INTRODUCTION

Cerebral palsy

I) Historical review:

Cerebral palsy (CP) is a well-recognized neurodevelopmental condition that begins in early childhood persisting through the lifespan. Originally reported by Little in 1861 and originally called 'cerebral paresis'. In over 20 years of orthopaedic practice, Little came to the conclusion that there is a causal relationship between birth complications and disorders of mental and physical development after birth, he based his opinion on approximately 200 well-documented personal cases of spasticity with birth complications in their history. Little's conclusion on the causal relationship between asphyxia (and other complications) during birth and spasticity was even generalized to all clinical types of CP. (1)

At the end of the 19th century, Sigmund Freud and Sir William Osler both began to contribute important perspectives on the condition.

Sigmund Freud was the first to write about cerebral palsy as a descriptive category, uniting various infantile motor deficits of brain origin. (2)

Mac Keith and Polani 1959 defined CP as a persisting but not unchanging disorder of movement and posture, appearing in the early years of life due to nonprogressive disorder of the brain. (3)

In 1964, Bax stated that CP is a disorder of movement and posture due to a defect or lesion of the immature brain. But the concept of sensory, cognitive, behavioral and other associated impairments were not included in this definition. (4)

An International Workshop on Definition and Classification of Cerebral Palsy was held in 2004, underlined that CP is not an etiologic diagnosis, but a clinical descriptive term. (5)

II) Definition of CP:

Cerebral palsy describes a group of permanent disorders of the development, movement and posture, causing activity limitation, that are attributed to nonprogressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication, behavior, epilepsy and by secondary musculoskeletal problems. (6)

III) Risk factors of CP:

1) Prenatal risk factors as:

1- Maternal infections: Viral infections as rubella, cytomegalo virus and mumps. Protozoal infections as toxoplasmosis. Spirochaetal infections as syphilis.
2- Sever toxaemia of pregnancy may lead to fetal cerebral haemorrhage.
3- Maternal nutritional and vitamin defeciencies.
4- Uncontrolled maternal diabetes mellitus.

5- Improper fetal implantation, placental infarction or premature placental separation. [7]

2) Natal and perinatal risk factors as:

It includes complications during delivery and/or first week of life as:

1- Birth asphyxia.
2- Prematurity.
3- Low birth weight.
4-Neonatal convulsions and neonatal jaundice.
5- Neonatal head trauma.
6- Perinatal infections. [8]

3) Postnatal risk factors as:

1- Intracranial infections (meningitis or encephalitis).
2- Skull fractures with intracranial hemorrhage.
3- Vascular embolism or thrombosis.
4- Severe Dehydration. [9]

IV) Classification of cerebral palsy:

1) Classification according to the site brain of lesion:

1- Pyramidal tract lesion: resulting in spastic type of CP.
2- Extrapyramidal tract lesion: resulting in dyskinetic type.
3- Cerebellar lesion: resulting in ataxic type of CP.

2) Topographic classification:

1- Quadriplegic CP: where the four limbs are involved, it may be tetraplegic if all limbs are affected to the same degree, diplegic if the lower limbs affected more than the upper limbs or double hemiplegic if one side of the body is affected than the other side.
2- Hemiplegic CP: where one side of the body is affected.
3- Paraplegic CP: involvement of lower limbs, most of cases turn to be diplegic.
4- Triplegic CP: involvement of three limbs usually both lower limbs and one upper limb.
5- Monoplegic CP: one limb involvement, most of cases turn to be hemiplegic.

3) Classification according to the severity of motor involvement:

This classification is based upon the degree of functional limitation in CP children and classified to mild, moderate, severe and profound type.

4) Classification according to the etiology:

CP can be due to prenatal, perinatal and postnatal factors. [10-12]

V) Pathology:

More than 80% of children with CP have abnormal findings on neuroimaging. These abnormal findings can provide valuable clues to pathogenesis.

The most common abnormality on neuroimaging is found in the white matter near the lateral ventricles, often termed periventricular leukomalacia (PVL), with reports of up to 56% of all cases of CP demonstrating abnormalities in this location, PVL occurs much more commonly in premature infants than in term infants, and is a common outcome of intraventricular hemorrhage in premature infants. The corticospinal tract fibers supplying the lower limbs are medial to those of the upper limbs in the periventricular white matter so children with PVL typically have spastic diparesis. PVL was present in 71% of the children with diparesis, 34% of those with hemiparesis, and 35% of those with quadriparesis.

Deep grey matter lesions to the basal ganglia and thalamic region are mainly associated with dystonic CP, and have been found in approximately 12% of children with the condition.

