# INTRODUCTION

Cerebral palsy (CP) is a term describes a group of permanent disorders of the development of movement and posture, resulting in limitation of different activities that are due to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of CP are often associated with disturbances of sensation, perception, cognition, communication, and behavior; by epilepsy, and by secondary musculoskeletal problems ***(Rosenbaum et al., 2007)***.

In developed countries, the overall estimated prevalence of cerebral palsy is 2-2.5 cases per 1000 live births. The prevalence of this disorder among preterm and very preterm infants is much higher. In the developing world, the prevalence of cerebral palsy is not well established but estimates are 1.5-5.6 cases per 1000 live births ***(Stanley et al., 2000).***

In addition to motor manifestations, children with CP frequently develop cognitive and sensory impairments, epilepsy, gastrointestinal and sleep problems ***(Wayte, 2012)***. Sleep disturbance is found to be very common in children with cerebral palsy and between 23% to 46% of children with cerebral palsy suffer from sleep problems. This is significantly higher than that reported for typically developing children (20%–30%) ***(Tikotzky, 2001).***

The normal sleep circadian rhythm is largely regulated by the light/dark cycle (melatonin) and, to a lesser degree, temperature ***(Heraghty, 2003).***

Melatonin, a hormone secreted by the pineal gland in a circadian manner, promotes sleep through its regulation of the activity of the suprachiasmatic nucleus and other sleep-related brain networks. Its production is suppressed by light and stimulated by darkness, with a rise of serum levels preceding the onset of sleep by about 90 minutes ***(De Leersnyder, 2011).***

Melatonin not only can exert a positive effect on the frequency of epileptic attacks in children with sleep disturbances of various etiologies, but also it has been proved to have a role in immune modulation, disorders of the GI tract and different sleep disorders ***(Song, 2005).***

There is general agreement that melatonin therapy has a remarkably benign safety profile, even when children are treated with pharmacological doses ***(Jan, 2007).***

# Aim of the Work

The purpose of this study is to assess the effect of Melatonin supplementation for Children with CP on the following:

1- Seizure control.

2- Sleep problems.

3- Gastrointestinal problems as GERD and functional constipation.

4- Growth.

CHAPTER ONE

# CEREBRAL PALSY

## Introduction:

Among the different disorders that severely impair motor function in young children, cerebral palsy can be considered the most common one. In birth cohorts from developed countries, the prevalence is 1-2/1000 live births. The prevalence increases with decreasing gestational age at birth as among very low gestational age newborns (i.e., gestational age < 28 weeks); the prevalence is about 100 per 1000 of surviving infant, a 100-fold higher risk than infants born at term. As a function of all live births, the prevalence has been almost stable for decades, but this has not been the case among very low birth weight and very preterm infants, among whom the incidence increased after the introduction of neonatal intensive care and has begun to decrease in the past decade ***(Paneth et al., 2006).***

In addition to motor manifestations, children with cerebral palsy frequently develop cognitive and sensory impairments sleep problems, epilepsy, and nutritional deficiencies. Except in the mildest cases, cerebral palsy has a severe impact on families' well being and social health care costs.

The morbidity and mortality of cerebral palsy relate to the severity of this condition and the associated medical complications, such as respiratory and gastrointestinal

difficulties. In patients with quadriplegia, the likelihood of epilepsy, severe cognitive impairment, extrapyramidal abnormalities are greater than in those with diplegia or hemiplegia.

## Risk factors of CP:

Cerebral palsy can be derived from any event that will affect the fetal and neonatal developing brain. Indeed, congenital malformations, hypothyroidism, multiple gestations, fetal growth restriction, infection during the fetal and neonatal period, birth asphyxia, untreated maternal, preterm delivery, perinatal stroke, and thrombophilia were all recognized as risk factors for CP ***(Hankins et al., 2003).***

### *1- Placenta-Mediated Pregnancy Complications:*

The effect of fetal growth restriction on the prevalence of CP is well known. The prevalence of this disease among neonates weighing <1,500 g is 59.2/1,000 live births, in comparison to 1.33/1,000 live births among those weighing >2,500 g. This association is not related to gestational age at delivery and depends mainly on the presence of congenital anomalies, especially of the central nervous system ***(Croen et al., 2001).***

