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Cerebral Palsy-A Curse: Etiology, Pathophysiology and Current Approach of Treatment

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ABSTRACT

Cerebral palsy is Non-progressive, non-contagious motor conditions that cause physical disability in human development, chiefly in the various areas of body movement. Spastic cerebral palsy is by far the most common type of overall cerebral palsy, occurring in 80% of all cases. CT or MRI is warranted when the etiology of a patient's cerebral palsy has not been established – an MRI is preferred over CT due to diagnostic yield and safety. When abnormal, the neuroimaging study can suggest the timing of the initial damage. Botulinum toxin is used in focal treatment i.e. a limited number of muscles can be injected at the same time. The effect of the toxin is reversible and a reinjection is needed every 4–6 months. Selective dorsal rhizotomy (SDR) is a surgical procedure recommended only for cases of severe spasticity when all of the more conservative treatments – physical therapy, oral medications and intrathecal baclofen have failed to reduce spasticity or chronic pain. Transplanting stem cells into the brain could support and/or replace deteriorating brain tissue during the process of white matter damage in cerebral palsy.

Key Words: *Non-progressive, neuroimaging study, Botulinum toxin, rhizotomy, stem Cells*

INTRODUCTION

Non-progressive, non-contagious motor conditions that cause physical disability in human development, chiefly in the various areas of body movement. Scientific consensus still holds that CP is neither genetic nor a 'disease', and it is also understood that the vast majority of cases are congenital, coming at or about the time of birth, and/or are diagnosed at a very young age rather than during adolescence or adulthood. The use of "palsy" in the term cerebral palsy makes it important to note that paralytic disorders are in fact not cerebral palsy – meaning that the condition of quadriplegia, which comes from spinal cord injury or traumatic brain injury.

There are several antenatal factors, including preterm delivery, low birth weight, infection/inflammation, multiple gestations and other pregnancy complications, that have been associated with CP in both the preterm and term infant, with birth asphyxia playing a minor role. Cerebral palsy is caused by damage to the motor control centre of the developing brain and can occur during pregnancy, during childbirth or after birth up to about age three.

Resulting limits in movement and posture cause activity limitation and are often accompanied by disturbances of sensation, depth perception, and other sight-based perceptual problems, communication ability; impairments can also be found in cognition and epilepsy is found in about one-third of cases [1].

Table 1: Demographic characterization of cerebral palsy prevalence estimates by site, Autism and Developmental Disabilities Monitoring Network, 2006 (per 100, 8-year old children).

	Alabama	Georgia	Missouri	Wisconsin	All Sites
Total no. of CP cases	117	178	84	97	476
Total of 8-yrs old.[a]	35126	46621	26533	34058	142338
Total prevalence[b] (95% CI)	3.3(2.8-4.0)	3.8 (3.3-4.4)	3.2 (2.6-3.9)	2.9 (2.3-3.5)	3.3 (3.1-3.7)
Sex specific prevalence (95% CI)					
Boy	3.2 (2.2-4.2)	4.1 (3.4-5.0)	3.6 (2.7-4.5)	3.5 (2.7-4.5)	3.6 (3.2-4.1)
Girl	3.4 (2.7-4.4)	3.5 (2.8-4.4)	2.8 (2.0-3.8)	2.2 (1.6-3.0)	3.0 (2.7-3.5)
Boy;girl ratio	0.9:1	1.2:1	1.3:1	1.6:1	1.2:1
White, non-Hispanic	3.1 (2.5-3.9)	3.8 (3.0-4.8)	2.8 (2.1-3.7)	3.0 (2.4-3.8)	3.2 (2.8-3.6)
Black or African American, non-Hispanic	4.3 (3.2-5.9)	3.9 (3.1-4.8)	3.4 (2.3-5.2)	2.8 (1.7-4.4)	3.7 (3.2-4.4)
Hispanic	1.2 (0.3-5.0)	3.3 (2.2-5.2)	1.3 (0.2-9.1)	1.0 (0.4-2.6)	2.2 (1.5-3.1)
American Indian/Alaska native, non-Hispanic	-	-	-	5.5 (0.8-39.2)	1.8 (0.3-12.6)
Asian/Pacific-Islander, non-Hispanic	-	2.6 (1.2-5.4)	1.3 (0.2-9.2)	3.3 (1.2-8.8)	2.4 (1.4-4.2)

[a]Demographic data obtained from National Centre on Health Statistics' bridged-race postcensal populationestimates for 2006.
[b]All children included in the total regardless of race or ethnicity, as well as children for whom race of ethnicity is unknown.