Large numbers of children acquired athetoid CP following a diagnosis of kernicterus, due to concentrated damage to the basal ganglia with bilirubin encephalopathy.

Focal cortical infarcts involving both the grey and white matter are found almost exclusively in patients with hemiparesis, and are typically related to middle cerebral artery strokes. In a group of children with hemiparetic CP, 27% were found to have a focal infarct on imaging.

Brain malformations can be detected by neuroimaging approximately in 10% of children with CP. Some maternal infections such as cytomegalovirus can cause brain malformations.

A wide range of findings may be detected by magnetic resonance imaging (MRI), including multiple cysts, cortical thinning, white and grey matter loss, and microcephaly.

Children with diffuse brain lesions or anomalies typically demonstrate spastic quadriparesis and are at high risk for additional medical and cognitive problems. [13, 14]

VI) Epidemiology:

CP is the most common motor disability of childhood. In United States it affects approximately 3.6 per 1,000 school-age children, with at least 8,000 new cases each year. The population of children with CP may be increasing due to premature infants who are surviving in greater numbers. [15-17]

A central database was set up to include information on over 6000 children with CP from 13 geographically defined populations in Europe. The overall rate was 2.08/1000 live births. One in five children with CP was found to have a severe intellectual deficit and was unable to walk. Among babies born weighing less than 1500g, the rate of CP was more than 70 times higher compared with those weighing 2500g or more at birth. [18]

In Egypt Prevalence rate of CP among living children in El- Kharga District, New Valley was 2.04/1000 live births, this rate increases to 40–100 per 1000 live births among babies born very early or with very low birth weight. [19]

VII) Initial evaluation and clinical findings:

Early identification of CP children allows early therapeutic intervention and screening for associated conditions. CP is a descriptive term that does not infer a single etiology, pathology or prognosis so there is no specific diagnostic test.

It is a diagnosis of exclusion based on a careful history and physical exam. It can be difficult to make a definitive diagnosis in infants less than 6 months old.

Before this age, the infant has a limited repertoire of volitional movements, which makes milder delays in motor development difficult to detect. In addition, abnormalities in tone and reflexes are often subtle in early infancy, as the cortex matures in the second half of the first year; the diagnosis typically becomes more apparent.

1) Comprehensive history:

Including a detailed account of potential risk factors and family history.

Detailed history of developmental milestones is important. Prematurity must be considered when evaluating development because milestones are generally corrected for the degree of prematurity. Certain deviations in developmental milestones are associated with CP. For example, early hand preference or asymmetric use of the extremities may be the first indication of hemiparesis.

Early head control or rigid standing are all associated with abnormally increased tone and/or exaggerated primitive reflexes.

The parent may also describe unusual means of mobility, such as bunny hopping, combat crawling or bottom scooting.

The most important aspect of the developmental history is to confirm that the child has not lost any skills or milestones, as this would suggest a neurodegenerative disorder.

2) Physical examination:

Careful neurologic exam is an essential piece of the evaluation. In infancy, the neurologic exam focuses on tone and infantile developmental reflexes. Deep tendon reflexes, plantar responses and the presence of clonus are more informative in the older child.

Commonly examined primitive reflexes include the Moro reflex, palmar grasp reflex, asymmetric tonic neck reflex, and tonic labyrinthine reflex.

During the first six months of life, maturation of the cortex gradually overrides these primitive responses and voluntary motor activity should increase.

Persistence of these primitive reflexes past six months of age or asymmetry of the response should be considered highly suspicious for a significant motor impairment. As the

primitive reflexes become suppressed, postural or protective reactions such as the parachute and the equilibrium or tilting reactions should emerge. In children with CP, postural reactions may be less effective, appear later than usual or fail to develop. A definitive diagnosis of CP should be made cautiously especially in the first six months of life. [20, 21]

VIII) Imaging:

Neuroimaging can be helpful in determining the etiology of CP and the timing of the insult. The Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society published two practice parameters that address the use of neuroimaging in the neonate and the child with suspected CP.

Recommendations for imaging in the preterm neonate include a screening cranial ultrasonography on all infants <30 weeks gestation between 7 and 14 days of age to be repeated between 36 and 40 weeks of postmenstrual age.

This recommendation was based on the fact that a 10-fold elevation in the risk of adverse outcome for the very low birth-weight infant was identified with ultrasound as intraventricular hemorrhage, periventricular cystic lesions, or moderate to severe ventriculomegaly.

Fullterm infants with neonatal encephalopathy, the practice parameter recommends a non-contrast computed tomography (CT) to detect hemorrhagic lesions or when there is a history of birth trauma, low hematocrit, or coagulopathy.