The relation between preeclampsia and development of CP was under usual debate. However, a recent population-based cohort study revealed that early-onset preeclampsia is an

independent risk factor for CP after adjustment for fetal growth restriction and gestational age at delivery. This was not the case regarding preeclampsia at term ***(Mor et al., 2015).***

## ***2- Congenital Malformations:***

The association between CP and congenital malformations is well documented. Major birth defects were the most frequently occurring risk factor in children with CP, and when occur with fetal growth restriction; they were associated with the highest risk. Congenital microcephaly is the most common birth defect in CP. Other non-cerebral malformations were also frequently coexisting with CP, especially cardiac (12%), urinary (5.4%), and musculoskeletal (5.4%) ***(Rankin et al., 2010).***

## ***3- Perinatal Stroke:***

Fetal and neonatal cerebral accidents are associated with elevated risk for development of CP. Indeed, among 100 full-term neonates with the diagnosis of neonatal arterial ischemic stroke, born in Switzerland between 2000 and 2010, 39% were diagnosed as having CP at the age of two ***(Grunt et al., 2015)***.

The association between CP and thrombophilia is not that clear. In an Australian population-based case–control study, among term neonates, there was no association between a single thrombophilic mutation and CP. Among preterm neonates with the MTHFR C677T mutation, those who were

homozygous and were born between 32 and 36 weeks of gestation had an odd ratio (OR) of 2.55 (95% CI 1.12–5.74), while the heterozygous ones had an OR of 1.91 (95% CI 1.01–3.66) to develop any type of CP ***(Gibson et al., 2005).***

## ***4- Multiple Gestations:***

Twins have a higher incidence of malformations and CP than singletons ***(Bonellie et al., 2005)***. The prevalence of CP in an Australian study was 1.6, 7.3, and 28 per 1,000 births in singletons, twins, and triplets, respectively. The authors also reported that in the case of co-twin death, the risk for CP increases by a factor of 8, from 12/1,000 to 96/1,000. The explanation for this observation was that the dissolving twin releases thromboplastin and emboli that may lead to brain injury of the surviving twin and subsequent development of CP ***(Petterson et al., 1993).***

## ***5- Genetics Contributions to CP:***

There are indications of genetic involvement in CP, and its contribution is estimated to be as high as 48% of term and 24% of preterm idiopathic cases ***(Costeff and Ann, 2004)***.

Genetic investigations of CP were done using population-genetic and pedigree inquiries. Population-based genetic studies have identified several specific genes, whose variants were more common in CP patients in certain populations, some of which are associated with processes of inflammation, coagulation, and blood flow ***(Gibson et al., 2008).***

## Measures to prevent or reduce incidence of CP:

Any intervention that will lead to modification of the risk factors for CP as well as for the prevention or treatment of the underlying causes that leads to this syndrome eventually will affect its prevalence. Therefore, we have three main approaches that will help to decrease the rate of CP:

### *1- Prevention of Risk Factors:*

The corner stone for a successful preventive program is the ability to identify patients at risk and to identify the treatment according to the mechanisms of disease. A good example for this is the progress made during the last decade in the prevention of spontaneous preterm labor. This progress is relevant to the potential reduction of CP since about half of the cases of this disease are due to prematurity and its complications. Indeed, the evidence that 17α-hydroxyprogesterone caproate can prevent recurrent preterm labor was proved at the end of the twentieth century ***(Meis et al., 2003).***

The second step in that program was the fact that women who have a short cervix with or without a history of preterm labor can benefit from vaginal progesterone for the prevention of premature birth and improvement of neonatal outcome. Overall, the administration of progesterone for the prevention of preterm labor reduced its rate in about 50% ***(Romero et al., 2012).***