Because of lack of appropriate denominator, multiracial or other race or ethnicity categories are not presented

Etiology

Problems in intrauterine development (e.g. exposure to radiation, infection), asphyxia before birth, hypoxia of the brain and birth trauma during labour and delivery and complications in the prenatal period or during childhood. CP is also more common in multiple births.

Premature infants are vulnerable, in part because their organs are not fully developed, increasing the risk of hypoxic injury to the brain that may manifest as CP. A problem in interpreting this is the difficulty in differentiating between cerebral palsy caused by damage to the brain that results from inadequate oxygenation and CP that arises from prenatal brain damage that then precipitates premature delivery. Recent research has demonstrated that intrapartum asphyxia is not the most important cause, probably accounting for not more than 10 percent of all cases; rather, infections in the mother, even infections that are not easily detected, may triple the risk of the child developing the disorder, mainly as the result of the toxicity to the fetal brain of cytokines that are produced as part of the inflammatory response. Low birth weight is a risk factor for CP—and premature infants usually have low birth weights, less than 2.0 kg, but full-term infants can also have low birth weights. Multiple-birth infants are also more likely than single-birth infants to be born early or with a low birth weight. After birth, other causes include toxins, severe jaundice, lead poisoning, physical brain injury, shaken baby syndrome, incidents involving hypoxia to the brain (such as near drowning), and encephalitis or meningitis. The three most common causes of asphyxia in the young child are: choking on foreign objects such as toys and pieces of food, poisoning and near drowning. Many cases of cerebral palsy are caused by the death in very early pregnancy of an identical twin [2].

Infections during pregnancy that may damage a fetus' developing nervous system. These include rubella (German measles), cytomegalovirus (a herpes-type virus), and toxoplasmosis (an infection caused by a parasite that can be carried in cat feces or inadequately cooked meat). Other infections in pregnant women that may go undetected are being recognized now as an important cause of developmental brain damage of the fetus.

- **Severe jaundice in the infant**. Jaundice is caused by excessive bilirubin in the blood. Normally bilirubin is filtered out by the liver. But often, newborns' livers need a few days to start doing this effectively, so it's not uncommon for infants to have jaundice for a few days after birth. In most cases, phototherapy (light therapy) clears up jaundice, and there are no lasting health effects. However, in rare cases, severe, untreated jaundice can damage brain cells.
- **Rh incompatibility between mother and infant**. In this blood condition, the mother's body produces antibodies that destroy the fetus's blood cells. This, in turn, leads to a form of jaundice in the newborn and may cause brain damage.

- **The physical and metabolic trauma of being born**. This can precipitate brain damage in a fetus whose health has been threatened during development [3].
- **Severe oxygen deprivation to the brain or significant trauma to the head during labor and delivery**. Disruption of Blood and Oxygen Supply to the Developing Brain
- Ischemic stroke, when a blood clot blocks a blood vessel in the brain, is recognized to cause brain damage that can result in CP. It can occur in the developing fetal brain during pregnancy or shortly after birth.
- Disruption of the oxygen supply during birth (birth hypoxia) has been estimated to account for less than 10% of CP cases.

Various Types of Cerebral Palsy

Cerebral palsy (CP) is divided into four major classifications to describe different movement impairments. These classifications also reflect the areas of the brain that are damaged. The four major classifications are: spastic, ataxic, athetoid / dyskinetic and mixed.

Spastic

Spastic cerebral palsy is by far the most common type of overall cerebral palsy, occurring in 80% of all cases. People with this type of CP are hypertonic and have what is essentially aneuromuscular mobility impairment (rather than hypotonia or paralysis) stemming from an upper motor neuron lesion in the brain as well as the corticospinal tract or the motor cortex. This damage impairs the ability of some nerve receptors in the spine to properly receive *gamma*-Aminobutyric acid, leading to hypertonia in the muscles signaled by those damaged nerves.