If the CT is inconclusive, MRI should be performed between 2 to 8 days of life in order to assess the location and extent of injury.

Abnormalities of the thalamus and basal ganglia were associated with increased neurodevelopmental disability. Neuroimaging can also be useful in determining the etiology of CP in older children.

The practice parameter on the diagnostic assessment of the child with CP found that an abnormal MRI scan was found in about 89% of CP children and that MRI was more likely to show an abnormality when compared to CT (about 77%). Therefore, the practice parameter recommends neuroimaging in the evaluation of a child with CP if the etiology has not been established and MRI is preferred to CT. [22, 23]

IX) Laboratory Findings:

Metabolic or genetic causes for CP are unusual, and laboratory studies to investigate these conditions are not routinely recommended.

Metabolic or genetic testing is recommended in the following conditions: if neuroimaging does not determine a specific structural abnormality, if it reveals a developmental malformation, if there is evidence of developmental deterioration, or if there is a family history of a childhood neurologic disorder associated with a diagnosis of "cerebral palsy". The practice parameter also recommends consideration of diagnostic testing for a coagulation disorder in children with an unexplained cerebral infarction on neuroimaging. [23]

X) Associated Disorders:

1) Cognitive Impairments:

Cognitive impairments are common in CP. It is difficult to make generalizations about the specific relationship of CP and cognitive function because CP is a heterogeneous disorder.

In addition, assessment of intellectual functioning can be difficult in patients with severe motor and communication difficulties, which may lead to an underestimation of cognitive function. The overall frequency of mental retardation defined as an IQ score of 69 or below, is reported to be 50% to 70%.

Spastic diplegic CP is characterized by normal cognition because the lesion is in the periventricular white matter, i.e. sparing the cortical grey matter and a patient with athetosis secondary to a discrete lesion in the basal ganglion is likely to have normal intelligence. However, there is a relationship between the severity of CP and mental retardation. Children with spastic quadriplegic CP have greater degrees of mental retardation than children with spastic hemiplegia. Other factors associated with increased cognitiveimpairment include epilepsy and cortical abnormalities on neuroimaging. [24, 25]

2) Sensory Impairments:

Deficits in two-point discrimination, proprioception, and stereognosis have been described in CP. Sensory deficits are believed to be most common in children with hemiparesis. A study of children with spastic hemiparesis found that 97% of the spastic limbs had a stereognosis deficit, 90% had a two-point discrimination deficit, and 46% had a proprioception deficit. [26]

Sensory deficits can also be found in the limbs that do not appear to be affected by CP. Bilateral sensory deficits were found in 88.8% of children with hemiparesis in one study. Stereognosis and proprioception were the most common bilateral abnormalities, and the extent of sensory loss did not mirror the motor deficit. [27]

Another study identified abnormalities of tactile spatial discrimination in the hands of children with spastic diparesis with apparent normal motor function in their upper extremities. Sensory deficits are important to recognize because they can significantly affect functional use of the extremity. [28] Kholief., 2000 mentioned that there was no clinical superficial or deep sensory abnormality, however there was some sensory evoked potential latencies of the median nerve, but not the posterior tibial nerve, were significantly prolonged on the hemiplegic side compared to the non hemiplegic side or the control group.[29]

3) Visual Problems:

Visual problems are common in children with CP, with a reported prevalence about 39% .Visual impairments can be cortical due to damage to the visual cortex of the occipital lobes, If not diagnosed and managed early, visual deficits can interfere with developmental progress and rehabilitation.

Some visual deficits demonstrate a relationship to the underlying etiology, such as retinopathy of prematurity in premature infants, cortical visual impairment in hypoxic ischemic encephalopathy, and homonymous hemianopsia in hemiparesis. [30]

One study demonstrated a relationship between visual deficits and severity of CP as measured by the Gross Motor Functional Classification System (GMFCS). This study concluded that children with the most severe CP were at greatest risk for high myopia, absence of binocular fusion, dyskinetic strabismus, severe gaze dysfunction, and optic neuropathy or cortical visual impairment. [31]

4) Hearing Impairments:

Certain etiologies, such as kernicterus, post-meningitis and congenital rubella, increase the risk for hearing loss. If not diagnosed and treated early, hearing loss can interfere with developmental progress and rehabilitation. [32]

5) Psychological Impairments:

The prevalence of emotional and behavioral problems in different populations of children with CP is reportedly 30% to 80%. [33]

Wide variety of behavior and emotional disorders, including attention deficit disorder, passivity, immaturity, anger, sadness, impulsivity, emotional liability, low self-esteem, anxiety, dependency, being headstrong, and hyperactivity. [24]

6) Epilepsy:

Up to 60% of children with CP have epilepsy, with onset in the first year of life in 70%. Focal seizures with or without secondary generalization are most common with frequently focal Electroencephalogram (EEG) abnormalities.

