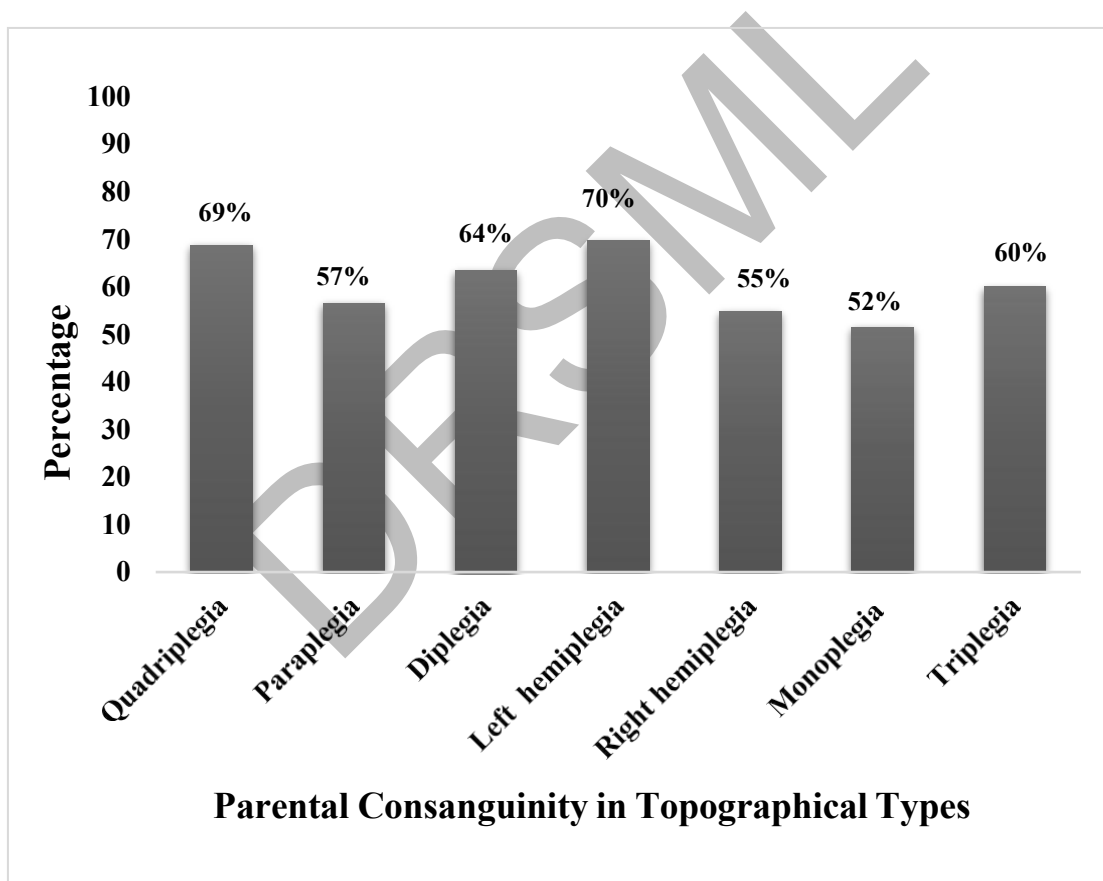


**Fig. 3.2.11: Classification of index subjects based on parental consanguinity in topographical types.**

### 3.2.12. Classification of index subjects based on parental consanguinity in dyskinetic types

Parental consanguinity was found very high in athetosis (68%), choreoathetosis (67%) and dystonic (58%) cases as compared to non-consanguineous marriages (Fig. 3.2.12). But, no significant association was observed when data were distributed with respect to parental consanguinity and dyskinetic types (Table 3.2d).
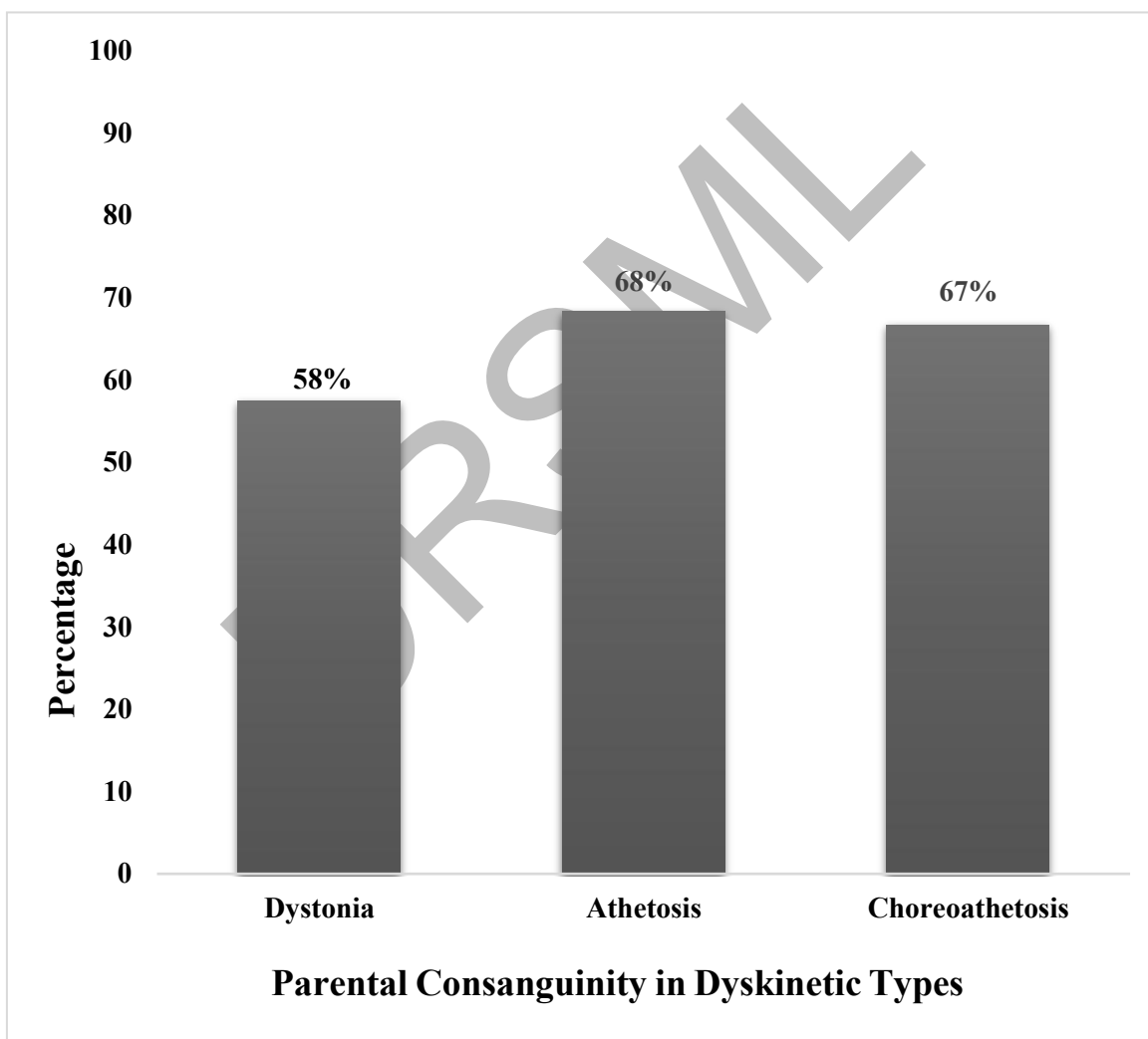


**Fig. 3.2.12: Classification of index subjects based on parental consanguinity in dyskinetic types.**

**Table 3.2d: Distribution of index subjects based on parental consanguinity in cerebral palsy.**

| Cerebral palsy types | Parental consanguinity | | | | Total No. | Percentage |
|---|---|---|---|---|---|---|
| | Yes (No) | Yes (%) | No (No) | No (%) | | |
| Spastic CP | 330 | 63 | 196 | 37 | 526 | 53 |
| Athetoid CP | 178 | 62 | 108 | 38 | 286 | 29 |
| Ataxic CP | 89 | 63 | 52 | 37 | 141 | 14 |
| Mixed CP | 25 | 69 | 11 | 31 | 36 | 4 |
| Grand Total | 622 | 63 | 367 | 37 | 989 | 100 |
| $\chi^2$ test | $\chi^2$=0.72; df=3; p=0.868 | | | | | |
| **Topographical distribution** | | | | | | |
| Quadriplegia | 110 | 69 | 50 | 31 | 160 | 30 |
| Paraplegia | 56 | 57 | 43 | 43 | 99 | 19 |
| Diplegia | 61 | 64 | 35 | 36 | 96 | 18 |
| Left hemiplegia | 46 | 70 | 20 | 30 | 66 | 13 |
| Right hemiplegia | 34 | 55 | 28 | 45 | 62 | 12 |
| Monoplegia | 17 | 52 | 16 | 48 | 33 | 6 |
| Triplegia | 6 | 60 | 4 | 40 | 10 | 2 |
| $\chi^2$ test | $\chi^2$=8.94; df=6; p=0.176 | | | | | |
| **Dyskinetic/athetoid type** | | | | | | |
| Dystonic | 92 | 58 | 68 | 43 | 160 | 56 |
| Athetosis | 84 | 68 | 39 | 32 | 123 | 43 |
| Choreoathetosis | 2 | 67 | 1 | 33 | 3 | 1 |
| $\chi^2$ test | $\chi^2$=3.47; df=2; p=0.176 | | | | | |

## 3.2.13. Distribution of index subjects based on paternal age at birth

Paternal age was divided into 3 classes. The paternal age interval (≥19-35 years) had the highest representation of subjects (74%). Followed by paternal age interval ≥35 years (25%) and paternal age interval ≥18 had the lowest representation of disorder (1%). Mostly, seen in spastic CP cases (40%) than athetoid CP (21%), ataxic CP (11%,) and mixed CP type (3%,) in paternal age interval ≥19-35 years. A similar pattern was seen in all age intervals (Fig. 3.2.13). No significant association was observed when data were distributed with respect to paternal age and clinical types (Table 3.2e).
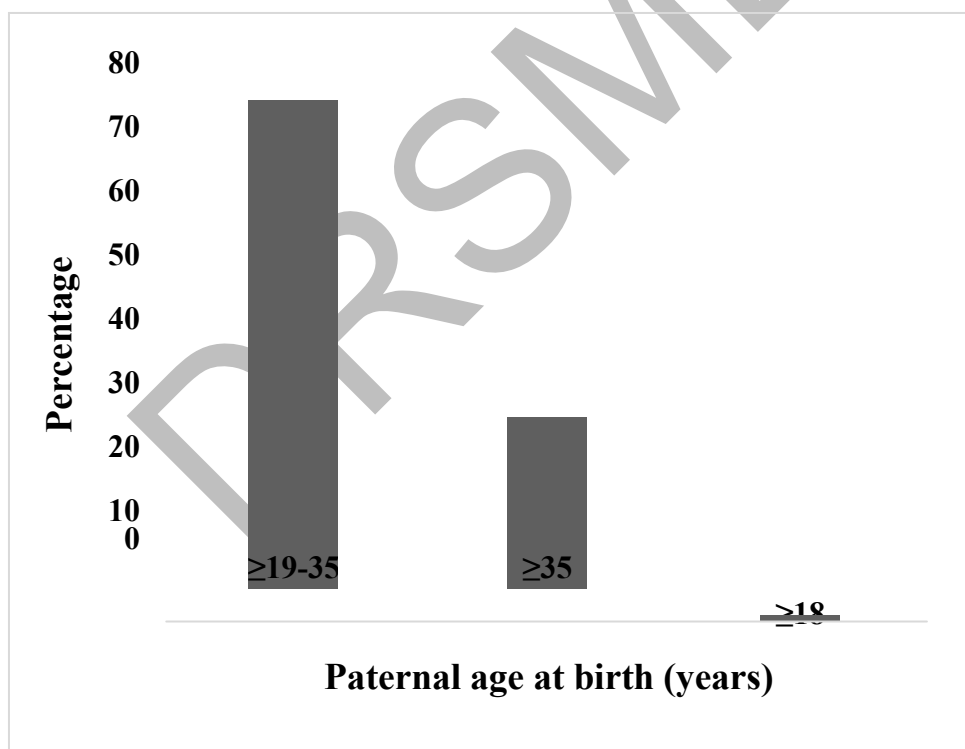


**Fig. 3.2.13: Distribution of index subjects based on paternal age at birth.**

### 3.2.14. Distribution of index subjects based on maternal age at birth

Maternal age was also divided into 3 classes. The maternal age interval (≥19-35 years) had also the highest representation of subjects (86%). Followed by paternal age interval ≥35 years (10%) and paternal age interval ≥18 had the lowest representation of disorder (5%). Mostly, seen in spastic CP cases (47%) than athetoid CP (24%), ataxic CP (12%,) and mixed CP type (3%,) in maternal age interval ≥19-35 years. A similar pattern was seen in all age intervals (Fig. 3.2.14). No significant association was observed when data were distributed with respect to paternal age and clinical types (Table 3.2e).



