INTRODUCTION

Cerebral palsy (CP) is a diagnostic term used to describe a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non progressive disturbances in the developing fetal or infant brain. The motor disorders of CP are often accompanied by disturbances of sensation, perception, cognition, communication and behavior as well as by epilepsy, and secondary musculoskeletal problems ***(Johnston, 2011).*** Although the primary impairment in CP is in motor function, growth and nutrition disorders are common ***(Rosenbaum et al., 2007).***

It has been reported that major causes of CP involve prematurity, abnormal intrauterine development due to fetal-maternal infections, asphyxia during delivery, brain trauma during labor and delivery and complications in the perinatal period ***(Bax et al., 2005).***

Cerebral palsy being the most common physical disability in children its prevalence in the United states was found to be 3.6/1,000 children ***(Yeargin-Allsop et al., 2008).*** The average cumulative incidence rate of CP is 2.7 per 1000 live births. In recent years, the incidence rate of CP has been increasing internationally due to increased survival of low birth weight infants ***(Rosen et al., 1992; Suzuki et al., 2002; Colver et al., 2000).***

The frequency of risk factors of CP was prenatal complications (cyanosis, preterm, jaundice, low birth weight and obstructed labor of mothers), first baby and recurrent abortions ***(El-Tallawy et al., 2011).***

In cerebral palsy patients muscle weakness, muscle spasticity and coordination problems can contribute to a number of complications either during childhood or later during adulthood including failure to thrive, oromotor dysfunction as language delay drooling of saliva and dysphagia**,** reflux, constipation and aspiration and orthopedic problems such as scoliosis, hip dislocation, contractures and osteoporosis ***(Henderson, 2005).***

Growth is an important biological process during childhood ***(Mohammadian and Khoddam, 2007).*** It has been shown that children with CP often have poor linear growth during childhood, resulting in a diminished final adult height, an issue that has received little attention so far ***(Kruse et al., 2009).*** Children with CP often struggle to gain or maintain weight and failure to thrive is a common problem ***(Henderson, 2005).***

The impact of altered growth on skeletal development and bone density is a significant health problem. In typically growing children the accrual of peak bone mass follows peak height velocity. However, in children with CP, differences in linear growth become more accentuated over time compared with their typically growing peers ***(Houlihan et al., 2009).***

In addition to diminished linear growth, children with CP often sustain painful pathologic fractures due to poor mineralization of bone, often with minimal trauma ***(Lohiya et al., 1999; Palisano et al., 2007).***

Given the complexity of GH neuroregulation ***Nia and Salehi,(2008)*** it seems logical to postulate that severe brain damage may affect a number of neurotransmitter pathways involved in GH control, thus affecting the normal secretion of the hormone ***(Reimunde et al., 2010)***.

IGF-1 is synthesized by liver in response to pituitary growth hormone (GH) and affects growth processes; however, many other tissue, including the brain, are also able to synthesize IGF1 locally, out of GH control ***(Sun et al., 2005).***

The secretion patterns of IGF-1 and syntheses are primarily controlled by GH. Unlike GH secretion, which is pulsatile and demonstrates significant diurnal variation, IGF-1 levels shows only minor fluctuations. IGF-1 serum level therefore represents a stable and integrated measurement of GH production ***(Monzavi and Cohen , 2002).***

Assessment of Bone Density using Dual Radiograph Absorptiometry (DEXA) is the most widely used method for assessment of BMD and is considered the "gold standard" ***(Houlihan and Stevenson, 2009).*** The assessment of bone density is also important in association with Gh-IGF axis which plays an important role in bone metabolism ***(Ali et al., 2007)***.

Antiepileptic medication use is also correlated with decreased bone mineral density in children and adults ***(Pack and* Alison*, 2003; Valsamis et al., 2006; Sheth, 2004; Farhat et al., 2002)*** and fractures are increased two to six times in patients with epilepsy compared to the general population ***(Mattson, 2004; Vestergaard et al, 1999).*** Age and duration of AED use correlated significantly with low femoral BMD ***(Andress et al., 2002).*** Similar associations were also reported in children where significant decreases in height to less than 10^{th} percentile in children were seen with AED use ***(Guo et al., 2001).***