Epilepsy can be an indicator of the severity of neurological injury (quadriplegic CP) or cortical insult (hemiplegic CP).

Children with spastic diplegic CP are at a lower risk for epilepsy mainly because their pathology predominantly involves the periventricular white matter. [34]

7) Oromotor Impairments:

Oromotor impairments are associated with more severe CP. A weak suck, poor coordination of the swallowing mechanism, tongue thrusting, and a tonic bite reflex may all lead to feeding difficulties and increased risk for aspiration.

Speech disorders range from mild articulation disorders to anarthria, and are most commonly seen in children with spastic quadriparesis or athetosis. Oromotor dysfunction may also lead to difficulty controlling oral secretions and drooling. [35]

8) Nutritional Disorders:

The assessment of growth and nutrition in children with CP can be difficult due to the lack of a reliable means of measuring stature in children with contractures and scoliosis and the lack of appropriate reference data or growth curves specific to CP. Poor oromotor

skills, gastroesophageal reflux, and the inability to self-feed or communicate can all increase the risk for malnutrition in children with CP.

About 30% are undernourished, and many show reduced linear growth below the third percentile, although malnutrition is a primary concern, children with CP are also at risk for overfeeding and obesity. Constipation is common in children with CP and results from multiple factors including poor feeding, reduced water intake and immobility. [36]

9) Genitourinary Disorders:

The development of urinary continence is typically delayed in children with CP. A study of 601 children with cerebral palsy found that by the age of 6 years, 54% of children with spastic quadriparesis and 80% with spastic hemiparesis or diparesis had gained urinary continence spontaneously. [37]

10) Respiratory Disorders:

Children with CP are at increased risk for respiratory illnesses. Impaired control of respiratory muscles, ineffective cough and aspiration due to an impaired swallow, gastroesophageal reflux or seizures all increase the risk for chronically increased airway secretions. Increased airway secretions may lead to wheezing, atelectasis, recurrent aspiration pneumonia, restrictive lung diseases or bronchiectasis. [38]

11) Sleep Disturbances:

Sleep disorders are common in children with CP, particularly those with visual impairment, occurring in 30% - 50% of cases. [39]

12) Bone and Mineral Density Disorders:

Decreased bone mineral density and increased risk of fracture with minimal trauma is common in patients with moderate to severe CP, especially those who are nonambulatory, by the age of 10 years, most nonambulatory children have osteopenia. [40]

13) Musculoskeletal Disorders:

The developing bones grow in the direction of the forces placed upon them. Spasticity can lead to progressive joint contractures, shortened muscles, and hip or foot deformities, these manifestations are more common with severe motor disability and immobility, such as quadriplegia.

Examples of musculoskeletal deformities:

a) Foot/ankle:

Equinus deformity, due to increased tone or contractures of the gastrosoleus complex, is a common musculoskeletal deformity in CP.

Equinovarus foot deformity is primarily due to a combination of spasticity of the posterior tibialis muscle and the gastrosoleus complex, resulting in inversion and supination of the foot and a tight heel cord, this deformity is most common in a child with hemiparesis.

Equinovalgus foot deformity is due to spasticity of the gastrosoleus complex and the peroneal muscles, as well as weakness in the posterior tibialis muscle. This deformity is common in older children with spastic diparesis and quadriparesis.

Hallux valgus deformities are associated with valgus deformities of the foot, which may lead to a painful bunion at the head of the first metatarsal.

b) Knee:

Knee flexion contractures are common due to spasticity in the hamstring muscles and static positioning in a seated position. If a severe knee flexion is present, hip flexion will be limited, resulting in lumbar kyphosis in the seated position.

Flexion contractures at the knee are associated with hip and ankle flexion contractures and patella alta. Genu valgus may also occur, and is most commonly associated with excess femoral anteversion.

c) Hip:

Acquired hip dysplasia is common in cerebral palsy and often leads to progressive dislocation.

d) Spine:

Spinal deformities, including kyphosis, lordosis, or scoliosis are common in children with CP. Kyphosis is often seen in conjunction with significant weakness of the spinal extensor muscles, and tightness in the hamstrings, leading to a posterior pelvic tilt.

