INTRODUCTION

Cerebral palsy (CP) is a clinical description, not an etiological diagnosis. It describes a group of disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain **(Rosenbaum et al., 2007)**, CP may be classified by the predominant type of motor disturbance as spastic, dyskinetic, or ataxic, and sometimes hypotonic **(Leonard et al,2011)**.

Incidence of cerebral palsy is about 2 per 1000 live births **(Valley, 2007)**. The incidence is higher in males than females; the surveillance of cerebral palsy in Europe (SCPE) reports a male: female ratio 1.33:1 **(Johnson & Ann, 2002).**

Cerebral palsy encompasses a wide range of brain disorders associated with impaired motor function. As a result, the definition of cerebral palsy varies depending on the purpose for which the term is being used **(Badawi et al., 1998c).**

Consensus is lacking on whether a child with a known underlying pathologic condition (e.g, neuronal migrational defect, metabolic disease) should be included under the rubric of cerebral palsy, or whether the degree of disability also should be taken into account **(Nelson and Ellenberg, 1982).**

A number of neurodegenerative, including metabolic and genetic disorders may present with similar symptoms and signs. Some of these disorders which are slowly progressive are more likely to be misdiagnosed as CP. Individually these disorders may be rare, but collectively they are not. It is important that these disorders are correctly diagnosed as early as possible for better management **(Gupta & Appleton, 2001).**

In most cases, CP is defined as damage to brain tissue that occurs in the perinatal period, due to environmental rather than genetic causes.

Usually the condition does not progress, and improves with physiotherapy. In about 50% of cases there is mental retardation in addition to motor problems. There are a number of genetic diseases whose clinical manifestations are similar to those of CP,these constitute

about 10% of the cases of children with a clinical picture of muscle weakness and rigidity **(Genetics of pregnancy encyclopedia, 2009-2011).**

The risk that the child has a hereditary, genetic type of CP is increased in the following cases: absence of an environmental factor indicating acquired damage, progression and deterioration of the neurological damage over time, the presence of involuntary dystonic movements, the presence of mental retardation that is

more severe than the motor problems, the absence of signs indicating environmental damage in brain scans (CT or MRI), or the presence of signs indicating a genetic disease in an examination of the child or in laboratory and/or imaging tests **(Genetics of pregnancy encyclopedia, 2009-2011).**

Regarding inheritance pattern;most cases of CP are not genetically transmitted. However, in the approximately 10% of cases that are due to genetic causes rather than environmental, there may be recurrence in future children of the couple **(Genetics of pregnancy encyclopedia, 2009-2011).**

The possibility of an inborn error of metabolism should be considered in every child with diagnosis of cerebral palsy without history of perinatal or postnatal brain injury (prematurity, hypoxia, infections & traumatic brain injury). Inborn error of metabolism, spasticity tends to be syndromic or complicated (other neurological signs and/ or other organs are involved). However, spasticity may remain isolated for a long time. Spasticity is probably the most common neurological sign in neurometabolic disorders. It is therefore important to search carefuly for other associated clinical signs **(Hoffmann et al, 2010)**.

Metabolic diseases infrequently produce symptoms immediately at birth, and they can manifest with slowly

progressive encephalopathies. Inborn errors of metabolism also can manifest with rapid clinical deterioration in the newborn period or after an interval period of good health. Presenting clinical features are often non-specific, and they may be misdiagnosed as infection, cardiovascular compromise, other causes of hypoxemia, trauma, primary brain anomalies, or the effects of a toxin **(Ennset al., 2006).**

Although individually rare, inborn errors of metabolism represent a potentially preventable cause of death and disability. The development of tandem mass spectrometry enables a wide variety of compounds to be assayed on the dried blood spots routinely collected from subjects **(Leonard, 2002).**

Tandem mass spectrometry is an analytical method which is being implemented for neonatal screening. The method can determine the content of amino acids and acyl carnitines in neonatal screening samples in one integrated analysis. This allows detection of more than 20 inherited disorders of amino acid, fatty acid and organic acid metabolism **(Simonsen, 2002)**.