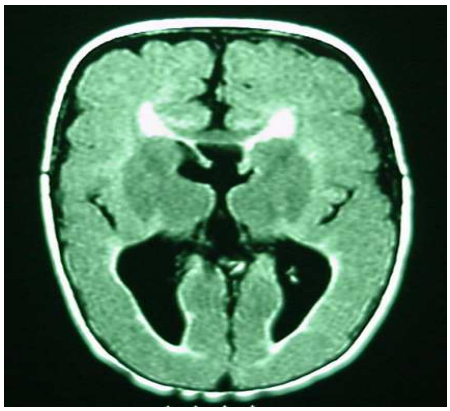

Fig 1

Fig. 1. Magnetic resonance image (MRI) of a 1-year-old boy who was born at gestational week 27. The clinical examination was consistent with spastic diplegic cerebral palsy. Pseudocolpocephaly and decreased volume of the white matter posteriorly were consistent with periventricular leukomalacia. Evidence of diffuse polymicrogyria and thinning of the corpus callosum is noted in this image. (http://emedicine.medscape.com/article/1179555)

Ataxic

Ataxia-type symptoms can be caused by damage to the cerebellum. Ataxia is a less common type of cerebral palsy, occurring between 5 and 10% of all cases. Some of these individuals havehypotonia and tremors. Motor skills such as writing, typing or using scissors might be affected as well as balance, especially while walking. It is common for individuals to have difficulty with visual and/or auditory processing. They usually have an awkward gait and as well with some dysarthria [4].

Athetoid or dyskinetic

Athetoid cerebral palsy or dyskinetic cerebral palsy is mixed muscle tone – both hypertonia and hypotonia mixed with involuntary motions. People with Dyskinetic CP have trouble holding themselves in an upright, steady position for sitting or walking, and often show involuntary motions. For some people with dyskinetic CP, it takes a lot of work and concentration to get their hand to a certain spot (like scratching their nose or reaching for a cup). Because of their mixed tone and trouble keeping a position, they may not be able to hold onto objects, especially small ones requiring fine motor control (such as a toothbrush or pencil). About 10% of individuals with CP are classified as

dyskinetic CP but some have mixed forms with spasticity and dyskinesia. The damage occurs to the extrapyramidal motor system and/or pyramidal tract and to the basal ganglia. In newborn infants, high bilirubin levels in the blood, if left untreated, can lead to brain damage in the basal ganglia (kernicterus), which can lead to dyskinetic cerebral palsy [5].

Table 2: Prevalence of Four Developmental Disabilities Among Children Aged 8 Years – Metropolitan Atlanta Developmental Disabilities Surveillance Program, 1996 and 2000

	Spastic	Dyskinetic	Ataxic	Hypotonic	Other/Mixed
Percent of cerebral palsy cases	76.9%	2.6%	2.4%	2.6%	15.4%
Number per thousand children	2.8%	0.1%	0.09%	0.1%	0.6%

Co-Occurring Developmental Disabilities

The ADDM site that tracks CP in metropolitan Atlanta is the Metropolitan Atlanta Developmental Disabilities Surveillance Program (MADDSP). MADDSP 2006 data show that approximately 60% of 8-year-old children with CP had another developmental disability. More than 40% of children with CP had intellectual disability, 35% had epilepsy and more than 15% had vision impairment. Nearly one-quarter of children with CP had both intellectual disability and epilepsy.