Beside the prevention of spontaneous preterm birth; the reduction of placental-mediated pregnancy complications that necessitate preterm birth can also attribute for the reduction in CP prevalence. It was proved that there is an association between early-onset preeclampsia as well as IUGR and subsequent development of CP ***(Mor et al., 2016).*** Therefore, any intervention that will decrease the rate of early-onset disease or the development of IUGR will have a chance to reduce the risk of CP. Preliminary evidence suggests that aspirin, as well as low molecular heparins, may be effective in the secondary prevention of placental-mediated diseases ***(Mastrolia et al., 2016).***

## *2- Affecting the Disease Process:*

The treatment of women with early preterm parturition with magnesium sulfate ($MgSO_4$) has lately been proved to have a protective effect against the subsequent development of CP, especially the severe phenotype. The large randomized controlled trial conducted by the Maternal-Fetal Medicine Units Network included 2,241 pregnant females with threatened preterm birth who were randomized to magnesium vs. placebo. In the primary composite outcome of neonatal death and CP, there was no statistical difference between the study groups. However, a secondary analysis revealed that the rate of moderate and severe CP was reduced substantially (relative risk, 0.55; 95% CI 0.32–0.95) ***(Rouse et al., 2008).***

A recent study suggests that the prenatal administration of antenatal corticosteroids for fetal lung maturity is associated with marked reduction in the rate of CP. This meta-analysis included 14 studies, and the antenatal administration of corticosteroids was associated with a significant reduction in the risk of CP, especially in neonates born prior to 28 weeks of gestation ***(Sotiriadis et al., 2015).***

Therefore, the current evidence suggests that antenatal treatment with corticosteroids and $MgSO_4$ is associated with a marked reduction in the incidence of development of CP in preterm neonates, especially those who were born prior to 32 weeks of gestation.

### *3- Post exposure treatment of the affected neonate:*

Cooling has become a standard of care, and the hallmark of treatment of neonate who had birth asphyxia ***(Azzopardi et al., 2009).*** The trials of hypothermic neural rescue therapy for infants with neonatal encephalopathy that have recently been well constructed and analyzed. The data suggest that either selective head cooling or total body cooling reduces the risk of death or disability after birth asphyxia.

Nanomedicine is a new trend in the development of therapies for the treatment of brain injury resulting in CP. Nanomaterials such as dendrimers provide opportunities for the targeted delivery of multiple drugs that can modify several pathways involved in injury and can be delivered specifically to

the cells that are responsible for injury ***(Balakrishnan et al., 2013).***

Another emerging topic in the area of post exposure management of birth asphyxia is stem cell therapy. Recent studies researched the use of embryonic stem cells (EST) in the treatment of CP. EST were found to improve the sight of children with CP and cortical visual affection. Out of 40 children in the study, 39 have shown improvement in sight after this treatment ***(Novak et al., 2015).***

## Diagnosis of CP:

The diagnosis of cerebral palsy is based mainly on a clinical assessment, and not on laboratory testing or neuroimaging.

In clinical practice, the diagnosis of cerebral palsy is typically based on observations of acquisition of motor milestones, such as sitting, pulling to stand, and walking, and evaluation of posture, deep tendon reflexes, and muscle tone. Because the diagnosis of cerebral palsy depends in part on neurological findings that are subject to inter-examiner variation, with regard to both the method used to elicit the neurological finding as well as the interpretation of the finding, and because neurological abnormalities may be transient, many clinicians avoid basing the diagnosis on a single aspect of the parent's report or the clinician's examination and typically will make a definitive diagnosis only after repeated examination(s).