**Fig. 3.2.14: Distribution of index subjects based on maternal age at birth.**

**Table 3.2e: Distribution of index subjects based on parental age at birth in cerebral palsy.**

| Parental age (years) | ≤18 | ≤19-35 | ≥35 | Grand Total |
|---|---|---|---|---|
| **Paternal Age** | | | | |
| Spastic CP | 4 | 359 | 129 | 492 |
| Athetoid CP | 3 | 193 | 56 | 252 |
| Ataxic CP | 2 | 96 | 33 | 131 |
| Mixed CP | 0 | 25 | 6 | 31 |
| Grand Total | 9 | 673 | 224 | 906 |
| $\chi^2$ test | $\chi^2$=2.88; df=6; p=0.824 | | | |
| **Maternal Age** | | | | |
| Spastic CP | 20 | 421 | 48 | 489 |
| Athetoid CP | 15 | 217 | 21 | 253 |
| Ataxic CP | 6 | 109 | 18 | 133 |
| Mixed CP | 1 | 28 | 2 | 31 |
| $\chi^2$ test | $\chi^2$=4.49; df=6; p=0.611 | | | |

# 3.3 : Risk factors distribution in cerebral palsy

## 3.3.1. Distribution of risk factors in cerebral palsy

In all cerebral palsy types combined (prenatal, natal, postnatal) cause of risk factor is found to be very high (54%), followed by postnatal (19%), natal (16%), prenatal (7%) and cases in which cause not known (4%). The combined cause of risk factors was found to be high in athetoid CP (24%), followed by spastic CP (21%), ataxic CP (7%) and mixed CP (3%). While postnatal, natal and prenatal causes found high in spastic CP (8%, 7%, 5%, respectively) than athetoid CP (8%, 4%, 1%, respectively), ataxic CP (2%, 3%, 1%, respectively) and mixed CP (1%, 1%, 0.2%, respectively) (Fig. 3.3.1). A significant association was observed between clinical types and the cause of risk factors (Table 3.3a).
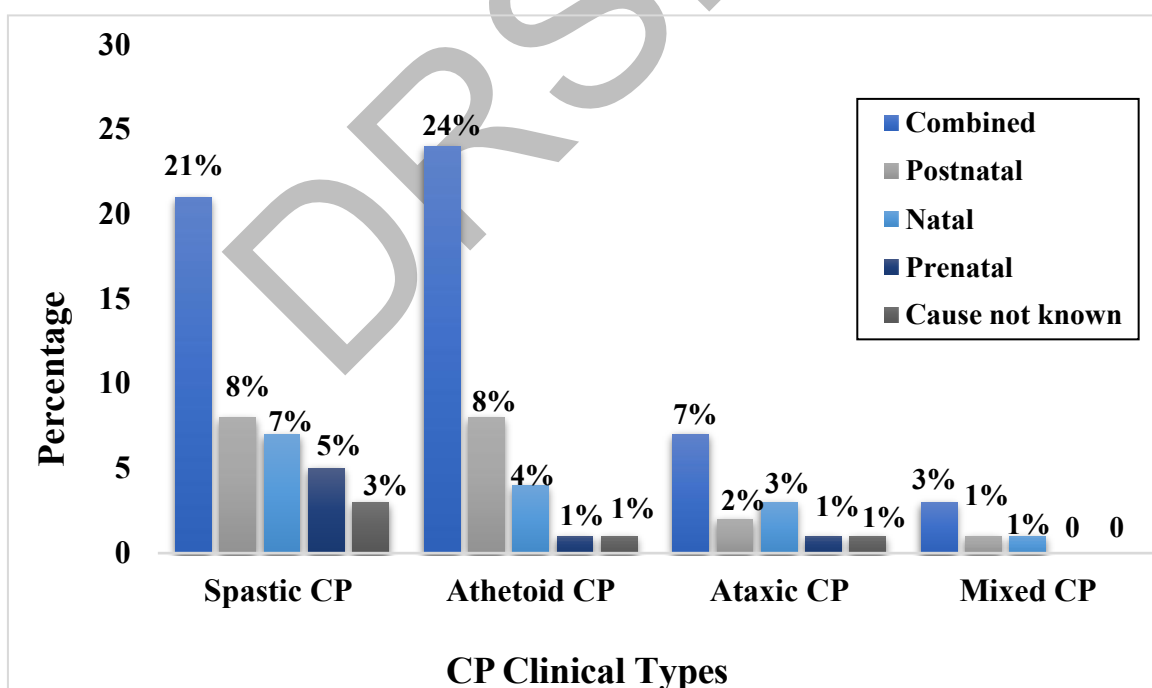


**Fig. 3.3.1: Distribution of risk factors in cerebral palsy.**

**Table 3.3a:-Distribution of risk factors in cerebral palsy.**

| Cerebral Palsy Types | Prenatal | Natal | Postnatal | Combined | Cause not known | Grand Total |
|---|---|---|---|---|---|---|
| Spastic CP | 22 | 30 | 33 | 83 | 11 | 179 |
| Athetoid CP | 3 | 16 | 31 | 97 | 5 | 152 |
| Ataxic CP | 3 | 13 | 6 | 30 | 2 | 54 |
| Mixed CP | 1 | 4 | 5 | 10 | 0 | 20 |
| Grand Total | 29 | 63 | 75 | 220 | 18 | 405 |
| $\chi^2$ test | $\chi^2$=27.64; df=12; p=0.006; ** | | | | | |

## 3.3.2. Distribution of index subjects based on the prenatal cause of cerebral palsy

In cerebral palsy disorders, secondary prenatal causes were found much higher (62%) than the primary causes (38%). A secondary cause was found to be high in athetoid CP (26%) followed by spastic CP (24%), ataxic CP (9%) CP and mixed CP (4%). While, the primary cause was found to be high in spastic CP (23%) than athetoid CP (9%), ataxic CP (6%) and mixed CP (1%) (Fig. 3.3.2). A significant association was observed between the prenatal cause of disease and clinical types (Table 3.3b)
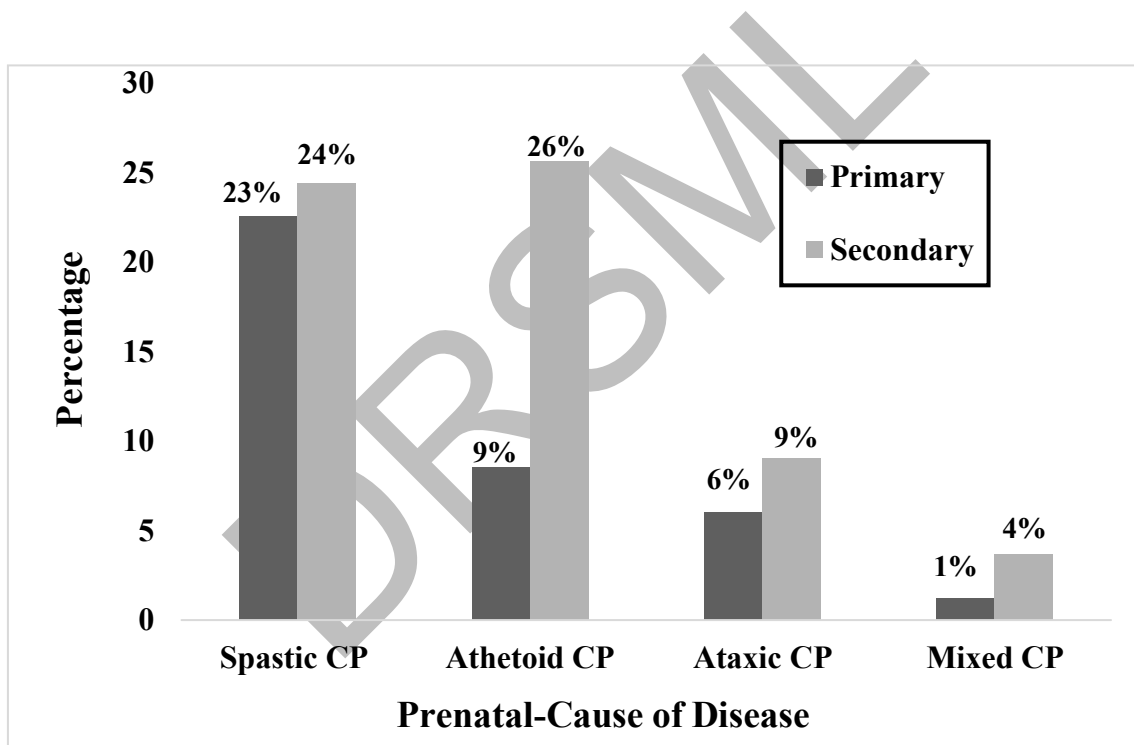