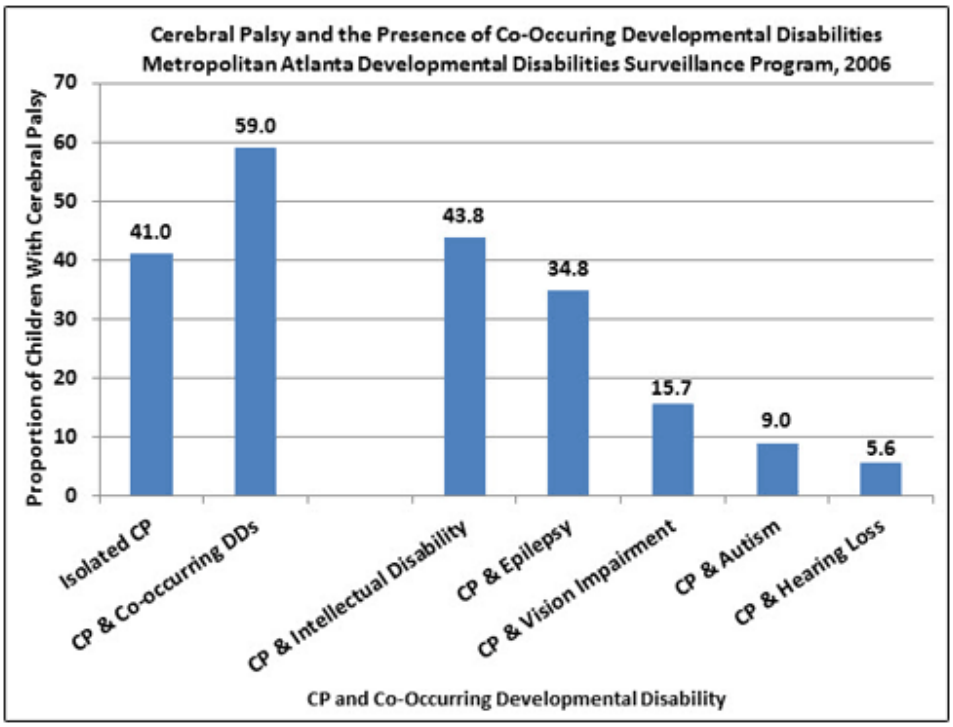

Figure 2: Statistical data analysis on Co-Occurring Developmental Disabilities

Diagnosis

Cranial ultrasound. This test is used for high-risk premature infants because it is the least intrusive of the imaging techniques, although it is not as successful as the two methods described below at capturing subtle changes in white matter – the type of brain tissue that is damaged in cerebral palsy.

CT or MRI is warranted when the etiology of a patient's cerebral palsy has not been established – an MRI is preferred over CT due to diagnostic yield and safety. When abnormal, the neuroimaging study can suggest the timing of the initial damage. The CT or MRI is also capable of revealing treatable conditions, such as hydrocephalus, porencephaly, arteriovenous malformation, subdural hematomas and hygromas and a vermian

tumor (which a few studies suggest are present 5 to 22%). Furthermore, an abnormal neuroimaging study indicates a high likelihood of associated conditions, such as epilepsy and mental retardation.

The diagnosis of cerebral palsy can sometimes be made shortly after birth but is often postponed until the child is 18–24 months of age, in order to evaluate the functional status and the progression or regression of the symptoms [6].

Modern Approach of Treatment

The earlier treatment begins the better chance children have of overcoming developmental disabilities or learning new ways to accomplish the tasks that challenge them. Botulinum toxin injections are given into muscles that are spastic or sometimes dystonic, the aim being to reduce the muscle hypertonus that can be painful. A reduction in muscle tone can also facilitate bracing and the use of orthotics. Most often lower extremity muscles are injected. Botulinum toxin is focal treatment meaning that a limited number of muscles can be injected at the same time. The effect of the toxin is reversible and a reinjection is needed every 4–6 months. The earliest proven intervention occurs during the infant's recovery in the neonatal intensive care unit (NICU). Treatment may include one or more of the following: physical therapy; occupational therapy; speech therapy; water therapy; drugs to control seizures, alleviate pain or relax muscle spasms (e.g. benzodiazepines, baclofen and intrathecal phenol/baclofen); hyperbaric oxygen; the use of Botox to relax contracting muscles; surgery to correct anatomical abnormalities or release tight muscles; braces and other orthotic devices; rolling walkers and communication aids such as computers with attached voice synthesizers. For instance, the use of a standing frame can help to reduce spasticity and improve range of motion for people with CP who use wheelchairs [7].

Constraint-induced movement therapy (CIMT) has shown promising evidence in helping individuals with neurological disorders that have lost most of the use of an extremity. Positive benefits of CIMT realized for people who have had a stroke and traumatic brain injury. However, later studies have addressed the application of CIMT for children with CP challenged with hemiparesis that show a significant benefit in constraint induced movement therapy for children with cerebral palsy who are challenged with hemiparesis.

Physiotherapy programs are designed to encourage the patient to build a strength base for improved gait and volitional movement, together with stretching programs to limit contractures. Many experts believe that lifelong physiotherapy is crucial to maintain muscle tone, bone structure and prevent dislocation of the joints. Speech therapy helps control the muscles of the mouth and jaw and helps to improve communication. Just as CP can affect the way a person moves their arms and legs, it can also affect the way they move their mouth, face and head. This can make it hard for the person to breathe, talk clearly, bite, chew and swallow food. Speech therapy often starts before a child begins school and continues throughout the school years.