Lordosis is frequently associated with hip flexion contractures. The likelihood of scoliosis increases with the severity of CP. An overall incidence of approximately 20% has been reported, with an incidence as high as 68% in children with spastic quadriparesis.

e) Upper extremity:

Spasticity and muscle imbalances can often lead to joint deformities in the upper extremity. The shoulder is often positioned in an adducted and internally rotated position. Spasticity in the biceps, brachioradialis, and the brachialis frequently result in elbow flexion contractures. Forearm pronation deformities are common and can significantly affect functional use of the hand. A thumb in palm deformity is commonly seen with adduction at the carpometacarpal joint, which may be associated with hyperextension of the metacarpophalangeal and interphalangeal joints. [41-45]

XI) Management:

Therapeutic challenges include formulating an individualized treatment plan that is functional, goal-oriented, time-limited, and cost-effective. Physical therapists focus on gross motor skills, including sitting, standing, walking, wheelchair mobility, transfers, and community mobility. Occupational therapists address the visual and fine motor skills that enable coordinated functions of activities of daily living such as dressing, toileting, eating, bathing, and writing. Orthotic interventions are aimed at the prevention and/or correction of deformities, provision of support, and facilitation of skill development and gait improvement. [46, 47]

1) Medical Treatment:

a) Oral medications:

Are often used as an early treatment strategy for global spasticity. Medications that are most frequently used include Lioresal, dantrolene sodium, clonidine, diazepam, and tizanidine. (48)

b) Botulinum Neurotoxin:

It is a protein composed of a heavy chain, which binds nerve terminals at the neuromuscular junction, and a light chain, which is transported into the nerve terminal to block it. Following injection, muscle relaxation is evident within 48 to 72 hours and persists for a period of 3 to 6 months. Abd El-Ghani.,2003 mentioned that botulinum toxin has shown promising results when used in treating spasticity with cerebral palsy, the best results is achieved after physical treatment. (49)

c) Alcohol Blocks:

Alcohol nerve and motor point blocks have been used for many years to reduce focal spasticity. Phenol injections, at 3% to 5% solutions, either at motor points of selected muscles or perineurally, denatures proteins and disrupts efferent signals from hyperexcitable anterior horn cells by inducing necrosis of axons. (50)

d) Intrathecal Baclofen:

Baclofen is delivered directly to the cerebrospinal fluid via a catheter connected to an implanted device in the abdomen. (51)

2) Physical therapy:

a) Stretching:

Children with CP are at significant risk for contracture formation due to muscle imbalances and static positioning. There is no clear evidence to support its efficacy or provide guidance regarding the ideal frequency or duration. There is some evidence to suggest that a sustained stretch is preferable to manual stretching Positioning techniques, orthotic devices, splints, and casting are often recommended to provide a more prolonged stretch. (52)

b) Strengthening:

Deficits in voluntary muscle contraction in CP are felt to be due to decreased central nervous system motor unit recruitment, increased antagonist coactivation, and changes in muscle morphology, including muscle fiber atrophy and increased fat and connective tissue. The strengthening exercise program could be used to help improve gait function of individuals with spastic cerebral palsy. (53)

c) Partial Body Weight Support Treadmill Training:

Reduces the amount of weight required to support patients ambulating on a treadmill by utilizing a postural control system consisting of a harness.

The theoretical basis of this treatment is an activation of spinal and supraspinal pattern generators described in animal experiments with subsequent development of locomotion patterns. Partial Body Weight Support Treadmill Training in nonambulatory subjects with CP has demonstrated significant improvements. (54)

d) Constraint-Induced Movement Therapy:

It developed for treating adults with hemiparesis following a stroke defined as restraint of the unaffected limb in conjunction with at least three hours per day of therapy for at least two consecutive weeks, whereas the modified type requires restraining the unaffected limb for fewer than three hours per day with therapy. (55)

e) Electrical Stimulation:

Interest in the use of electrical stimulation in CP is growing. Theories that support electrical stimulation suggest that it increases strength and motor function, and it is an attractive alternative for strengthening in children with poor selective motor control (56). Abd El-Ghani., 2003 reported that the electrical stimulation can also reduce the spasticity.(49)

f) Hydrotherapy:

It is a series of gentle exercises which carried out in a heated pool ,while the water supports much of the body weight, the resistance of the water helps to strengthen the muscles. The warmth increases circulation and also reduces muscle spasms and helps to relieve the pain. (54)

3) Surgical treatment:

As Selective Dorsal Rhizotomy which is a neurosurgical procedure that involves partial sensory deafferentation at the levels of L1 through S2 nerve rootlets. Also surgical release of the spastic or contracted muscle can be done, the muscles that are most frequently addressed surgically are those that cross two joints, including the hip adductors, hip flexors, hamstrings, rectus femoris, and gastrocsoleus complex. Orthopedic surgery is ideally delayed until the age of 4 to 7 years, due to the high risk of recurrence of tightness and contracture formation in younger children. (57)

4) Orthoses:

Many children with cerebral palsy utilize orthotic devices for maintaining or increasing range of motion, protection or stabilization of a joint, or promotion of functional activity.

a) Upper Extremity Orthoses:

Static wrist hand orthoses are commonly used in CP to improve hand position for functional activities and to maintain range of motion.