**Fig. 3.3.2: Distribution of index subjects based on prenatal cause of CP.**

### 3.3.3. Distribution of index subjects based on the postnatal cause of cerebral palsy

Secondary postnatal causes were found much higher (94%) in cerebral palsy disorder than the primary cause (6%). Both primary and secondary causes found higher in athetoid CP (3%, 42%) than spastic CP (2%, 35%), ataxic CP (0.1%, 11%) and mixed CP (0.4%, 5%) (Fig. 3.3.3). No significant association was observed when data were distributed with respect to the postnatal cause of disease and clinical types (Table 3.3b).
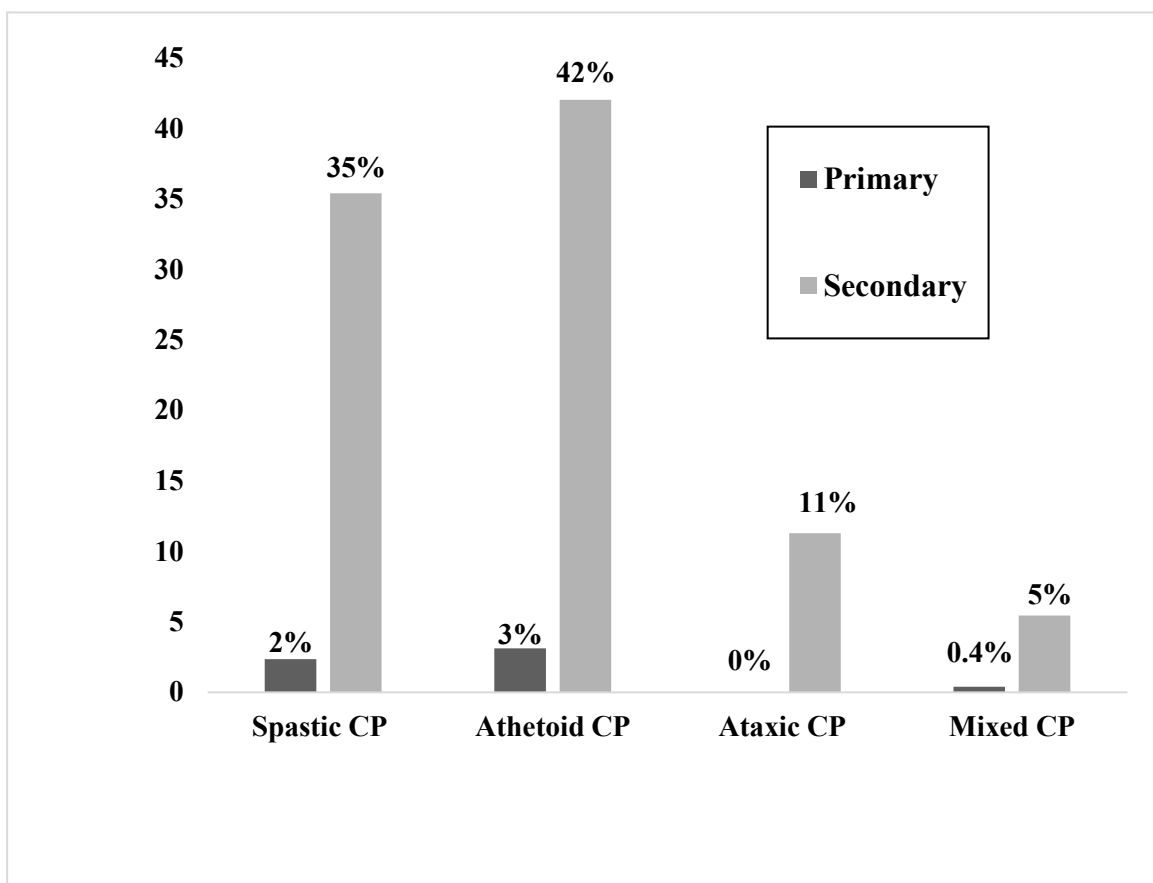


**Fig. 3.3.3: Distribution of index subjects based on the postnatal cause of CP.**

**Table 3.3b: Distribution of index subjects based on cause of cerebral palsy.**

| Cause of disease | Primary | Secondary | Grand Total | Percentage |
|---|---|---|---|---|
| **Prenatal** | | | | |
| Spastic CP | 37 | 40 | 77 | 47 |
| Athetoid CP | 14 | 42 | 56 | 34 |
| Ataxic CP | 9 | 14 | 23 | 14 |
| Mixed CP | 2 | 6 | 8 | 5 |
| Grand Total | 62 | 102 | 164 | 100 |
| $\chi^2$ test | $\chi^2$=2.08; df=3; p=0.55 | | | |
| **Postnatal** | | | | |
| Spastic CP | 6 | 91 | 97 | 38 |
| Athetoid CP | 8 | 108 | 116 | 45 |
| Ataxic CP | 0 | 29 | 29 | 11 |
| Mixed CP | 1 | 14 | 15 | 6 |
| $\chi^2$ test | $\chi^2$=2.08; df=3; p=0.557 | | | |

### 3.3.4. Distribution of neonatal risk factors in subjects with cerebral palsy

Various neonatal risk factors potentially affecting CP types were evaluated which include; neonatal jaundice, neonatal pneumonia, congenital heart defect, neonatal typhoid, neonatal meningitis, neonatal seizures, neonatal fever, premature birth, low birth weight (at time of birth). Among those factors distribution of neonatal seizures, low birth weight (at time of birth), premature birth and neonatal fever was observed to be higher in CP types (Fig. 3.3.4). The most prominent risk factors neonatal seizure (54%) and low birth weight (24%) were found to be statistically significant in CP types (Table 3.3c).
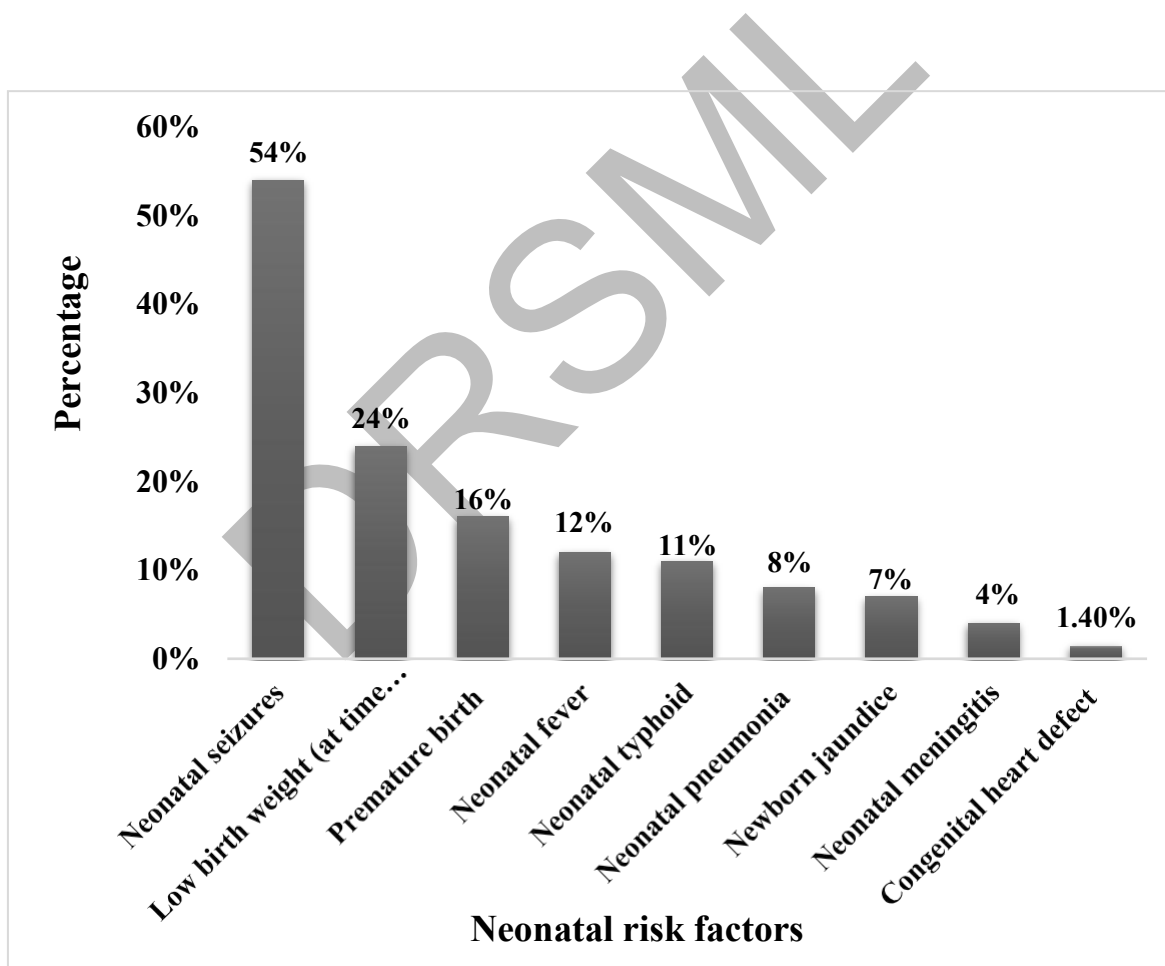


**Fig. 3.3.4: Distribution of neonatal risk factors in subjects with cerebral palsy**

**Table 3.3c: Distribution of neonatal risk factors in subjects with cerebral palsy**

| Variable | Spastic CP | Athetoid CP | Ataxic CP | Mixed CP | Grand Total |
|---|---|---|---|---|---|
| **Newborn jaundice** | | | | | |
| No | 183 | 142 | 54 | 17 | 396 |
| Yes | 12 | 13 | 2 | 3 | 30 |
| Grand Total | 195 | 155 | 56 | 20 | 426 |
| $\chi^2$ test | $\chi^2$=3.63; df=6; p=0.727 | | | | |
| **Neonatal pneumonia** | | | | | |
| No | 188 | 137 | 52 | 19 | 396 |
| Yes | 9 | 18 | 4 | 1 | 32 |
| $\chi^2$ test | $\chi^2$=6.43; df=6; p=0.377 | | | | |
| **Congenital heart defect** | | | | | |
| No | 191 | 152 | 56 | 20 | 419 |
| Yes | 3 | 3 | 0 | 0 | 6 |
| $\chi^2$ test | $\chi^2$=1.42; df=6; p=0.965 | | | | |
| **Neonatal typhoid** | | | | | |
| No | 172 | 137 | 55 | 14 | 378 |
| Yes | 23 | 18 | 1 | 5 | 47 |
| $\chi^2$ test | $\chi^2$=9.55; df=6; p=0.145 | | | | |
| **Neonatal meningitis** | | | | | |
| No | 191 | 151 | 54 | 19 | 415 |
| Yes | 8 | 4 | 3 | 1 | 16 |
| $\chi^2$ test | $\chi^2$=1.09; df=6; p=0.982 | | | | |
| **Neonatal seizures** | | | | | |
| No | 126 | 55 | 25 | 5 | 211 |
| Yes | 86 | 109 | 35 | 16 | 246 |
| $\chi^2$ test | $\chi^2$=30.25; df=6; P<0.0001, *** | | | | |

| Neonatal fever | | | | | |
|---|---|---|---|---|---|
| No | 178 | 131 | 50 | 17 | 376 |
| Yes | 20 | 24 | 6 | 3 | 53 |
| $\chi^2$ test | $\chi^2$=2.60; df=6; p=0.857 | | | | |
| **Premature birth** | | | | | |
| No | 168 | 136 | 46 | 12 | 362 |
| Yes | 32 | 18 | 11 | 8 | 69 |
| $\chi^2$ test | $\chi^2$="11.16; df=6; p=0.083 | | | | |
| **Low birth weight (at time of birth)** | | | | | |
| No | 149 | 122 | 38 | 8 | 317 |
| Yes | 42 | 29 | 18 | 12 | 101 |
| $\chi^2$ test | $\chi^2$=18.48; df=3; p=0.0003, *** | | | | |

