

Cerebral Palsy

- [About cerebral palsy](#)
 - [Background](#)
 - [Symptoms & Diagnosis](#)
 - [Causes](#)
 - [Treatment](#)
- [How can stem cells help with understanding cerebral palsy?](#)
- [Research and clinical directions](#)
 - [Learning more about mesenchymal stem/stromal cells](#)
 - [Learning more about neural stem cells](#)
- [Future challenges](#)
- [Web Resources](#)
- [Selected Reading List](#)

About cerebral palsy

Background

As the most common childhood physical disability, cerebral palsy (CP) strikes approximately 2.5 of every 1000 live term births and increases to 22 of every 1000 live premature births, with more boys affected than girls. Cerebral palsy (CP) is not a single entity but rather an overarching term describing a group of permanent disorders that cause a range of life-long motor and posture-related impairments. Although a diagnosis of CP refers to problems with neural control of motor function, individuals may also have complications in behaviour, learning, epilepsy, communication, vision, hearing, perception and sensation.

The causes of CP are complex and not entirely understood. Many risk factors may be present and can be interrelated. Common risk factors include preterm birth, multiple births, shortage of oxygen (hypoxia) or blood supply (ischemia) and gestational infections/inflammation.

The range of motor disability experienced by people with CP is extremely variable. Because it is a permanent condition, many individuals will require intensive, life-long access to health services, social services and rehabilitative interventions. With no cure in sight, the ensuing burden to the individual, caregivers and healthcare system is substantial.

Symptoms & Diagnosis

Historically, the discovery of CP was considered a group effort: Dr. William John Little's pioneering insights in 1880 defined the condition, Sir William Osler recognized the spectrum of disease and coined the phrase 'cerebral palsy' and Sigmund Freud first postulated its preterm origin due to abnormal development.

The name 'cerebral palsy' describes both location and function, with 'cerebral' referring to the brain and 'palsy' referring to impaired motor control. There are two main subgroups of CP, spastic and dyskinetic. Spastic describes an increased muscle tightness and stiffness and together with descriptors indicates the extremities affected – quadriplegia (4 limbs), triplegia (3 limbs), hemiplegia (one side of the body). Dyskinetic refers to an involuntary movement disorder. The majority of individuals are classified as having spastic quadriplegia (35%), followed by spastic diplegia (21%) or spastic hemiplegia (21%) and a minority with dyskinetic CP (13%).

Individuals affected with CP exist within a continuum of severity – some requiring no daily assistance and living a normal life span, others requiring life-long care and having a higher chance of early mortality.

The most common injury observed in the white matter of the brain of individuals with CP is called 'periventricular leu-

Research is a dynamic activity that creates new ideas. It provides a forum for generating observations and testing why they occur. Because people and their diseases are so diverse, clinical trials are the ONLY WAY it is possible to test whether new ideas about how to diagnose or treat human disease will work. But the process of taking research from bench to bedside is a lengthy one and demands not only vision but also years of teamwork and dedication on the part of scientists, physicians and individuals with cerebral palsy.

This document presents basic information about cerebral palsy and frames the context for the discussion that follows about how stem cells could be used to better understand and eventually treat these disorders. Readers may also wish to peruse additional web resources or speak with their physicians for more information about cerebral palsy.

komalacia', which describes white matter cell death surrounding the motor pathways in the brain, effectively stripping the neural wiring of its protective insulating myelin sheath. This type of injury is most often present in premature babies. Alternatively, just like in adults, infants can have strokes or bleeds in the brain that injure and/or destroy neuronal cells. If the injury is on both sides of the brain, individuals can get bilateral involvement of the limbs. Injury on one side of the brain leads to decreased motor control on the opposite side of the body (hemiplegia).

The motor symptoms of CP typically begin to appear before the age of two and include lack of coordination when performing voluntary tasks, stiff, tight muscles or increased reflexes and stiff gait, dragging one foot or leg, walking on the toes, or floppy muscles. As a child with CP grows older musculoskeletal complications from having a brain injury can progress. Examples include hip dislocation and the development of a curve in the spine (scoliosis). In some children, spasticity in the legs may cause joints to dislocate and they will need surgery to set them back in place.

Although adults with CP are faced with many challenging prospects, such as worsening mobility, or increased pain/discomfort, most have a normal life expectancy. A shortened lifespan has been associated with the severity of the physical disability (for example the lack of the ability to roll) and the presence of seizures or a severe intellectual disability.

Because the spectrum of symptoms varies so considerably from person to person, there are guidelines that help the health professional to grade the severity of the disability. Clinicians use tools such as the Gross Motor Function Classification System and the Manual Ability Classification System to classify the severity of motor disabilities. Neuroimaging of the brain (for example, ultrasound images to detect bleeding in the brain and magnetic resonance imaging) provides more detail on the underlying brain abnormality.