As the brain continues to develop postnatally, abnormalities of motor tone or movement in the first few weeks or months of life may gradually improve over the first 2 years of life. The Collaborative Perinatal Project found that almost 50% of individuals diagnosed with cerebral palsy and 66% of children diagnosed with spastic diplegia outgrew findings that were suggestive of cerebral palsy by age 7 years. Others did not manifest full motor signs suggestive of this disorder until aged 1-2 years ***(Kuban et al., 2005).***

Initial assessments (Fig.1) for children diagnosed with CP include neuroimaging if the diagnosis has not been established and metabolic and genetic studies if clinical history and findings on neuroimaging do not prove a specific etiology or if there are aspects of the history or physical examination that suggestive of a metabolic or genetic etiology (including a brain malformation). Morover, testing for prothrombotic abnormalities of coagulation should be considered in individuals with hemiplegia. All children with cerebral palsy should be screened for mental retardation, ophthalmologic and hearing impairment, and speech and language disorders, and nutrition and growth should be monitored ***(Ashwal et al., 2004).***

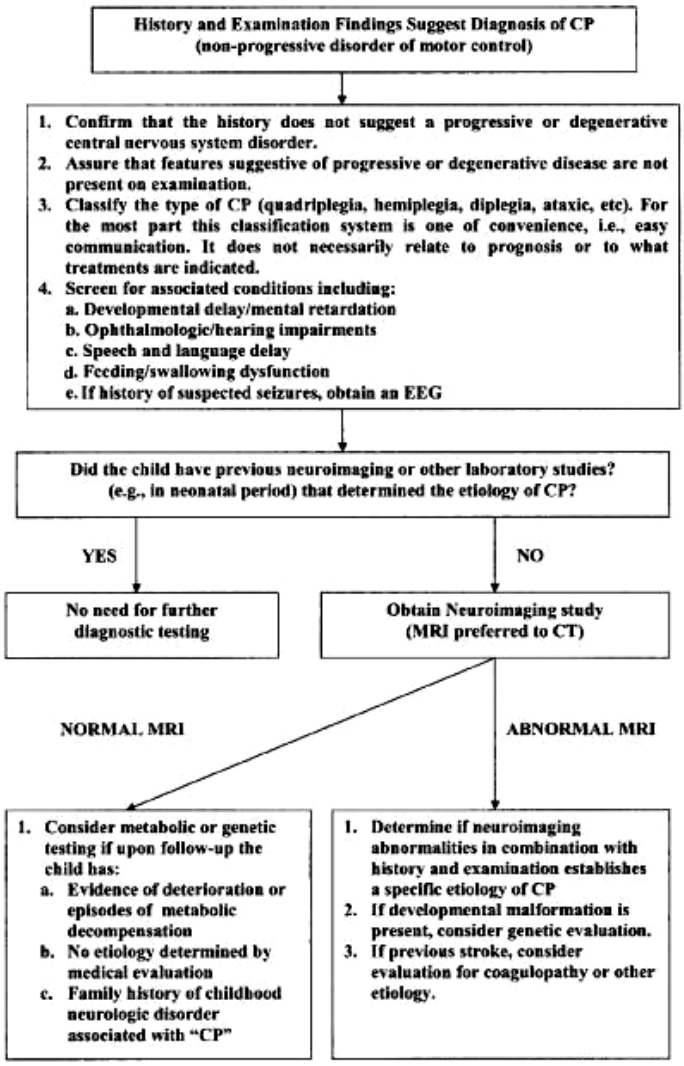


**Fig. (1):** Algorithm for evaluation of the child with cerebral palsy ***(Ashwal et al., 2004).***

## Classification of CP:

For both clinical as well as research purposes, cerebral palsy has often been classified according to the nature of the movement disorder (spasticity, ataxia, dystonia, and athetosis) and the anatomic or topographic distribution of the motor abnormalities.

More agreement has been based on classification of cerebral palsy in relation to the functional severity. More than a decade ago, Palisano and his colleagues developed the Gross Motor Function Classification System (GMFCS), which defines five levels of gross motor function, which have been shown to correspond to five distinct "trajectories" of motor development. For example, among children younger than 2 years, those at level II can "maintain floor sitting but may need to use their hands for support to maintain balance," whereas those at level IV have head control but trunk support is required for floor sitting". The GMFCS correlates strongly with the World Health Organization International Classification of Impairments, Disabilities and Handicap code, but is considerably less time-consuming and can be derived from medical records ***(Palisano et al., 1997).***(Fig.2)