*** = highly significant

### 3.3.5. Distribution of maternal risk factors in subjects with cerebral palsy

Many maternal risk factors in cerebral palsy types have been found which include; mode of delivery, maternal malnutrition, supplement use (folic acid), parity, twin pregnancy, late delivery, the status of second last pregnancy, ABO and RH incompatibility, oligohydramnios, fertility treatment, thyroid problem (mother), maternal fever, Maternal substance use (Clay/Fuller's earth), hypotension, preeclampsia, gestational diabetes. Among these $1^{st}$ and $2^{nd}$ parity, mode of delivery, supplement use (folic acid), preeclampsia, the status of second last pregnancy, ABO and RH incompatibility was observed to be higher in CP types (Fig. 3.3.5). The only most prominent maternal risk factor preeclampsia (23%) was found to be statistically significant in CP types (Table 3.3d).
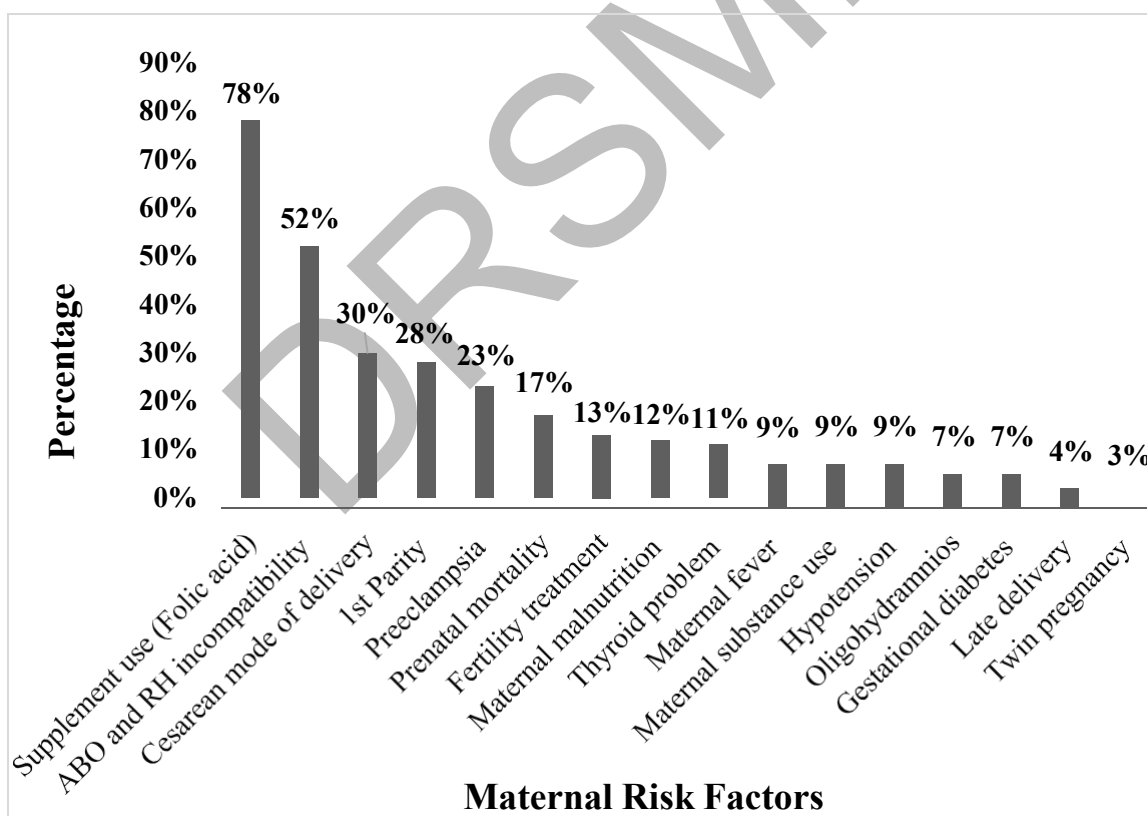


**Fig. 3.3.5: Distribution of maternal risk factors in subjects with cerebral palsy**

**Table 3.3d: Distribution of maternal risk factors in subjects with cerebral palsy.**

| Variable | Spastic CP | Athetoid CP | Ataxic CP | Mixed CP | Grand Total |
|---|---|---|---|---|---|
| **Mode of delivery** | | | | | |
| Vaginal | 164 | 124 | 47 | 11 | 346 |
| Cesarean | 77 | 47 | 17 | 10 | 151 |
| Grand Total | 241 | 171 | 64 | 21 | 497 |
| $\chi^2$ test | $\chi^2$=4.350, 6; df=6; p=0.629 | | | | |
| **Maternal malnutrition** | | | | | |
| No | 213 | 149 | 58 | 17 | 437 |
| Yes | 27 | 22 | 6 | 4 | 59 |
| $\chi^2$ test | $\chi^2$=1.66; df=6; p=0.948 | | | | |
| **Supplement use (Folic acid)** | | | | | |
| Yes | 192 | 127 | 53 | 14 | 386 |
| No | 48 | 44 | 11 | 7 | 110 |
| $\chi^2$ test | $\chi^2$=4.35; df=6; p=0.630 | | | | |
| **Parity** | | | | | |
| 1st | 60 | 58 | 15 | 6 | 139 |
| 2nd | 65 | 38 | 20 | 4 | 127 |
| 3rd | 48 | 29 | 10 | 4 | 91 |
| 4th | 27 | 23 | 9 | 4 | 63 |
| 5th | 20 | 8 | 2 | 2 | 32 |
| ≤6th | 20 | 16 | 8 | 1 | 45 |
| $\chi^2$ test | $\chi^2$=31.66; df= 33; p=0.534 | | | | |
| **Twin pregnancy** | | | | | |
| No | 232 | 162 | 64 | 21 | 479 |
| Yes | 8 | 9 | 0 | 0 | 17 |
| $\chi^2$ test | $\chi^2$=4.76; df=6; p=0.574 | | | | |
| **Late delivery** | | | | | |
| No | 190 | 147 | 55 | 20 | 412 |
| Yes | 9 | 7 | 2 | 0 | 18 |
| $\chi^2$ test | $\chi^2$=1.05; df=6; p=0.984 | | | | |

**Status of second last pregnancy**

| | | | | | |
|---|---|---|---|---|---|
| Normal | 180 | 132 | 48 | 17 | 377 |
| Prenatal mortality | 43 | 26 | 12 | 3 | 84 |
| CP affected child | 15 | 11 | 4 | 1 | 22 |
| $\chi^2$ test | $\chi^2$=0.86; df=6; p=0.990 | | | | |

**ABO and RH incompatibility**

| | | | | | |
|---|---|---|---|---|---|
| Yes | 27 | 23 | 8 | 4 | 62 |
| No | 22 | 23 | 8 | 4 | 57 |
| $\chi^2$ test | $\chi^2$=0.30; df=6; p=0.999 | | | | |

**Oligohydramnios**

| | | | | | |
|---|---|---|---|---|---|
| No | 185 | 143 | 50 | 18 | 396 |
| Yes | 10 | 11 | 6 | 2 | 29 |
| $\chi^2$ test | $\chi^2$=2.56; df=3; p=0.465 | | | | |

**Fertility treatment**

| | | | | | |
|---|---|---|---|---|---|
| No | 167 | 141 | 45 | 16 | 369 |
| Yes | 27 | 12 | 11 | 4 | 54 |
| $\chi^2$ test | $\chi^2$=6.88; df=3; p=0.076 | | | | |

**Thyroid problem (Mother)**

| | | | | | |
|---|---|---|---|---|---|
| No | 184 | 148 | 53 | 19 | 404 |
| Yes | 10 | 6 | 3 | 1 | 20 |
| $\chi^2$ test | $\chi^2$="0.368; df=3; p=0.947 | | | | |

**Maternal fever**

| | | | | | |
|---|---|---|---|---|---|
| No | 178 | 141 | 49 | 20 | 388 |
| Yes | 19 | 14 | 7 | 0 | 40 |
| $\chi^2$ test | $\chi^2$=2.76; df=3; p=0.430 | | | | |

**Maternal substance use (Clay/Fuller's earth/Uncooked rice)**

| | | | | | |
|---|---|---|---|---|---|
| No | 179 | 138 | 52 | 17 | 386 |
| Yes | 15 | 16 | 4 | 3 | 38 |
| $\chi^2$ test | $\chi^2$=1.87; df=3; p=0.601 | | | | |

| **Hypotension** | | | | | |
|---|---|---|---|---|---|
| No | 183 | 137 | 52 | 16 | 388 |
| Yes | 12 | 18 | 4 | 4 | 38 |
| $\chi^2$ test | $\chi^2$=6.46; df=3; p=0.091 | | | | |
| **Preeclampsia** | | | | | |
| No | 159 | 117 | 47 | 10 | 333 |
| Yes | 39 | 39 | 9 | 11 | 98 |
| $\chi^2$ test | $\chi^2$=13.42; df=3; p=0.004, ** | | | | |
| **Gestational diabetes** | | | | | |
| No | 183 | 145 | 54 | 18 | 400 |
| Yes | 12 | 12 | 2 | 2 | 28 |
| $\chi^2$ test | $\chi^2$="1.56; df=3; p=0.669 | | | | |

** = highly significant

### 3.3.6. Distribution of obstetric risk factors in subjects with cerebral palsy

Numerous obstetric risk factors in cerebral palsy types have been found which include; injury to the child during pregnancy, birth attendant problem, meconium, perinatal asphyxiation, crying of the baby after birth, induced labor, improper use of birth-assisted tools during delivery and premature rupture of membrane (PROM). Perinatal asphyxiation, crying of baby after birth, birth attendant problem, and induced labor were observed to be higher in CP types (Fig. 3.3.6). Late crying of the baby after birth (41%) and induced labor (3%) were found significant in CP types (Table 3.3e).
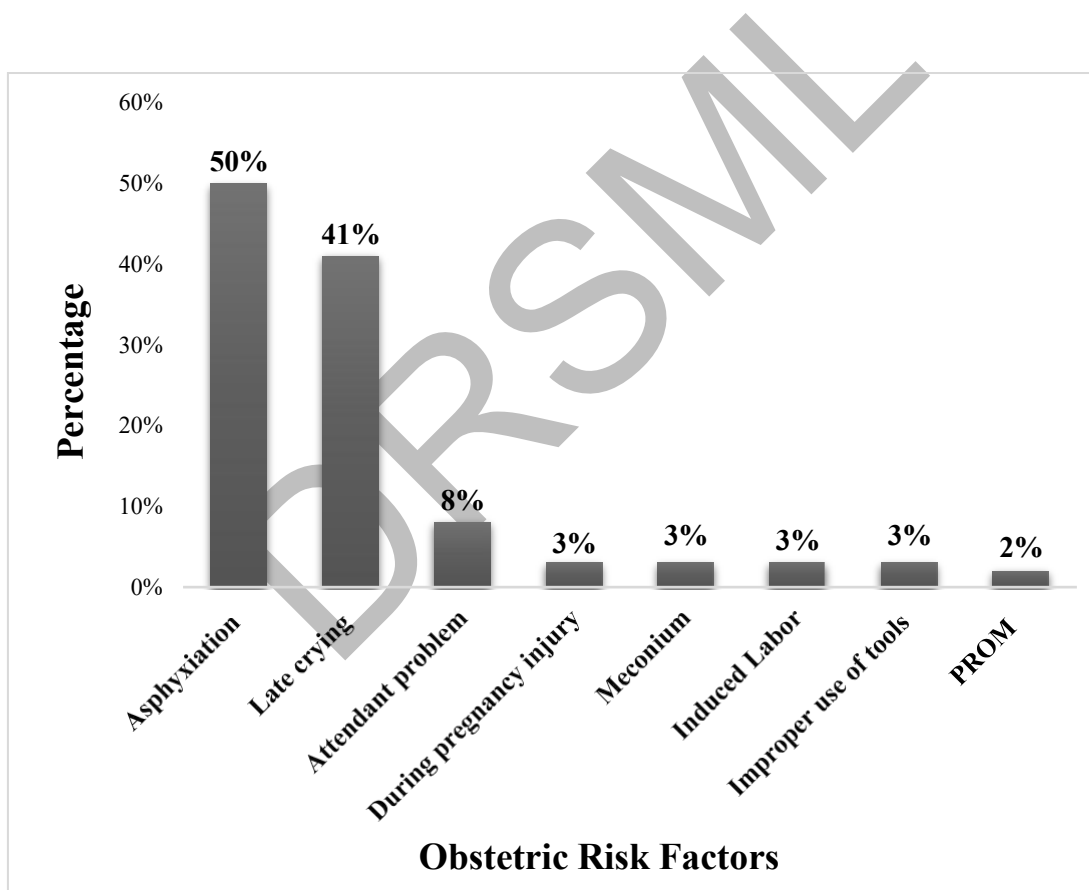