Newborn screening programs using tandem mass spectrometry typically have reported an incidence of 1 in 2000 to 1 in 4000 **(Enns et al., 2006).**

Children with certain inherited metabolic disorders excrete diagnostic acylcarnitines which reflect unusual acyl-CoA

intermedites accumulating at the metabolic block **(Roe et al., 1986)**. These metabolites can be detected in urine, if their concentration exceeds about 50nmol/ml, by fast atom bombardment mass spectrometry (FAB-MS).By applying tandem mass spectrometry (MS/MS) it is possible to lower the detection limit to nmol/ml in urine or blood**(Millington et al., 1989).**

Hypothesis and Objective:

Metabolic disorders can present clinically with a picture simulating cerebral palsy. Therefore our aim was to screen for some of the inborn errors of metabolism in patients with cerebral palsy to determine the prevalence of these disorders in these patients. Furthermore, the study willpointout clinical syndromes of these patients.

CEREBRAL PALSY

Overview:

Background:

In recent years “cerebral palsy” has received much attention from pediatricians. It would be helpful if neurologists, pediatricians and others working with “cerebral palsy” would agree on its definition and on the meaning of the terms employed, for each group has somethingto give the others. Because the cases included in the term “cerebral palsy” are not all identical from clinical, etiological, and morbid anatomicalaspects, the term “cerebral palsy” is not an exact one. Meanwhile, however, for *research purposes,* the term “cerebral palsy” is useful in the study of a group of conditions often of obscure origin affecting the brain and arising in early life. Astrict definition is necessary and should be adhered to if the term is to be used for certain types of research andinthe exchange of information. Finally, in *common usage* the term has administrative usefulness and a practical value largely because the affected children in many cases have certain special motor, intellectualand emotional difficulties, and so may have certain special therapeuticand educational needs in common**(Alcock et al., 1959).**

Cerebralpalsy (CP) is a well-recognized neurodevelopmentalcondition beginning in early childhood and persisting through the lifespan and originally called ‘cerebral paresis’ as recognized by *Little, 1861*,beginning at theend of the 19th century contribution of the important perspectives on the condition **(Freud 1897 & Osler 1899).** Moving the concepts and descriptions of CP forward, and caused this condition to become the focus of treatment services, advocacy, and research efforts **(Carlson et al., 1940)**. **(Bax, 1964)** stated that *Mac Keith & Polani, 1959*considered that CP is a persisting but not unchanging disorder of movement and posture, appearing in the early years of life and due to a non-progressive disorder of the brain, the result of interference during its development. CP is ‘a disorder of movement and posture due to a defect or lesion of the immature brain**.** For practical purposes it is usual to exclude from cerebral palsy those disorders of posture and movement which are (1) of short duration, (2) due to progressive disease, or (3) due solely to mental deficiency **(Bax, 1964).** The term " minor neuromotor dysfunction" to designate children with minor motor delay, which has also been described as children who"outgrow" CP **(Knoblock &Pasamanick, 1959; Nelson &Ellenberg, 1982).** Clinically, it is represented by the "clumsy child "syndrome; these children are at increased risk for preschool communicative disorders or school age learning disabilities **(Amiel-Tayson, 1997).**CP is an umbrella term

covering a group of non-progressive, but often changing, motor impairment syndromes secondary to lesions or anomalies of the brain arising in the early stages of development **(Mutchet al., 1992).** This definition emphasized the motor impairment and acknowledged its variability, previously underscored in Mac Keith's and Polani's definition, and excluded progressive disease, a point introduced in Bax's annotation.