As many children who start on antiepileptic medications in childhood will be on those medications for many years, the fracture risk by adulthood is substantial. These antiepileptic drugs decrease bone density through effects on vitamin D metabolism and subsequent hypocalcemia ***(Valsamis et al., 2006).*** These drugs also act on the bone, increasing activity of the osteoclasts, the cells responsible for bone breakdown in the dynamic process of remodeling ***(Holick , 2005; Yanase et al., 2003).***

Many children on these medications may also have **restricted movement** due to **cerebral palsy**, which also decreases bone mineral density. Children with CP have a higher fracture rate than the general population ***(Stevenson et al., 2006)*** and this fracture rate may be even higher in children with CP on antiepileptic medications ***(Leet et al., 2006).***

Deficiency of vitamin D may adversely affect mineralization of bone matrix and compromise bone strength and is an established independent risk factor for low bone mass and fracture ***(Holick , 2003).*** Vitamin D is an important modulator of osteoblastic function and also facilitates differentiation along the osteoclastic lines ***(Holick and Krane , 2001).***

Importance of the study:

The actual overall prevalence of cerebral palsy ranges from 1.5 to 3.6 per 1000 live births.

There is growing importance of cerebral palsy studies due to:

- The increased survival of very low birth weight preemies, the incidence of spastic diplegia has increased and associated with underestimation of diagnosis cerebral palsy cases.
- Multiple gestation carries an increased risk of CP.

Bone mineral density is an important factor to be measured in cerebral palsy since its decrease can lead to multiple fractures and further motor disabilities in these patients. It is also important to determine the level of IGF-1 as a marker of growth & its effect on growth and on bone mineral density in cerebral palsy patients for the possibility of early interference and achieving best possible outcome.

Concepts of the study:

- **Cerebral Palsy (CP)**: is the term used for a group of nonprogressive disorders of movement and posture caused by abnormal development of, or damage to, motor control centers of the brain.
- **The GH-IGF axis:** GH that is secreted by pituitary gland acts directly and indirectly through Insulin-like Growth Factor-1 (IGF-1). Together GH and IGF play an important role in bone growth and influence regulation of metabolism.
- **Bone mineral Density:** A measurement of bone mass, expressed as the amount of mineral–in grams divided by the area scanned in cm2.It is measured by any of several methods of determining bone mass by measuring radiation absorption by the skeleton (DXA).
- **Linear growth**: the progressive increase in size, especially the process by which the body reaches its point of complete physical development it grows by the same amount in each time step. It is affected by hormones mainly IGF-1 & vitamin D.

Relation of the study to the goals of the department:

Cerebral palsy (CP) is a catastrophic acquired disease, occurring during development of the fetal or infant brain. It mainly affects the motor control centers of the developing brain, but can also affect cognitive functions, and its

accompanied symptoms including lack of communication, epilepsy, and alterations in behavior. Most children with cerebral palsy exhibit short stature, resulting in a diminished final adult height. It is important to know whether lack of normal growth is due to an impaired or deficient growth hormone (GH) secretion and due to decreased bone mineral density or not. Independent of causal factors responsible for the development of CP, the disease has a strong socioeconomic impact. Currently there is no cure for CP and the therapeutic approaches of physical therapy, occupational therapy, speech therapy, neuropsychology, pharmacology and surgery achieve only partial benefits for affected individuals ***(krageloh-Mann and Canns, 2009).***

AED-induced disturbances of bone metabolism are usually accompanied by a fall in the 25(OH)D level, hypocalcemia, secondary hyperparathyroidism, and increased bone turnover with a decrease in bone density.

AIM OF THE STUDY

The aim of the present study is to determine bone mineral density and serum insulin like growth factor-1 (IGF-1) in children with cerebral palsy and to correlate these levels with growth parameters.