**Fig. 3.3.6: Distribution of obstetric risk factors in subjects with cerebral palsy**

**Table 3.3e: Distribution of obstetric risk factors in subjects with cerebral palsy.**

| Variable | Spastic CP | Athetoid CP | Ataxic CP | Mixed CP | Grand Total |
|---|---|---|---|---|---|
| **Injury to child during pregnancy** | | | | | |
| No | 192 | 148 | 55 | 20 | 415 |
| Yes | 6 | 7 | 1 | 0 | 14 |
| **Grand Total** | **198** | **155** | **56** | **20** | **429** |
| $\chi^2$ test | $\chi^2$=5.27; df=4; p=0.601 | | | | |
| **Birth attendant problem** | | | | | |
| No | 174 | 149 | 53 | 19 | 395 |
| Yes | 22 | 6 | 3 | 1 | 32 |
| $\chi^2$ test | $\chi^2$=7.42; df=6; p=0.284 | | | | |
| **Meconium** | | | | | |
| No | 191 | 146 | 55 | 20 | 412 |
| Yes | 4 | 9 | 1 | 0 | 14 |
| $\chi^2$ test | $\chi^2$=5.11; df=6; p=0.529 | | | | |
| **Perinatal asphyxiation** | | | | | |
| No | 108 | 74 | 23 | 9 | 214 |
| Yes | 87 | 81 | 34 | 11 | 213 |
| $\chi^2$ test | $\chi^2$=4.89; df=3; p=0.179 | | | | |
| **Crying of baby after birth** | | | | | |
| Yes | 126 | 70 | 25 | 9 | 230 |
| Late crying | 63 | 77 | 29 | 6 | 175 |
| Yes(less) | 8 | 9 | 3 | 5 | 25 |
| $\chi^2$ test | $\chi^2$=29.76; df=9; p=0.0005, *** | | | | |
| **Induced Labor** | | | | | |
| No | 194 | 147 | 52 | 20 | 413 |
| Yes | 0 | 7 | 4 | 0 | 11 |
| $\chi^2$ test | $\chi^2$=12.60; df=3; p=0.005, ** | | | | |

| Improper use of birth assisted tools during delivery | | | | | |
|---|---|---|---|---|---|
| No | 184 | 143 | 51 | 20 | 398 |
| Yes | 6 | 8 | 0 | 0 | 14 |
| $\chi^2$ test | $\chi^2$=4.19; df=3; p=0.242 | | | | |
| **Premature rupture of membrane (PROM)** | | | | | |
| No | 184 | 148 | 50 | 20 | 402 |
| Yes | 6 | 2 | 1 | 0 | 9 |
| $\chi^2$ test | $\chi^2$=1.81; df=3; p=0.614 | | | | |

** or *** = highly significant

### 3.3.7. Distribution of gynecological problems in subjects with cerebral palsy

Many gynecological problems in cerebral palsy types have been found which include; breech position, placental problems, and maternal bleeding in later week of pregnancy. Placental problems and maternal bleeding in the later week of pregnancy were found higher in CP types (Fig. 3.3.7). Maternal bleeding in the later week of pregnancy (4%) was found statistically significant in CP types (Table 3.3f).
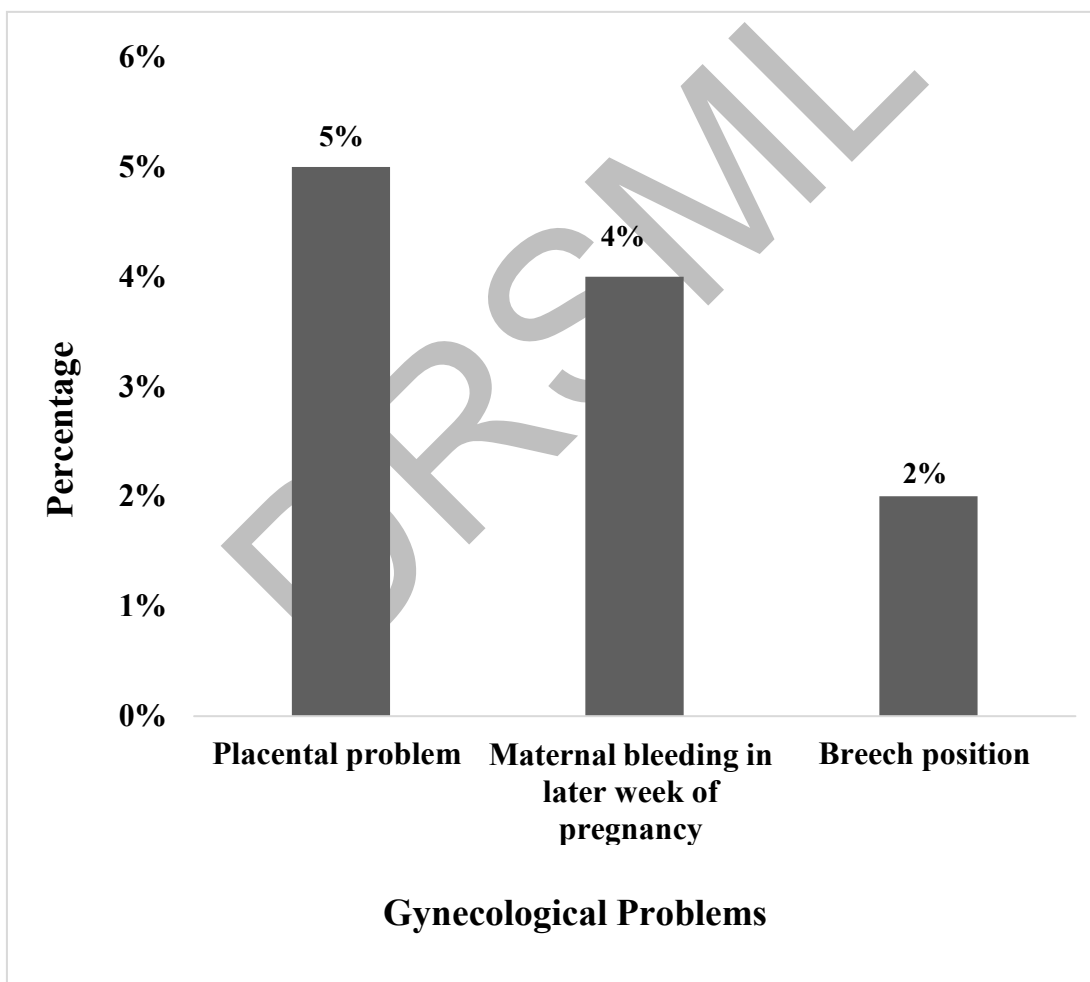


**Fig. 3.3.7: Distribution of  gynecological problems in subjects with cerebral palsy**

**Table 3.3f: Distribution of gynecological problems in subjects with cerebral palsy.**

| Variable | Spastic CP | Athetoid CP | Ataxic CP | Mixed CP | Grand Total |
|---|---|---|---|---|---|
| **Breech position** | | | | | |
| No | 185 | 151 | 55 | 20 | 411 |
| Yes | 7 | 1 | 0 | 0 | 8 |
| $\chi^2$ test | $\chi^2$=5.82; df=3; p=0.121 | | | | |
| **Placental problem** | | | | | |
| No | 175 | 148 | 50 | 19 | 392 |
| Yes | 14 | 3 | 1 | 1 | 19 |
| $\chi^2$ test | $\chi^2$=6.53; df=3; p=0.089 | | | | |
| **Maternal bleeding in later week of pregnancy** | | | | | |
| No | 189 | 141 | 53 | 20 | 403 |
| Yes | 2 | 11 | 3 | 0 | 16 |
| $\chi^2$ test | $\chi^2$=9.99; df=3; p=0.019, * | | | | |

* = significant

## 3.4. Distribution of associated anomalies in subjects with cerebral palsy

The most common associations were speech impairment occurring in 20% of patients, followed by epilepsy (16%), DMS (13%), visual and eye defect (9%), hearing impairment (4%), intellectual disability (8%), microcephaly (7%), talipes (6%) and remaining disorders are shown in Fig. 3.4 and Table 3.4. A significant association was observed when data were distributed between the associated anomalies and cerebral palsy.
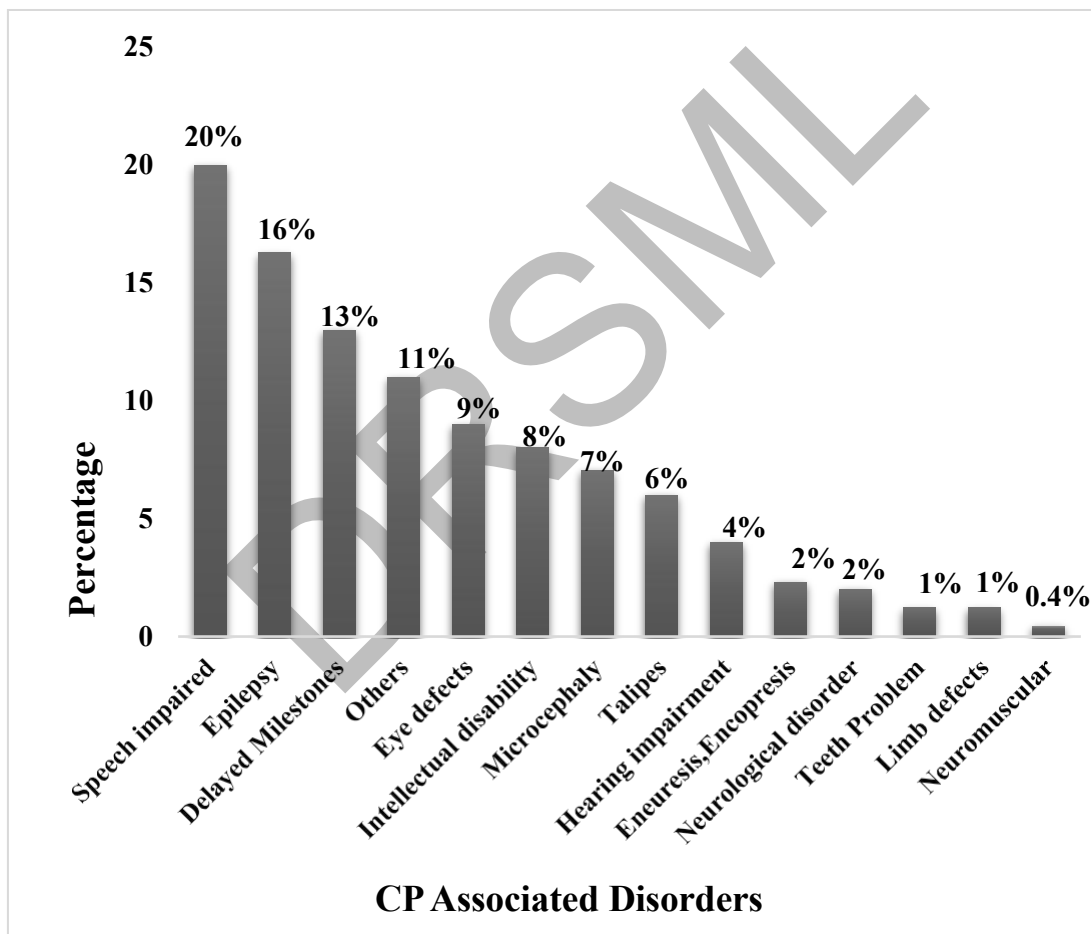