Reassessment of the definition of CP was prompted by a host of factors:

Changes in delivery of care to children with disabilities; recognition that children with slowly progressive inborn errors of metabolism can present with motor difficulties at times indistinguishable from those of children with non-progressive disease; increased availability of high-quality brain imaging to identify impairments in brain structure; acknowledgment that developmental motor impairment is almost invariably associated with a range of other disabilities; and increased understanding about associated antecedents and correlates of CP **(An International Workshop on Definition and Classification of Cerebral Palsy, 2004).**

CP is not an etiologic diagnosis, but a clinical descriptive term.

To underline the idea that a comprehensive approach to CP needs to be multidimensional and that management of patients with CP almost always requires a multidisciplinary

setting, disorders commonly accompanying the motor aspects of CP have been identified in the refined definition. This addition reflects the idea that CP is one of a group of neurodevelopmental disorders which involve numerous developing functions. As in other neurodevelopmental disorders, various manifestations of disordered brain function may appear more significantin different persons or at different periods, e.g. some aspects of the motor impairment, intellectual disability, epilepsy, attentional difficulties, and many others may be more prominent, or more problematic, at different stages of the life of a person with CP **(Bax et al., 2005).**

The definition of cerebral palsy:

Cerebral palsy (CP) describes a group of disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, cognition, communication, perception, and/or behaviour, and/or by a seizure disorder**(Bax et al., 2005).**

Explanation of this definition:

Cerebral palsy (CP): it was generally agreed that the CP concept, essentially a clinical formulation based onphenomenology, remains useful in the current state of

nosology. Although the word ‘palsy’ has become largely obsolete in medical nosography and it has no univocal connotation, the term ‘cerebral palsy’ is entrenched in the literature andit is used universally by clinicians, therapists, epidemiologists, researchers, policy makers, health care funding organizations, and lay persons. The term ‘CP’ has, however, been variably used, with poor comparability across different places and times, indicating the need for a consensual definition. Epidemiologists in particular require consistent terminology and concepts across time and space in order to identify changing patterns of diseases and disorders. It was proposed to retain the term to relate future research in CP to existing published work, but to clarify several aspects of the definition in this report**(Bax et al., 2005).**

A group: there is general agreement that CP is a heterogeneous condition in terms of etiology as well as in types and severity of impairments. Several groupings are possible and warranted to serve different purposes. These groupings may show overlap. Therefore, the singular form ‘CP’ is used (as opposed to ‘cerebral palsies’) as an umbrella term**(Bax et al., 2005).**

Disorders: this refers to conditions in which there is disruption of the usual orderly processes of child biopsychosocial development. The disorders are persistent. we preferred the term

‘disorders’ over ‘syndromes’, because we describe disturbed neurobiological processes, and not distinctive clinical patterns, as implied in the term ‘syndromes’**(Bax et al., 2005).**

Development : the notion of alteration in development is essential to the CP concept. It distinguishes CP from phenotypically similar disorders in children or adults due to late-acquired lesions, at a time when motor development is relatively well developed. The ‘developmental’ aspect of CP is also important with regard to management strategies that may include interventions that address the developmental consequences of the functional limitations associated with CP, and interventions that are directed at the underlying neurobiological processes. The developmentalnature of CP almost always implies impacts on the developmental trajectories of the people who have CP. The motor impairments of CP manifest very early in child development, usually before 18 months of age, with delayed or aberrant motor progress. The clinical picture of CP evolves with time, development, learning, training, therapies, and other factors**(Bax et al., 2005).**

Movement and posture: abnormal motor behavior (reflecting abnormal motor control) is the core feature of CP. It is characterized by various abnormal patterns of movement and posture related to defective coordination of movements and/or regulation of muscle tone. Patientswith CP may also have other

neurodevelopmental impairments that can affect adaptive functioning, sensory function, learning, communication, and behavior, as well as seizures. Abnormal motor control may be further impaired by features that are associated with CP. However, patients with neurodevelopmental disabilities that do not primarilyaffect movement and posture are not considered to have CP**(Bax et al., 2005).**