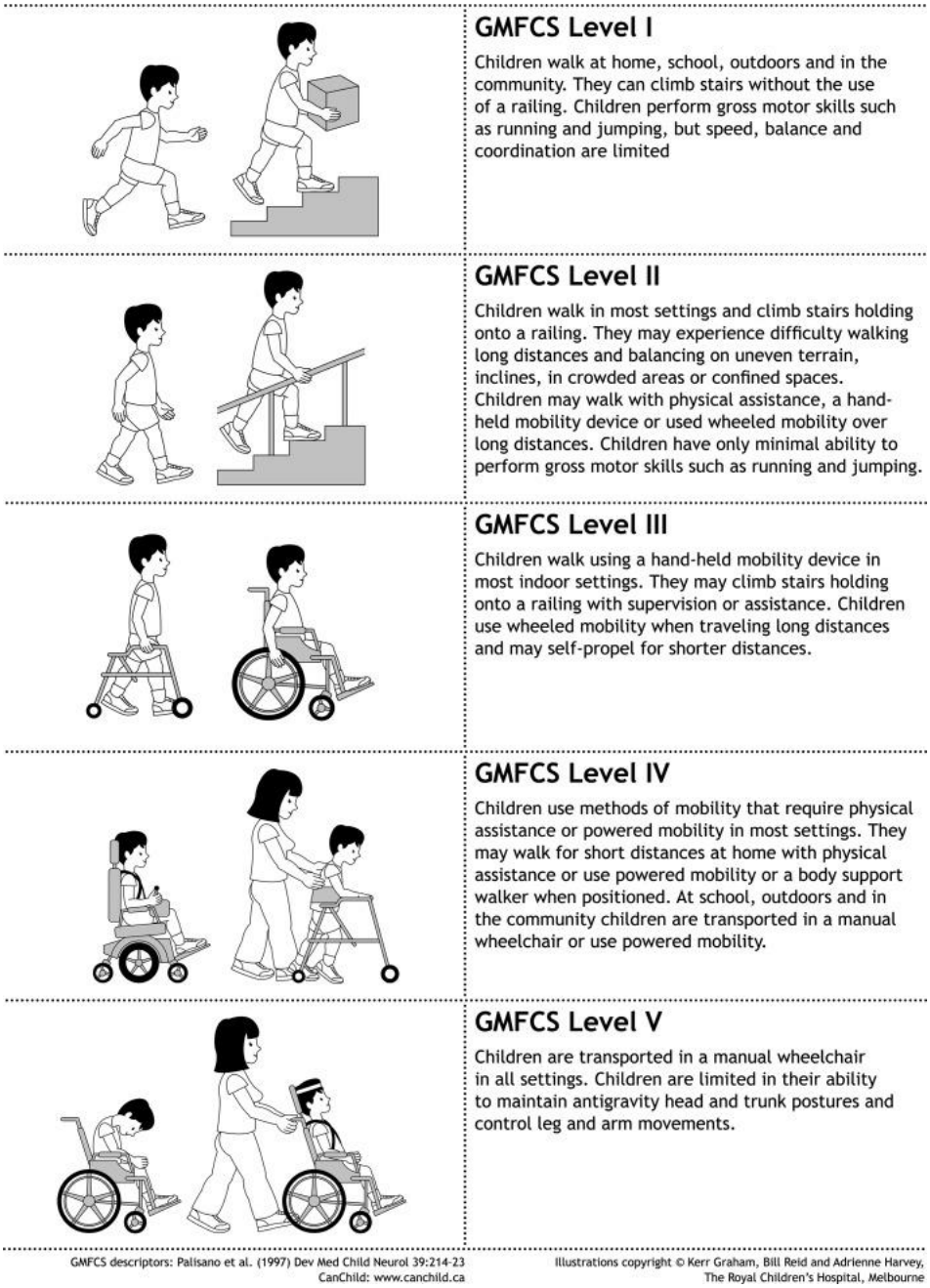


**Fig. (2):** Expanded and revised Gross Motor Function Classification System (GMFCS) for children from their 6–12th birthday: descriptors and illustrations.