**Fig. 3.4: Distribution of associated anomalies in subjects with cerebral palsy.**

**Table 3.4: Distribution of associated anomalies in subjects with cerebral palsy.**

| Associated Disorders | Spastic CP | Athetoid CP | Ataxic CP | Mixed CP | Total No. | Total (%) |
|---|---|---|---|---|---|---|
| Speech impaired | 129 | 116 | 64 | 17 | 326 | 19.8 |
| Epilepsy | 94 | 116 | 42 | 16 | 268 | 16.3 |
| Delayed milestones | 93 | 80 | 25 | 16 | 214 | 13.0 |
| Eye/visual anomalies | 53 | 58 | 25 | 9 | 145 | 8.8 |
| Intellectual disability | 80 | 28 | 20 | 2 | 130 | 7.9 |
| Microcephaly | 29 | 62 | 21 | 4 | 116 | 7.0 |
| Talipes | 60 | 16 | 18 | 2 | 96 | 5.8 |
| Hearing impairment | 19 | 36 | 8 | 2 | 65 | 3.9 |
| Enuresis/encopresis | 17 | 13 | 4 | 4 | 38 | 2.3 |
| Neurological disorders | 15 | 7 | 2 | 1 | 25 | 1.5 |
| Dental problems | 3 | 13 | 3 | 1 | 20 | 1.2 |
| Limb defects | 9 | 6 | 3 | 2 | 20 | 1.2 |
| Others | 65 | 87 | 22 | 9 | 183 | 11.1 |
| Sum | 666 | 638 | 257 | 85 | 1646 | 100.0 |
| $\chi^2$ test | $\chi^2$=112.6; df=39; P<0.0001;*** | | | | | |

\*\*\* = highly significant

## 3.5 : Treatments given to cerebral palsy patients

### 3.5.1. Distribution of treatments given to subjects with cerebral palsy

Data were collected with respect to the treatment given to cerebral palsy patients. It was observed that oral drugs were recommended to 71% of patients. Most of the drugs given were Diazepam, Phenytoin, Amphetamines, Intrathecal Baclofen Therapy/pumps, Botulinum Toxin A (BTA). Physiotherapy was given to 91% of patients, the most common recommendations were; Lap positioning, Grip scapula and protract, Bottom-up exercises, Gentle turning over facilitation, Prone on elbows, and Bridging exercises. Speech therapy received by 52% of patients which usually includes Oral motor exercises (OME), Honey exercises and Lip closure exercises was observed. Further analysis found that 7% of patients underwent surgical corrections for their disability symptoms. The most common corrections seen were Tendon Lengthening, Neurectomy, and Stabilization of joints (Arthrodesis) (Fig. 3.5.1 and Table 3.5a).
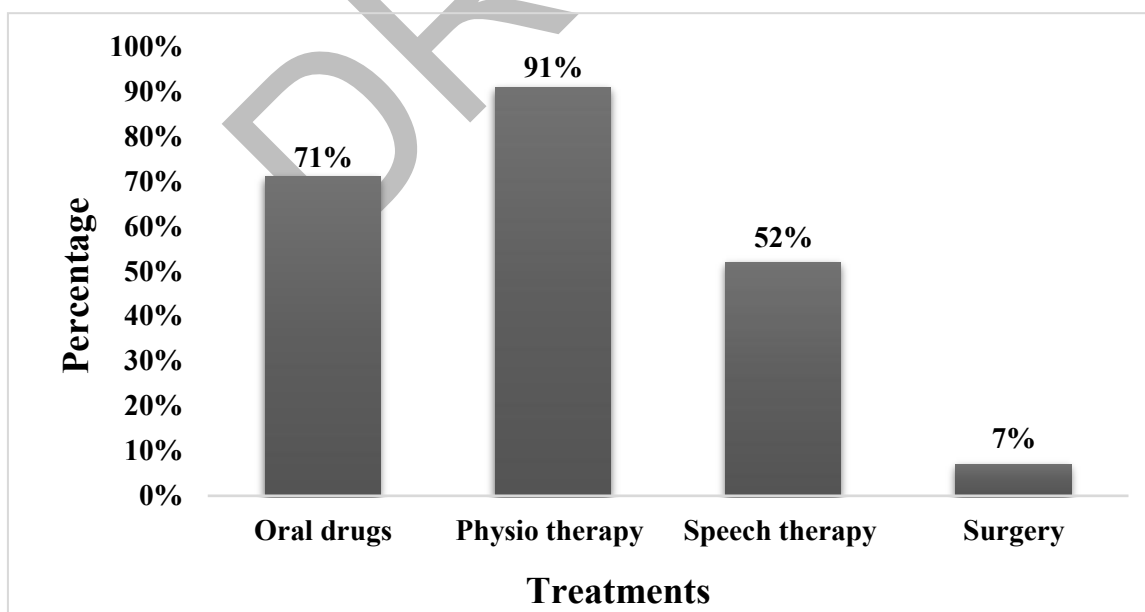


**Fig. 3.5.1: Distribution of treatments given to subjects with cerebral palsy.**

**Table 3.5a: Distribution of treatments given to subjects with cerebral palsy patients.**

| Treatments | Grand Total | Percentage (%) |
|---|---|---|
| **Oral drugs** | | |
| Yes | 355 | 71 |
| No | 142 | 29 |
| Grand Total | 497 | 100 |
| **Physio therapy** | | |
| Yes | 380 | 91 |
| No | 37 | 9 |
| **Speech therapy** | | |
| Yes | 220 | 52 |
| No | 202 | 48 |
| **Surgery** | | |
| No | 326 | 93 |
| Yes | 26 | 7 |

## 3.5.2. Distribution of improvement after treatment in subjects with cerebral palsy

According to the caregivers, the improvement seen in patients of cerebral palsy by oral drugs was 93%. It had been found that **diazepam** decreased muscle spasms, **phenytoin** reduced tension athetosis and generalized seizures, **amphetamines** help in improving behavior disturbances and hyperkinesia, and spasticity was reduced by **intrathecal baclofen therapy/pumps**.

Improvements seen due to physiotherapy were 78% in patients. Different exercises help in improving different muscles. **Lap positioning exercises help** to improve abdominal co-activation. **Grip scapula and protract** help child to play with mother's face, **bottom-up exercises** facilitate abdominals, **gentle turning over facilitation** improve righting reactions, **prone on elbows** slowly shift body weight on the affected arm in normal alignment

Improvements seen due to speech therapy in CP patients were 61%. Most often therapy used by speech therapists were honey exercises for tongue movement and lip closure exercises for movement of lips. Surgical corrections improvement was found only in 11% of patients. Most improvements seen due to surgical operation were tendon lengthening, neurectomy, and arthrodesis (Fig. 3.5.2 and table 3.5b).
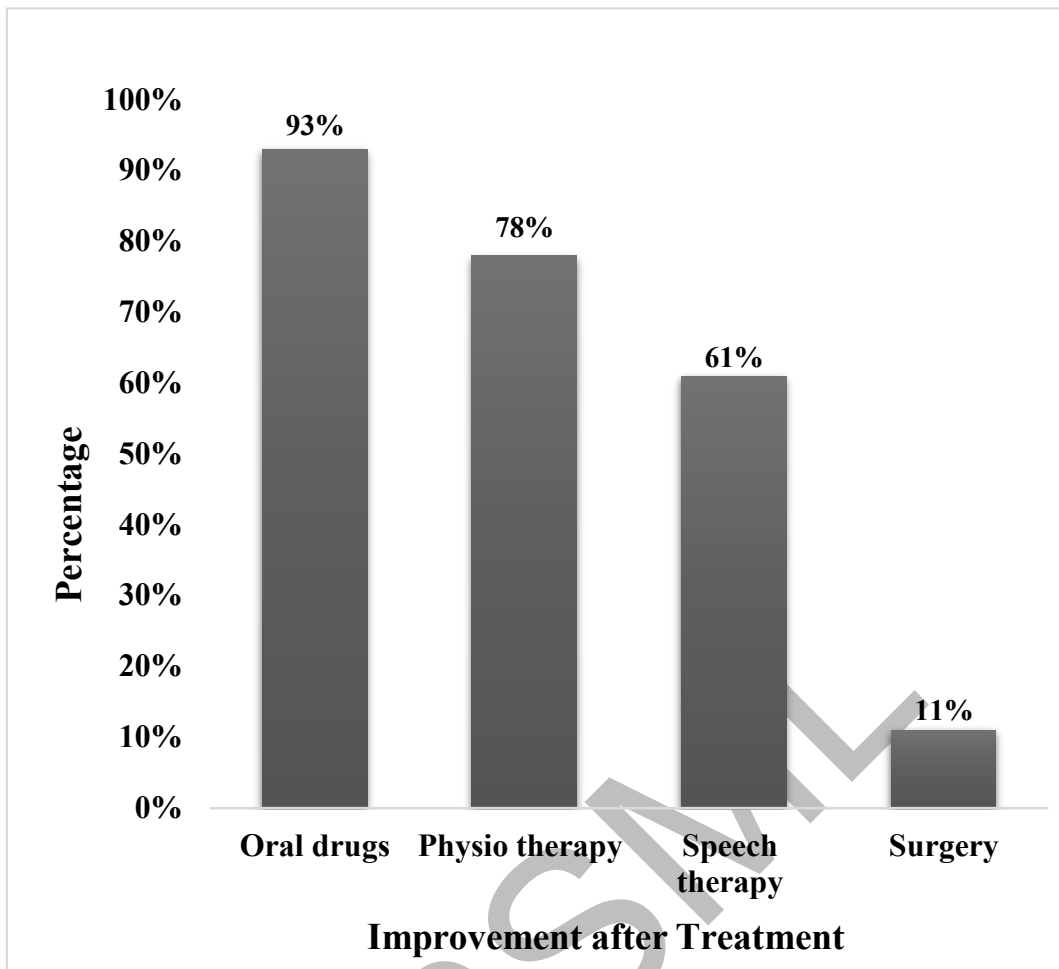
**Fig. 3.5.2: Distribution of improvement after treatment in subjects with cerebral palsy.**

**Table 3.5b: Distribution of improvement after treatment in subjects with cerebral palsy.**

| Improvement after treatment | Grand Total | Percentage (%) |
|---|---|---|
| **Oral drugs** | | |
| Yes | 295 | 93 |
| No | 23 | 7 |
| Grand Total | 318 | 100 |
| **Physiotherapy** | | |
| Yes | 322 | 78 |
| No | 91 | 22 |
| **Speech therapy** | | |
| Yes | 161 | 61 |
| No | 105 | 39 |
| **Surgery** | | |
| No | 185 | 89 |
| Yes | 22 | 11 |

# CHAPTER 4

# DISCUSSION

The current descriptive cross-sectional study was conducted at NIRM, Islamabad. The majority of the population residing in Islamabad is a sort of 'migratory population' from nearby as well as the remote areas of Pakistan. This study was conducted with a goal to highlight the etiological risk factors of CP and hence, to provide an epidemiological snapshot of the clinical types and associated anomalies of cerebral palsy in a Pakistani cohort. The study was conducted on 989 subjects and the data were acquired on various parameters including sociodemographic, parental factors, genetic and environmental factors, obstetric complications, birth parameters, and treatment. The variables like severity in cerebral palsy, associated disorders, causes and risk factors were also observed.