Dynamic wrist hand orthoses are much less commonly used in children.(58)

b) Lower Extremity Orthoses:

Many different types of lower limb orthoses are utilized in the management of CP; as supramalleolar orthotics, solid ankle foot orthotics, hinged ankle foot orthotics, posterior spring-leaf ankle foot orthotics, and ground-reactive ankle foot orthotics. [59]

c) Spinal Orthoses:

Spinal orthoses can prevent the progression of scoliosis. There is general agreement that if bracing controls the progression of scoliosis, it will not work in every patient and it is only helps in slowing progression and delaying surgery until the ideal time. Regardless of its effect on curve progression, a positive effect on sitting stability and function has been reported by parents and caregivers. [60]

d) Adaptive Equipments

The goal for the use of adaptive equipment is to improve positioning either in the supine or sitting position, or to improve level of function in self-care skills, including in the home, school, or community. These devices include, but are not limited to, seating or support systems, mobility devices and environmental control devices. [61]

Hyperbaric Oxygen Therapy

Hyperbaric oxygen therapy (HBOT) is an interesting therapeutic modality defined as the use of oxygen at greater than atmospheric pressure as a drug to treat basic pathophysiologic processes and the associated diseases.

The technology for delivering this treatment has been in development for about 350 years, until the middle of the last century hyperbaric treatment was administered using air rather than oxygen. HBOT is therefore a relatively young modality with most applications dating from the 1960's. [62]

Hyperbaric Oxygen Therapy is delivered using a compression chambers and an oxygen delivery system. These chambers may be designed for a single occupant (a monoplace chamber), or multiple occupants (a multiplace chamber). For therapeutic purposes they are identical, but each type of chambers suits particular individuals depending on both physical and psychological factors. The monoplace chamber is filled with oxygen and does not require a specific oxygen delivery system for respiration, while the multiplace chamber is filled with air and oxygen is delivered by mask, hood or anaesthetic circuit as required. [63]

Under normal atmospheric pressure at sea level—760 mm Hg or 1 atmosphere absolute (1 ATA)—hemoglobin in the blood is already 95% saturated with oxygen, with very little capacity for increasing oxygen transport . Oxygen is also dissolved directly in the plasma in a more bioavailable form. According to Henry's Law, the absorption of a gas is directly related to the partial pressure of the gas. Breathing 100% oxygen at 3 ATA will increase the plasma oxygen saturation up to 17 times. It is the increased oxygen dissolved in plasma, which is responsible for most of the beneficial effects of HBOT. [64]

I) Physical Basics:

The atmosphere is a gas mixture containing by volume 20.94% oxygen (O_2), 78.08% nitrogen, 0.04% carbon dioxide (CO_2), and traces of other gases. For practical purposes air is considered to be a mixture of 21% oxygen and 79% nitrogen. The total pressure of this mixture at sea level is 760 millimeters of mercury (mmHg). Dalton's law states that in a gas mixture, each gas exerts its pressure according to its proportion of the total volume.

Partial pressure of a gas = (absolute pressure) x (proportion of total volume of gas)

Thus, the partial pressure of oxygen (pO_2) in air is (760) x (21/100) = 160 mmHg.

Pressures exerted by gases dissolved in water or body fluids are certainly different from those produced in the gaseous phase. The concentration of a gas in a fluid is determined not only by the pressure, but also by the "solubility coefficient" of the gas. Henry's law formulates this as follows:

Concentration of a dissolved gas = (pressure) X (solubility coefficient)

The solubility coefficient varies for different fluids and it is temperature-dependent, with solubility being inversely proportional to temperature, CO_2 is 20 times more soluble than oxygen. [65]

II) Physiology of Oxygenation:

1) The Oxygen Pathway:

The oxygen pathway passes from the ambient air to the alveolar air and continues through the pulmonary, capillary, and venous blood to the systemic arterial and capillary blood.

It then moves through the interstitial and intracellular fluids to the microscopic points of oxygen consumption in the perioxomes, endoplasmic reticulum and mitochondria.

2) Ventilation phase:

Oxygen is continuously absorbed into the blood which moves through the lungs, and it thereby enters the systemic circulation.