Chapter One

CEREBRAL PALSY

Definition:

Cerebral palsy (CP) is a catastrophic acquired disease, occurring during development of the fetal or infant brain. It mainly affects the motor control centers of the developing brain, but can also affect cognitive functions, and is usually accompanied by a cohort of symptoms including lack of communication, epilepsy, and alterations in behavior ***(Devesa et al., 2010).*** The pathology is non-progressive, thus, excluding conditions such as cerebral tumors, the degenerative brain diseases or progressive multisystem diseases as Friedreich's ataxia. This does not mean that CP is a static condition, the clinical picture as brain maturation continues through out childhood resulting in dynamic clinical pattern despite a static pathology, so, the neurological features of CP often change or progress over time ***(Johnson, 2002).***

Children with CP are generally undernourished and growth retarded in comparison with normal children, and the growth patterns of these children were associated with their overall health and social participation. CP children with best growth had fewest days of health care use and fewest days of social participation missed ***(Stenberg et al., 2013).***

History:

CP was first described by ***William Little*** in ***1862*** and initially was called Little's disease. It was described as a disorder that appeared to strike children in the first year of life, affected developmental skill progression, and did not improve over time. Little also connected this disorder to lack of oxygen during birth ***(Accardo, 1982).*** Later, in 1897, Sigmund Freud suggested that CP might be rooted in the brain's development in the womb and related aberrant development to factors influencing the developing fetus. Birth asphyxia alone was the cause of CP until the 1980s ***(Moster et al., 2001).***

Epidemiology:

Cerebral palsy is the commonest physical disability in childhood, occurring in 2.0 to 2.5 per 1000 live births ***(Johnson, 2002).*** In Egypt it was found that 52 out of 25,540 children had CP yielding prevalence rate of 2.04/1000 (95% CI: 1.48–2.59) of living births. Mean age of children with CP, was 7.17 ± 4.38 years. The order of frequency of different subtypes of CP was as follows, 65.4% had spastic type, 26.9% mixed type and 3.8% for each ataxic and dyskinetic types of CP. The frequency of risk factors of CP is prenatal complications (cyanosis, preterm, jaundice, birth weight and obstructed labor), first baby, previous similar condition and recurrent abortions ***(El-Tallawy et al., 2011).***

Recent advances in neonatal management and obstetric care have not shown decline in the incidence of CP where with decline in infant mortality rate, there is an increase in incidence of CP ***(Barbara, 2008).*** Although children born before 32 weeks' gestation have an increased prevalence of CP (up to 10%), they contribute to less than 2% of neonatal survivors and to a minority (approximately 20% to 25%) of all CP in developed countries ***(Blair, 2010).***

Reported CP prevalence rates vary from 19 to 152 per 1,000 live births for very preterm and very low-birthweight (VLBW) infants ***(Vincer et al., 2006; Robertson et al., 2007).***

Cerebral palsy and related developmental disorders are more common in males (M) than in females (F).The surveillance of CP in Europe reports M:F ratio of 1.33:1 but reasons are uncertain ***(Barbara, 2008).*** Males born very preterm also appear to be more vulnerable to white matter injury and intraventricular haemorrhage than females. Other reports demonstrated major differences between male and female neurons grown separately in cell culture, suggesting that sex differences in the fetal or neonatal period result from intrinsic differences in cell death pathways. This information indicates that there are important neurobiological differences between males and females with respect to their response to brain injuries ***(Andrew et al., 2004).***

Figure (1): Children with spastic Cerebral Palsy **October 21, 2012.**

Pathology:

Cerebral palsy results from a permanent static lesion of the cerebral motor cortex that occurs prenatal, natal, postnatal or within the first two years of life ***(Pakula et al., 2009).*** Lesion itself doesn't change but the clinical picture changes while the child grows and develops. The rate of growth of the child with CP is slower than in unaffected child ***(Thorngren and Herbst, 2006).***

A specific hypoxic event associated with irreversible cell death explains the etiology of CP in less than 50% of cases ***(Bouiller et al., 2015).***

Some areas of the brain are more susceptible to damage than others. For example, variations in blood supply and unique metabolic requirement in some brain areas increase the sensitivity to hypoxia in the presence of bacterial and viral infection of the

fetus, maternal infection or chorioamnionitis ***(Bouiller et al., 2015).*** Selective vulnerability of the periventricular white matter occurs between 26-34 weeks of gestation, so fetal insults occurring during this period can produce periventricular leukomalacia with spastic diplegia. Similarly, the unique metabolic demands of the basal ganglia in the fetus at 38-40 weeks create selective vulnerability that can result in dystonia and movement disorder ***(Foster and Dickens, 2001).***