**Demographic attributes of index subjects**

Most epidemiological studies have shown that females are at lower risk of cerebral palsy than males. Than females males may be more vulnerable to genetic mutation (e:g copy or point number) and recessive X-linked chromosome variants found to be associated with this difference (Jacquemont et al., 2014). Our study also supports these studies. From the total of 989 patients studied during the survey, 61% of the patients were male and 39% of patients were female. The male to female ratio in this study was 1.6:1 which is similar to the previous study by Rafique and Naz et al. 2020 who witnessed a ratio of 1.4:1 in a cohort assembled at a tertiary care unit at Karachi. In India, ratio was found to be 1.9:1 (Laisram et al. 1992). In China, a similar male-to-female ratio was reported 1.9:1.2/1000 live births respectively (Liu et al. 1999).

From 989 cases, half of the patients 51% belong to Punjab followed by 30% belong to KPK. 12% belong to AJK and 5 % belong to Islamabad. The remaining 2% of patients belong to the province of Sindh, Baluchistan, and the FATA area. The reason is that a major study was conducted in Islamabad rehabilitation centers, so the majority of the patients

belong to Punjab. As KPK is near to Islamabad so second majority of the patients were from KPK. Third majority of the patients were from Azad Kashmir as it is also near to Islamabad. Less number of the affected individuals were from Islamabad and mostly were those who came to live here from remote areas of the country. As Sindh, Baluchistan, FATA area is far from Islamabad so few patients were from there. A study was conducted in the Dhaka division of Bangladesh in 2013, on exploring the factors associated with cerebral palsy children (Ester et al. 2008). This study found that the majority of the patients belong to the Dhaka division and the remaining from nearby divisions. In this study provincial distribution of children with cerebral palsy is the same as found in the literature. But no study is conducted in Pakistan to find an association between epidemiology and province.

Patients belong to rural areas constituting 68% while patients belong to urban areas making 32%. The reason is that a higher percentage of families who live in poverty are illiterate and they lack basic health facilities, while urban families are literate and had more protective factors to prevent the child from the negative impact of the environment. Rabia et al. 2019 also observed that the majority of cases of cerebral palsy originated from rural areas (75%) as compared to urban (25%). Also, a study in Taiwan shows that family of low income living in rural areas is associated with a higher prevalence of CP (Tseng et al. 2018). So, find an association of rural and urban areas with Cerebral palsy.

In this study majority of the patients had Punjabi as their mother tongue with 48%. Followed by Pushto 16%, Hindko 14%, Kashmiri/Pahari-Pothwari 7%, Khowar 6%, Urdu 5%, Saraiki 2%, and other 2%. This is because the majority of data is collected from Punjab and Islamabad rehabilitation centers, so many of the patients came from Punjab in Islamabad with Punjabi as their mother tongue. As KPK is situated close to Federal Capital Islamabad, therefore, the second majority of the patients were Pushto speaking. The third highest was Pahari/Kashmiri spoken in Azad Jammu and Kashmir. Saraiki spoke in southern Punjab and

Khowar in Gilgit as these areas are far from Islamabad, so a smaller number of patients were identified with these mother tongues. There is as such no study conducted on the linguistic distribution of children with cerebral palsy in Pakistan and in any other parts of the world. So, we find no association of cerebral palsy with the linguistic distribution.

In our study subjects studied were divided into 5 age groups. Majority of cases presented with cerebral palsy at very early age interval of 0–5 years (42%). Followed by ≥5.1-9 (22%),  ≥9.1-19 (24%), ≥19.1-29 (7%) and ≥29.1 (5%). It is because mostly the sign and symptoms of cerebral palsy appear during infancy or preschool years. Ahmad et al., 2017 identified three groups such as, 4-6, 7-8, and 9-10 years of age and the overall prevalence was reported as 1.22/1000 live births with a male to female ratio of 2.2:1. So our results are almost similar to previous literature as cerebral palsy was found to be lower in older age group children than higher age group children.

**Socio-economic and household attributes of index subjects**

In our study mostly cerebral palsy patients were unemployed 81% while employed were 19%. According to Benner et al. (2017), employment rates were specifically low in bilateral CP and intellectual impairment adults. So results in our study are almost similar to previous literature as employment opportunities for cerebral palsy individuals are less so fewer people are employed and more individuals are unemployed.

In our study mostly the cerebral palsy children are illiterate 79% and literate are 21%. Most of the literate cerebral palsy children have primary schooling 64%, followed by middle schooling (19%), high schooling (11%) and graduation and higher (6%). A study in India by Rathod and Alagesan, 2014, found 3% illiterate and 38% school going, 51% graduate and 8% postgraduate individuals. The results in our study are not similar to the previous study, the reason is that the patients on which the study was conducted, were children and had severe motor impairment.

In this study economic status is divided into four major categories; most of the patients belong to the low-mid category 34%, mid 32%, low 30%, high mid/high 3%. The reason is poor nutrition in low or low-mid economic status. A cohort study conducted in 2005 showed the linear association between the risk of cerebral palsy and socioeconomic status (Tseng et al. 2018). In this study social-economic status has a significant impact on cerebral palsy children and it is also seen in the literature.

In our study, the majority of the cerebral palsy patients were single 93%, only a few were married 7%. Jahnsen et al. 2004 studied the marital status of 406 cerebral palsy individuals, and observed that single/divorced/widowed were 76% and married/cohabitant were 24%. So, our results are almost similar to previous literature but further study is required in it.

The majority of the patients belonged to Extended family making 63%, while 37% belonged to the Nuclear family type. This is because in South Asia it is a prevailing tradition to live in a joint family system. There is as such no study conducted on the effect of family type on cerebral palsy children in literature. So we did not find any association between family type and cerebral palsy children.

In our data, almost all of the patients were Muslim 99% and 1% Christian. As the study was conducted in the Islamic Republic of Pakistan so the majority of the patients were Muslims. There is no as such study conducted on the religious distribution of children with cerebral palsy in Pakistan and any other parts of the world, so we did not find any association of religion with cerebral palsy.

Because of the sophisticated and intimate family system in Pakistan, consanguinity is a prevalent practice. In this study, 63% of patients' parents had parental consanguinity while 37% of patients' parents had no parental consanguinity. A hospital-based study carried out by Ghazal et al in Lahore also recorded the same result. Among 120 patients having

cerebral palsy, 65% of children have parental consanguinity and a significant association has been found between consanguinity and cerebral palsy.

**Clinical manifestations of cerebral palsy**

The study's findings are consistent with the global trend that spastic CP is the most frequent type of CP. In our study, 53% of patients were identified as having spastic cerebral palsy, 29% of athetoid cerebral palsy, 14% of Ataxic cerebral palsy, and 4% mixed cerebral palsy type. In Pakistan, a higher representation of Spastic cerebral palsy was also recorded (91%), followed by atonic (4%), ataxic (4 %), and athetoid (2%) (Khan et al. 2017). The results are almost similar to previous literature.

Quadriplegia was the most common presentation of spastic CP in our study, found in 30%, followed by paraplegia 19% and diplegia 18%. Left hemiplegic CP was found in 13% and Right hemiplegic CP was found in 12%. Monoplegia was seen in 6% and triplegia in 2%. A study in Pakistan by Aziz et al. 2017, find the higher rank of Quadriplegia children 50%, followed by hypotonic and diplegia 18%. A Saudi study on CP in a Riyadh hospital discovered the common presentation to be quadriplegia and diplegia in 26% and 31% respectively of the cerebral palsy children presenting in a Riyadh hospital (Rifai et al. 1984). The common presentation of cerebral palsy in developed countries is different than in developing countries.

Dyskinetic/Athetoid cerebral palsy is divided into three subtypes, in which dystonia cases were 55.9% followed by athetosis 43%, and choreo-athetosis 1%. A study in Belgium found that both dystonia 70% and choreoathetosis 27% were higher during activity than at rest (Monbaliu et al. 2016). Our study is consistent with previous literature.

In this study bilateral cases were 69% while unilateral cases were 31%. Children in this study had spastic cerebral palsy 53%, with bilateral being more common than unilateral

spastic cerebral palsy. Farin Soleimani et al. 2011 found spastic cerebral palsy 81%, with bilateral being more common than unilateral spastic CP. In this study, SCPE classification is similar to the studies found in the literature.

Of the total 989 patients, 98% of patients had the disorder by the age of two years while 2% of patients acquired it after two years. A population-based study by Charlene et al. confirmed congenital 92% cases and 8% cases. In another study, from overall 4584 children, 547 were diagnosed with congenital malformation. In this study identification of the onset of the diseases is similar to the studies found in the literature that indicate cerebral palsy onset at the time of birth.

**Classification of index subjects based on severity in CP**

With respect to their severity levels, the majority of the athetoid and ataxic types were presented with the severe phenotype (93% and 74% respectively) compared to spastic cerebral palsy in which 40% had a severe phenotype while 30% were moderate and 30% were mild. Mixed cerebral palsy is presented with 92% of severity as it is a combination of two or more types of CP (spastic+athetoid and spastic+ataxic). One of the reason of high prevalence of the severity in cerebral palsy males in Pakistan is untreated hyperbilirubinemia, which is one of the most common causes of athetoid CP. Secondly, the majority of the people live in rural areas are illiterate and lack basic medical facilities. The results of our study are similar to previous literature.

Topographically cerebral palsy is divided into seven subtypes; in our study, mostly severity is seen in quadriplegia (30%), followed by paraplegia (19%), diplegia(18%), left hemiplegia (13%), right hemiplegia (12%), monoplegia (6%) and triplegia (2%). At Kampala, Uganda study is conducted and saw higher number of spastic quadriplegia 46% and it is similar to previous clinical-based study in Africa, and Canada (Kakooza-Mwesige

et al. 2015). In this study severity is similar to the study conducted in literature so, it indicates that severity is associated with the topographical distribution.

From the total of 989 patients, the dystonia cases were 56%, athetosis 43%, and choreoathetosis 1%. Research conducted by Li et al. 2021 on athetoid cerebral palsy found a correlation of dystonia with disability level, more so than choreoathetosis. As a result of the research are almost similar to previous literature so a significant association was found between severity and athetoid cerebral palsy subtypes but still further research is required in it.

**Severity of motor impairment with respect to gender**

Most of the severity is seen in Mixed cerebral palsy (spastic+athetoid and spastic+ataxic) in males 72% than in females 19%. Second highest presentation of severity was seen in athetoid cerebral palsy males 57% than females 35%. 40% severity seen in males of ataxic cerebral palsy and 33% in females. As a global trend least severity seen in spastic cerebral palsy males 24% and than females 16%. Maximum moderate and mild cases seen in spastic cerebral palsy males (19% and 17%) than in females (11 and 13%). Presentation of moderate and mild cases in ataxic cerebral palsy females ( 6% and 4%) less than in males (11% and 6%). Least moderate and mild cases seen in athetoid cerebral palsy females (1% and 1%) than in males (4% and 1%). Firstly, it is necessary to investigate if there is a genetic predisposition in the Pakistani population that might induce harm to the basal ganglia directly or indirectly through metabolic pathways that may cause kernicterus. Secondly, males born very preterm also appear to be more vulnerable to white matter injury and intraventricular hemorrhage than females. Thirdly, the ratio of males are higher because fewer girls visited the rehabilitation centers for diagnosis and treatment. Previously no research is conducted to show the association of severity with gender in Pakistan and in any other parts of the world, so there is a need to conduct a survey for this potential prejudice.