Causing : activity limitations are presumed to be a consequence of the motor disorder. Thus disorders of movement and posture that are not associated with activity limitations are not considered part of the CP group**(Bax et al., 2005).**

Activity limitation : the World Health Organization's International Classification of Functioning, Disability and Health6 speaks of 'activity' as '…the execution of a task or action by an individual', and identifies 'activity limitation' as '…difficulties an individual may have in executingactivities'. This term amplifies the previous concept of 'disability' to recognize changing international concepts and terminology**(Bax et al., 2005).**

Another opinion stated that it is too imprecise a term to define the lower limit of severity required to be included in the group, and may, therefore, be incorrect **(Badawi et al., 2006**).

Avoiding the term ‘stages of development’ as it lacks biological precision, and adding a requirement for ‘activity limitation’ to set clinically and societally-relevant boundaries to the CP concept, following the model of the World Health Organization’s International Classification of Functioning, Disability and Health model**(World Health Organization 2001).**

Attributed to:understanding of developmental neurobiology (including the effects of genetic, chemical, and other influences on brain development) is increasing rapidly, such that it is becoming possible to identify structural and other evidence of brain maldevelopment in people with CP. As a consequence, structural-functional connections and correlations are becoming more clearly delineated than has previously been possible. It must, however, be acknowledged that at the present time a full understanding of causal pathways and mechanisms leading to CPremains elusive in many cases**(Bax et al., 2005).**

Disturbances: this term refers to processes or events that in some way interrupt, damage, or otherwise influence the expected patterns of brain maturation, and result in permanent (but non-progressive) impairment of the brain. In a proportion of cases it is currently not possible to identify a specific ‘disturbance’ or a specific timing of the events that appear to

impact on maturation. These disturbances may include cerebral dysplasia**(Bax et al., 2005).**

On contrary to this definition clarity is far more important, but we do not consider that the terms used in the new definition improve clarity. For example, ‘lesions or anomalies’ arereplaced by ‘disturbances’ which suggests an active agent – does that exclude genetic anomalies? Furthermore, the new definition states that the disturbances which occurred in the past were non-progressive. What constitutes a non-progressive disturbance? For example, it might be argued that asphyxia is a progressive condition in that, after the initialhypoxic insult there is a biochemical cascade that creates much of the resulting damage. Surely, what the authors meant is that the lesion or anomaly in the brain, once recognized in early childhood, is no longer progressive. Knowledge of this fact, however protracted the development of the lesion or anomaly might have been in the past, is very important to the child, their family and caregivers, and has long been a criterion for belonging to the cerebral palsy (CP) group **(Badawi et al., 2006).**

As a respond to this comment, their stress on lack of progressiveness was not intended to address clinical manifestations, but to refer to the lack of progression of the underlying pathologic process. However, the term ‘non-progressive disturbances’ refers to processes that do not progress

or whose progression has stopped while the fetal or infant brain is developing. These non-progressive disturbances include asphyxia, infection, inflammation, and other initially progressive, but distinctly time-limited, pathological processes **(Dan et al., 2006).**

Fetal or infant: the specification 'fetal or infant' reflects the idea that disturbances that occur very early in human biological development impact differently on motor function than disturbances that occur later, even those that occur in early childhood. There is no explicit upper age limit as, depending on aspects of motor functioning, the first two or threeyears of life may be concerned. Therefore, the notion of early lesion would appear more useful clinically than arbitrarily specified time limits. In practical terms, disturbance resulting in CP is presumed to occur before the affected function has developed (e.g. walking, manipulation, etc.)**(Bax et al., 2005).**

Brain: the term 'brain' includes the cerebrum, the cerebellum, and the brain stem. It excludes motor disorders of spinal, peripheral nerve, muscular or mechanical origin. (Note, however, that alterations in the neuromuscular and musculoskeletal systems may occur in CP as a consequence of the chronic motor impairment. These alterations may restrict further motor function of patients with CP, and be associated