At a ventilatory rate of 5 liters/min and oxygen consumption of 250 ml/min. The alveolar oxygen tension is maintained at 104mmHg.

During moderate exercise the rate of alveolar ventilation increases fourfold to maintain this tension and About 1,000 ml of oxygen are absorbed per minute. Carbon dioxide is being constantly formed in the body and discharged into the alveoli secretion is 40 mmHg. It is well known that the partial pressure of alveolar carbon dioxide (PCO_2) increases directly in proportion to the rate of CO_2 excretion, and decreases in inverse proportion to alveolar ventilation.

3) Transport phase:

The difference between partial arterial oxygen pressure (104 mmHg) and partial venous oxygen pressure (40mmHg), which amounts to 64 mmHg, causes oxygen to diffuse into the pulmonary blood.

It is then transported, mostly in combination with hemoglobin, to the tissue capillaries where it is released for use by the cells.

There the oxygen reacts with various other nutrients to form CO_2, which enters the capillaries to be transported back to the lungs. During exercise, the body oxygen requirement may be as much as 20 times normal, yet oxygenation of the blood does not suffer, because the diffusion capacity for oxygen increases fourfold during exercise.

This rise results in part from the increased number of capillaries participating, as well as dilatation of both the capillaries and the alveoli.

Another factor here is that the blood normally stays in the lung capillaries about three times as long as is necessary to cause full oxygenation.

Therefore, even during the shortened time of exposure on exercise, the blood can still become nearly fully saturated with oxygen.

Normally 97% of the oxygen transported from the lungs to the tissues is carried in chemical combination with hemoglobin of red blood cells, and the remaining 3% in a dissolved state in plasma. [63- 65]

III) Mechanism of action:

Under normal conditions, hemoglobin is 95% saturated by O_2 and 100 ml of blood carries 19 ml of O_2 in combination with hemoglobin and 0.32 ml dissolved in plasma. If the inspired O_2 concentration is increased to 100%, O_2 combined with hemoglobin can increase to a maximum of 20 ml when the hemoglobin is 100% saturated, and the amount of O_2 dissolved in plasma may increase to 2.09 ml. The role of HBO that in addition to the hemoglobin which is 100% saturated, the amount of O_2 dissolved in plasma will increase to 4.4 ml% at a pressure of 2 ATA, to 6.8 ml % at 3 ATA which is almost sufficient to supply the resting total oxygen requirement of many tissues without a contribution from oxygen bound to hemoglobin. And again, it is this increased oxygen in plasma which is responsible for most of the beneficial effects of hyperbaric oxygen. [66]

The therapeutic mechanisms for HBOT have been based on:

(1) Increase the ambient pressure and elevate partial oxygen pressure (pO_2), Increasing the ambient pressure leads to reduction in the volume of gas-filled spaces according to Boyle's law. This action is directly related to the treatment of pathological conditions in which gas bubbles are present in the patient's body as decompression sickness or gas embolism. However, most of the pathologies for which HBOT is used rely on an inflammatory background and have no pathophysiologic relation with gas bubbles. Thus, the mechanistic basis of HBOT in indications such as problematic wounds, traumatic injuries, necrotizing fasciitis, ischemia-reperfusion processes, refractory osteomyelitis, and compromised flap and grafts depends on the elevation in pO_2 in the body fluids and tissues. [62]

(2) Oxygen is needed to support cellular respiration, and consequently provides energy. Reduced delivery of oxygen can affect cell survival. Injury or disease decreases the body's ability to transport oxygen to tissues, increases the tissue demand for oxygen, and may extend the distance that the oxygen must travel from the capillary to reach the cell. By increasing arterial pO_2, more oxygen can be delivered deeper into the tissues. [66]

(3) HBOT affects and modulates the immune system, motivates phagocytosis and neutrophil activity within affected tissues, improves fibroblast activity, stimulates angiogenesis and suppresses pro-inflammatory cytokines, such as IL-1, IL-6 or TNF-α. [67]

(4) The stimulating effect on stem/progenitor cells to produce and release growth factors at the site of neovascularization, is of special importance for wound healing processes. In cerebral palsy, neovascularization and angiogenesis are responsible for the long term benefit of HBO in the brain which based on the ability to establish a continuous supply of oxygen and nutrients. [68]

IV) Indications of HBOT:

1- Decompression sickness.

2- Air or gas embolism.

3- Carbon monoxide poisoning; cyanide poisoning; smoke inhalation.

4- Clostridial myostitis and myonecrosis (gas gangrene).

5- Enhancement of healing in selected problem wounds.

6- Crush injuries, compartment syndromes and other acute traumatic peripheral ischaemias.