Topographically cerebral palsy is divided into seven subtypes; in our study, mostly severity is seen in quadriplegia males 41% than in females 26%. Secondly highest presentation of severity seen in triplegia males 40% than females 10%. Third highest severity seen in paraplegia males 24% than in females 17%. Less severity seen in diplegia males 16% and females 9%, followed by right hemiplegia males 13% and females 16%, monoplegia males 9% and females 3% and severity seen in left hemiplegia is same in both genders 8%. Moderate and mild cases in all males is higher than females except diplegia (13% males 14% females) and paraplegia( 2% males 6% females) in which females number was slightly higher than males. It represents the global trend that number of effected males were higher than females but in diplegia and paraplegia this is reversed. The reason might be that number of female patients visited the rehabilitation center were higher than males. But we find no significant association of severity with gender so further research is required in it.

From the total of 989 patients, the dystonia cases were 56%, athetosis 43%, and choreoathetosis 1% in which female number in dystonia and choreoathetosis (64% and 67%) was higher than males (36% and 33%). While severity in athetosis males 49% were higher than females 34%. Moderate and mild cases were also seen higher in males than in females. The results of our study show significant association of dystonia and choreoathetosis cases with females while athetosis was common in males. This strongly represent the genetics influence of severity on gender. Previously no research is conducted to find association of dyskinetic types with gender, so detailed study is required in it.

**Distribution of index subjects based on parental consanguinity in cerebral palsy**

From total 989 patients, parental consanguinity was found to be high among all types of CP i-e spastic CP and ataxic CP 63%, athetoid CP 62% and mixed CP 69% as compared

to non-consanguineous marriages. Although consanguinity is one of the major risk factor in causing cerebral palsy. Many national and international research has been conducted on it. Previously no research is conducted to found role of consanguinity in different clinical types in Pakistan or in any parts of the world, so there is a need to conduct a survey for this potential prejudice.

Topographically cerebral palsy is divided into seven subtypes, in our study, parental consanguinity was found very high in left hemiplegia (70%), followed by quadriplegia (69%), diplegia (64%), triplegia (60%), paraplegia (57%), right hemiplegia (55%) and monoplegia (52%) as compared to non-consanguineous marriages. Study by Kameel, 2009 found spastic quadriplegia 25%, spastic diplegia 19%, spastic hemiplegia 14%. The results of our study almost similar to previous literature. But, no significant association was observed when data were distributed with respect to parental consanguinity and topographical distribution types. However, further research is required in it.

Parental consanguinity was found very high in athetosis 68%, choreoathetosis 67%, and dystonic 58% cases as compared to non-consanguineous marriages. Consanguinity is a social issue that needs awareness through education and to be addressed by non-government and government institutes. Previously no research is conducted to find the role of consanguinity in dyskinetic types in Pakistan or in any part of the world, so there is a need to conduct a survey for this potential prejudice.

**Distribution of index subjects based on parental age at birth in cerebral palsy**

In our study paternal age was divided into 3 classes. The paternal age interval ($\geq$19-35 years) had the highest representation of subjects 74%. Followed by paternal age interval $\geq$35 years 25% and paternal age interval $\geq$18 had the lowest representation of disorder only 1%. The reason is that young paternal age had a significant impact on cerebral palsy. A study

conducted in 2012 recognized that younger paternal age is associated with an increased risk of low birth weight, preterm birth, low Apgar score, small size for gestational age, postnatal and neonatal mortality. While paternal age effect was detected in congenital hemiplegia and athetoid (dystonic) CP (Fletcher et al. 1993). However, no significant association was found between CP children and paternal age.

In our study maternal age was also divided into three classes. The maternal age interval (≥19-35 years) had also the highest representation of subjects (86%). Followed by paternal age interval ≥35 years (10%) and paternal age interval ≥18 had the lowest representation of disorder (5%). Advanced maternal age (>35 years) and low maternal age (<20 years) (Thomgren et al.2004), high parity (Topp et al. 1997), nulliparity (Thomgren et al.2004), and a short or long interpregnancy interval (Pinto-Martin et al.1998) are considered to be associated with CP. The results of our study are similar to previous studies. However, no significant found between the maternal age and cerebral palsy. Further research is required in it.

**Distribution of risk factors in cerebral palsy**

In all cerebral palsy types combined (prenatal, natal, postnatal) cause of risk factor is found to be very high 54%, followed by postnatal (19%), natal (16%), prenatal (7%), and cases in which cause not known (4%). Risk factors analysis revealed that the cause of CP was related to postnatal (22%), natal (35%), and prenatal factors (15%). While, more than one risk factor found in 28% (Yilmaz et al. 2014). The results of our study are almost similar to previous literature. Thus, a significant association has been found between the distribution of risk factors in cerebral palsy.

**Distribution of index subjects based on the cause of cerebral palsy**

In cerebral palsy disorders, secondary prenatal causes were found much higher 62% than the primary causes 38%. Secondary prenatal causes include; problems of the mother

such as preeclampsia, diabetes, toxemia during pregnancy, age of mother (above 40 years and below 20), differences between the Rh and blood of mother and chil, use of alcohol and smoking during pregnancy and exposure of the mother to various toxins. Primary prenatal causes include; maternal infections (to placental membranes), trauma during pregnancy, infections in the mother (toxoplasmosis/rubella/cytomegalovirus), any condition due to vascular problems, and inherited causes. Previously no research is conducted on the prenatal primary and secondary causes of cerebral palsy in Pakistan and in any other parts of the world, however, a significant association has been found in the study, so there is a need to conduct a survey for this potential prejudice.

Secondary postnatal causes were found much higher 94% in cerebral palsy disorder than the primary cause only 6%. Secondary causes include; injury to brain during the first two or three years of life, microcephaly, hydrocephalous, gas poisoning, lack of oxygen from drowning, and poisoning from pesticides sprayed on crops, lead glazes on pottery, and other poisons. Previously no research is conducted on the postnatal primary and secondary causes of cerebral palsy in Pakistan and in any other parts of the world, so there is a need to conduct a survey for this potential prejudice.

**Distribution of neonatal risk factors in subjects with cerebral palsy**

Various neonatal risk factors potentially affecting CP types were evaluated which include; neonatal jaundice, neonatal pneumonia, congenital heart defect, neonatal typhoid, neonatal meningitis, neonatal seizures, neonatal fever, premature birth. Hyperbilirubinemia called neonatal jaundice, serious infections defined as culture-proven sepsis, severe pneumonia or meningitis (Monokwane et al. 2017). The results of our study are almost similar to previous literature.

**Distribution of maternal risk factors in subjects with cerebral palsy**

Many maternal risk factors in CP types have been found which include; mode of delivery, maternal malnutrition, supplement use (folic acid), parity, twin pregnancy, late delivery, the status of second last pregnancy, ABO and RH incompatibility, oligohydramnios, fertility treatment, thyroid problem (mother), maternal fever, Maternal substance use (Clay/Fuller's earth), hypotension, preeclampsia, gestational diabetes. In a study CNS malformation, maternal hemorrhage, congenital infection, history of preeclampsia, maternal diabetes, maternal thyroid (Elmagrid and Magdy, 2021), instrumental/ emergency cesarean delivery, twin pregnancies (Hagberg and Jacobsson, 2004) has found. The result of our study is almost similar to previous literature.

**Distribution of obstetric risk factors in subjects with cerebral palsy**

Numerous obstetric risk factors in cerebral palsy types have been found which include; injury to the child during pregnancy, birth attendant problem, meconium, perinatal asphyxiation, crying of the baby after birth, induced labor, improper use of birth-assisted tools during delivery, and premature rupture of membrane (PROM). Premature rupture of membrane, prolonged labor, birth asphyxia, meconium-stained liqueur and hemorrhage in late pregnancy were significantly more common in the CP children mothers (Ozturk et al. 2007). The result of our study is almost similar to previous literature.

**Distribution of gynecological problems in subjects with cerebral palsy**

Many gynecological problems in cerebral palsy types have been also found which include; breech position, placental problems, and maternal bleeding in the later week of pregnancy. Breech delivery (Ozturk et al. 2007), hypoglycemia, placental abnormalities, neonatal infections and birth defects (Mclntyre et al. 2013) in a study found a significant association with CP. The result of our study is almost similar to previous literature

**Distribution of associated anomalies in subjects with cerebral palsy**

Of the total of 989 patients, with cases of speech impairment 20% were associated with cerebral palsy followed by 16% cases of epilepsy, 13% Delayed milestone, 9% eye defect, 8% intellectual disability, 7% microcephaly, 6% talipes, 4% hearing impairment, 2% Enuresis and Encopresis, 2% neurological disorder, 1% teeth problem and limb defects, and 11% others. A study in Pakistan by Ali et al. 2017 found an association between seizures in 36% of patients, contractures in 26%, gait disturbances, and ear and hearing problems in 58% patients. Soleimani et al. 2011 in Tehran find the associated disorders with cerebral palsy and observed Speech and language disorders in 33%, epilepsy in 30%, strabismus in 16%, hearing loss in 8%, and mental retardation in 7% of participants. In this study identification of cerebral palsy -associated diseases is almost similar to the study found in the literature and further research is required in the identification of other factors associated with cerebral palsy.

**Treatments given to cerebral palsy patients**

In our study, it was observed that oral drugs were recommended to 71% of patients. Physiotherapy was given to 91% and speech therapy to 52% of patients. Further analysis found that 7% of patients underwent surgical corrections for their disability symptoms, the improvement was seen in patients with cerebral palsy by oral drugs in 93%, through physiotherapy 78%, speech therapy 61%, and surgical corrections 11% of the patients. The use of drugs to provide symptomatic relief of the movement disorder is considered very effective (Monbaliu et al. 2017) such as, trihexphenidyl or glycopyrrolate, and BTX-A injection for controlling the flow of saliva (Gulati and Sondhi, 2018). Physiotherapy is considered very effective for the management and treatment of CP such as Bobath, NDT, strength-training and treadmill training programs (Barber, 2008). Speech therapy focus on the tongue, lips, palate and cheeks motor abilities that help improve speech production (Lima

et al. 2016). Orthopedic surgery has contributed to the treatment of CP (Pollock, 1962). In this study treatment given to cerebral patients are almost similar to the study found in the literature and further research is required in it.

**Conclusion**

The majority of research has been carried out in Pakistan is related to the treatment and management of CP. On various basic areas including its epidemiology, etiology, maternal factors, and molecular genetic diagnosis of CP there is a paucity of research conducted. Information on investigations of the role of inflammatory factors and coagulation, in the perinatal period exploration of the role of infection and the use of sophisticated brain imaging revealed the cause of CP. According to their clinical features by classifying the various types of cerebral palsy, infants born at different gestations it may be possible to determine factors unique to particular motor disorders. Ongoing research on CP about causes, risk factors, epidemiology, management, and treatment will be an essential step toward the goal of developing strategies for prevention.

# CHAPTER 5

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