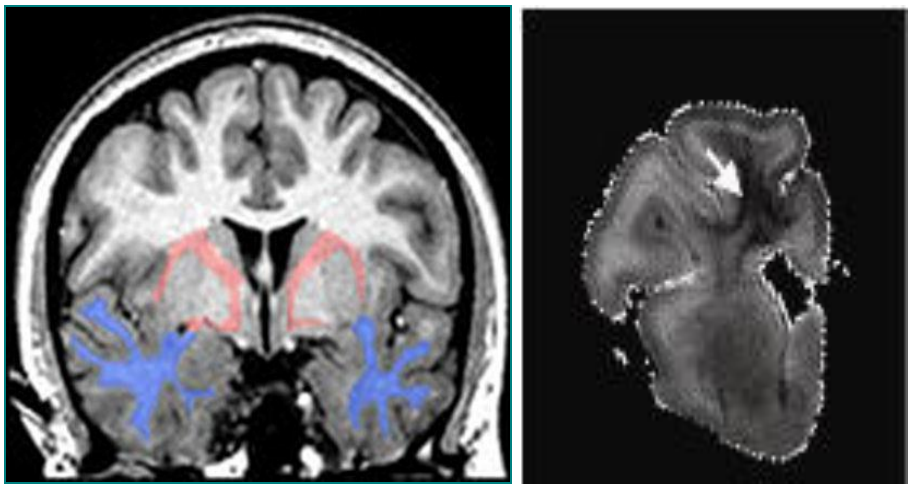

Figure (2): This MRI shows regions where white matter volumes were significantly reduced in boys born preterm. Blue marks the temporal lobe and red the deep cerebral region ***(Michelle, 2004).***

Injury to upper motor neurons decrease input to the reticulospinal and corticospinal tracts which in turn affects motor control, and produce abnormal muscle control and weakness. Also, the loss of descending inhibitory input through reticulospinal tract produce spasticity ***Andrew et al. (2004)*** which has been defined as a velocity – dependent resistance of muscle to stretch ***(Sanger and Delgado, 2003)*** or an

excessive, inappropriate involuntary muscle activity associated with upper motor neuron paralysis. Spasticity in patient with CP may lead to muscloskeletal complications such as contractures, pain and joint subluxation or dislocation ***(Rosenbaum et al., 2002).***

Injury to extrapyramidal tract results in movement disorder such as athetosis, chorea, dystonia or rigidity. Clinical manifestations depends on the extent and the type of CNS damage, the location of the irreversible insult and the ability of the CNS to reorganize after the insult example movement disorder occurs after hyperbilirubinemia and basal ganglia injury, diplegia occurs in association with periventricular leukomalacia, and quadriplegia occurs with diffuse brain injury ***(Fedrizzi et al., 2003).***

Etiology of Cerebral Palsy:

It is usual to divide the cerebral palsy into congenital and aquired types. In congenital CP, damage may arise from several causes (example genetic defects, migration defects, cerebral malformation, hypoxic ischemic encephalopathy, nutritional deficiency, trauma, infection, infarction and haemorrhage). Migration defects may result from mutation of genes responsible for the mechanisms that control the neuronal migration, like the radial glial fiber system that guides neurons to their proper site ***(Barbara, 2008).***

The injury to the developing brain may be prenatal, natal or postnatal. As much as 75%- 80% of the cases are due to prenatal injury with less than 10% being due to significant birth trauma or asphyxia ***(Skrablin et al., 2008).***

Risk factors of CP:

Factors Occurring before Pregnancy:

A child whose mother has long intervals between menses is at increased risk for cerebral palsy. The risk is increased if there has been an unusually short interval (less than three months) or an unusually long interval (more than three years) since the previous pregnancy. In addition, mothers of children with cerebral palsy are more likely than other mothers to have a history of spontaneous abortion and stillbirth. These findings indicate that maternal menstrual and obstetrical factors convey information about the risk of cerebral palsy ***(Skrablin et al., 2008).***

The association of a family history of early-onset, non progressive motor impairment with cerebral palsy, especially when the impairment is linked with specific chromosomal, metabolic, or morphologic aberrations, is in keeping with a genetic basis for some cases of the disease. The greater concordance for cerebral palsy among monozygotic twins also suggests a genetic basis, but it is compatible with placental problems that are unique to monozygotic twins as well ***(Sankar and Mundkur, 2006).***