7- Blood loss anemia.

8- Necrotizing soft tissue infections and diabetic infections.

9- Refractory osteomyelitis.

10- Skin flaps and grafts (compromised).

11- Delayed radiation injury (soft tissue and bony necrosis).

12- Thermal burns. [69]

V) Contraindications of HBOT:

Absolute contraindications:

Untreated pneumothorax.

Relative contraindications:

1- History of spontaneous pneumothorax.

2 - Severe sinus infection.

3- Upper respiratory infection.

4 - Asymptomatic pulmonary lesions on chest x-ray.

5- Uncontrollable high fever (greater than 39°C).

6- History of chest or ear surgery.

7- Congenital spherocytosis.

8- Uncontrolled epilepsy.

9- History of optic neuritis or sudden blindness.

10- Middle ear infection.

11- Uncontrolled Diabetes mellitus.

12- Emphysema with CO_2 retention. [70]

VI) Possible Complications of HBOT:

1- Barotrauma (middle ear-sinus- dental- pulmonary).

2- Ocular complications (progressive myopia- cataract).

3- Claustrophobia.

4- Anxiety.

5- Seizures. [71]

Hyperbaric Oxygen Therapy and Cerebral Palsy

Cerebral palsy is often caused by an ischemic/hypoxic injury during the perinatal period. This results in reduced blood flow and a major decrease in the supply of oxygen and nutrients to the affected region, and this deprives the brain not only of oxygen but also of glucose and of all other nutrients, as well as disrupting the nutrient/waste exchange process required to support brain metabolism. Cerebral ischemia occurs when blood flow to the brain decreases to a level.

Where the metabolic needs of the tissue are not met, dysfunction and death of brain neurons and neurological damage that reflects the location and size of the brain area affected. Ischemia is characterized by a complex sequence of events that evolves over hours or even days. [72]

Ischemic core and ischemic penumbra

Neuropathological analysis after focal brain ischemia reveals two separate areas: the ischemic core, and ischemic penumbra.

Once onset of a stroke has occurred, within minutes of focal ischemia occurring, the regions of the brain that suffer the most severe degrees of blood flow reduction experience irreversible damage. This region is the "ischemic core". This area exhibits a very low cerebral blood flow and very low metabolic rates of oxygen and glucose. Thus, reduced or interrupted cerebral blood flow has negative effects on brain structure and function. Neurons in the ischemic core of the infarction are killed rapidly by total bioenergetic failure and breakdown of ion homeostasis, lipolysis and proteolysis, as well as cell membrane fragmentation.

The result is cell death within minutes. Tissues in the ischemic core are irreversibly injured even if blood flow is re-established.

The necrotic core is surrounded by a region of brain tissue which suffers moderate blood flow reduction, thus becoming functionally impaired but remaining metabolically active; this is known as the "ischemic penumbra". This metabolically active border region remains electrically silent; the ability of neurons to fire action potentials is lost. However, these neurons maintain enough energy to sustain their resting membrane potentials and when collateral blood flow improves, action potentials are restored. The ischemic penumbra may comprise as much as half the total lesion volume during the initial stages of ischemia, and represents the region in which there is an opportunity to salvage functionality via postischemic therapy.

Ischemic penumbra refers to the region of brain tissue that is functionally impaired but structurally intact; tissue lying between the lethally damaged core and the normal brain, where blood flow is sufficiently reduced to result in hypoxia that is severe enough to arrest physiological function, but not so complete as to cause irreversible failure of energy metabolism and cellular necrosis. The ischemic penumbra has been documented in laboratory animals as severely hypoperfused, non-functional, but still viable brain tissue surrounding the irreversibly damaged ischemic core. [73, 74]

The penumbra can be identified by the biochemical and molecular mechanisms of neuron death and by means of clinical neuroimaging tools.

Cerebral Palsy is a form of ischemic brain injury where hypoxia causes leaking of blood vessels that eventually leads to edema, and edema further causes hypoxia. HBOT interrupts this vicious cycle by providing an increased amount of Oxygen, which is necessary to heal these capillaries. (75)

Hyperbaric Oxygen Therapy reduces the permeability of blood vessels thereby reducing the edema and making the tissue "Oxygen rich".

The effective blood supply is thus restored to previously Oxygen restricted brain tissue the “idling neurons”. HBOT cause a physiological change to the cells of this dormant area effectively waking them up-thus, increasing the capacity for recovery.

Hyperbaric Oxygen Therapy also stimulates angiogenesis and neovascularization, promotes osteoblastic and fibroblastic proliferation and collagen formation, and supports the growth of new blood vessels. (76)