Although numerous treatments for drooling have been tested over the years, there is no one treatment that helps reliably. *Anticholinergic drugs* – such as glycopyrolate - can reduce the flow of saliva but may cause unpleasant side effects, such as dry mouth, constipation, and urinary retention [8].

Selective dorsal rhizotomy (SDR) is a surgical procedure recommended only for cases of severe spasticity when all of the more conservative treatments – physical therapy, oral medications, and intrathecal baclofen - have failed to reduce spasticity or chronic pain. In the procedure, a surgeon locates and selectively severs over activated nerves at the base of the spinal column.

Because it reduces the amount of stimulation that reaches muscles via the nerves, SDR is most commonly used to relax muscles and decrease chronic pain in one or both of the lower or upper limbs. It is also sometimes used to correct an overactive bladder. Potential side effects include sensory loss, numbness or uncomfortable sensations in limb areas once supplied by the severed nerve [9, 10].

Spinal cord stimulation was developed in the 1980s to treat spinal cord injury and other neurological conditions involving motor neurons. An implanted electrode selectively stimulates nerves at the base of the spinal cord to inhibit and decrease nerve activity [11]. The effectiveness of spinal cord stimulation for the treatment of cerebral palsy has yet to be proven in clinical studies. It is considered a treatment alternative only when other conservative or surgical treatments have been unsuccessful at relaxing muscles or relieving pain.

Therapeutic (Subthreshold) electrical stimulation, also called neuromuscular electrical stimulation (NES), pulses electricity into the motor nerves to stimulate contraction in selective muscle groups. Many studies have demonstrated that NES appears to increase range of motion and muscular strength [12].

Threshold electrical stimulation, which involves the application of electrical stimulation at intensity too low to stimulate muscle contraction, is a controversial therapy. Studies have not been able to demonstrate its effectiveness or any significant improvement with its use.

Hyperbaric oxygen therapy. Some children have cerebral palsy as the result of brain damage from oxygen deprivation. Proponents of hyperbaric oxygen therapy propose that the brain tissue surrounding the damaged area can be "awakened" by forcing high concentrations of oxygen into the body under greater than atmospheric pressure. The Food and Drug Administration has not approved hyperbaric oxygen therapy for the treatment of cerebral palsy. Some scientific studies report no added benefit from hyperbaric oxygen therapy for cerebral palsy. Further research is needed to determine the efficacy of this treatment for individuals with cerebral palsy [13].

Stem Cell Therapy

Stem cells are primitive cells that can either "self-renew" and expand by creating daughter stem cells of the same type or create mature cells with specific functions of any organ in the body. They have varying degrees of "potency" ranging from the ability to differentiate into every cell in the body, to only a few cell types. Regenerative medicine: a type of medicine focusing on the renewal, growth and restoration of a body part, organ or tissue. This aims to copy and repeat the normal growth and development of the body following an injury [14].

Transplanting stem cells into the brain could support and/or replace deteriorating brain tissue during the process of white matter damage in cerebral palsy. Animal models used in research on cerebral palsy have shown that many types of stem cells can be used to reduce damage and return. New technological improvements make it possible for skin cells to be taken from a patient and turned into the exact cell needed to repair injured tissue, getting rid of the need for tissue donor waiting lists and anti-rejection drugs [15].

Table 3: Applications of various stem cells in Cerebral Palsy

Transplantable Cells	Applications
Mesenchymal Stem Cell (MSC): Isolated from the umbilical cord (UC-MSC) or bone marrow (BM-MSC) of the patient or a matched family member	Able to travel to and change the injured environment, increasing survival of neurons and making up for losses.
Neural Precursor Cell (NPC): Exist in small numbers in the brain with great potential for regeneration	Quickly differentiate to replace supporting cells and lost myelin and send out signals that enhance repair.
Pluripotent Stem Cell: Taken from an early embryo (ESC) or induced from a patient's skin cell (iPSC)	Can be turned into any cell in the body, such as NPCs. Of these, iPSCs are the newest and least proven type, but also the most promising, as they are made completely from patient's own tissue, eliminating the need for donor lists, anti-rejection drugs and destruction of an embryo. These cells can be used most widely for many different types of injury.

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