Causes

The precise mechanisms and causes of CP are not yet known, but there are certain predisposing events or 'risk factors' that can occur during the perinatal period (around the time of birth) that have been associated with damage to the developing fetal and infant brain. The factors most often cited include ischemia, infections/inflammation, growth restriction before birth, preterm delivery and hypoxia after birth.

Studies have shown that gestational age is very important because the chance of developing CP decreases substantially when babies are born closer to term, from 0.1% in infants born at term to 14.6% in children born at 22-27 weeks. Infections and inflammation have consistently been identified as important risk factors. Examples of infectious agents include viruses (cytomegalovirus, rubella, herpes simplex, syphilis, HIV, varicella-zoster, lymphocytic choriomeningitis virus) and parasites (toxoplasma gondii - carried predominantly by cats) that can be transferred via the placenta from mother to baby to cause central nervous system damage.

Other causal associations include congenital abnormalities, genetic factors, vascular diseases, metabolic diseases and head injuries. The reproductive history of the mother may also play a role in that higher maternal age, tendency towards stillbirths and long intervals between menstrual periods have all been linked with the development of CP in children.

On the backdrop of such a long list of predisposing factors and tremendous variation in symptoms among individuals, understanding CP continues to be a great challenge. In only a minority of cases can its cause be directly identified. Adding to the complexity, many scientists believe that most cases of CP arise from a combination of predisposing genetic and environmental factors that work synergistically rather than independently to change the developing brain.

Treatment

There is no cure for CP. However, experts agree that earlier treatment translates into a greater likelihood of children learning new ways to overcome their disabilities. Rehabilitative strategies focus on exercise, occupational therapy, speech therapy, surgery and drugs. Collectively, these measures endeavor to control seizures, improve daily activities, as well as reduce muscle spasms and pain. Surgical interventions aim to correct anatomical abnormalities or release tight muscles. Many individuals with CP rely on braces, orthotics, wheelchairs, rolling walkers and communication aids as supports for ongoing ambulation and retention of daily activities.

There are currently two treatments shown to minimize or prevent damage in newborns at risk for CP. First, therapeutic hypothermia induces a controlled drop in body temperature and can act to minimize damage done by perinatal hypoxia-ischemia. The second is magnesium sulfate, which can stabilize oxygen supply to the baby and reduce potential damage during preterm labour.

Although these preventative and rehabilitative therapies exist, there is currently no biological therapy for CP. Exploration of stem cells as a possible cell replacement therapy represents one of many efforts being made to provide novel and more effective therapies to this group of individuals.

How can stem cells help with understanding CP?

The development of stem cell-based treatments for CP is still in its infancy. Researchers have many years of hard work ahead of them before they can achieve the ultimate goal of mobilizing stem cells into replacing, repairing or protecting cells that have been injured in the central nervous system of individuals with CP.

Many lessons have been learned from pre-clinical and early phase clinical studies on neurological conditions other than CP, such as spinal cord injury, multiple sclerosis, eye diseases and Parkinson's. Collectively, this body of research suggests that stem cells have neuroprotective and regenerative properties that could someday be harnessed to repair damaged neural tissue. There are many ongoing trials testing the safety of stem cells for treating these neurological conditions in pediatric and adult populations and scientists are eagerly awaiting the outcome to gauge whether the findings are relevant to CP.

The candidate stem cells being investigated in the lab for CP derive from a number of different sources including embryonic, fetal and adult tissue/blood. The two types of stem cells that show the most promise in preclinical laboratory models are mesenchymal stem cells (MSCs) and neural stem cells (NSCs; also called neural precursor cells). These stem cells are discussed in more detail below.

Research and clinical directions

Learning more about mesenchymal stem/stromal cells (MSCs)

Mesenchymal stromal/stem cells, or MSCs for short, are under extensive investigation for a number of reasons. Many tissues in the body contain MSCs and they are easily collected from bone marrow, fat and umbilical cord. Although they have the flexibility to differentiate in the laboratory into a few different specialized cell types, their possible role in regenerating damaged neural tissue is complex and appears to be unrelated to this property.

At present, there are a number of factors that make MSCs such an attractive therapy. Scientists know how to isolate them, and years of doing bone marrow transplants for leukemia has proven that they are relatively safe. MSCs can modulate the immune response, inhibit inflammation, stimulate blood vessel formation, and stimulate the small numbers of neural cell types that normally reside in the brain (termed, "endogenous" neural precursors). One of the most remarkable traits is that MSCs do not seem to cause the same degree of graft rejection that typically accompanies other types of donated stem cell transplants.

Although researchers have been able to show that MSCs can stimulate neural cell types in the brain and provide physical scaffolding for elongating nerve axons, there is still relatively little evidence for MSCs being relevant for repairing neural damage. Nevertheless, a small collection of clinical trials testing MSCs from bone marrow and umbilical cord blood in people with CP are underway. Researchers find cord blood advantageous to use in that it is easy to obtain with little risk to the donor and little chance of transmitting infectious viruses. The findings from these trials are eagerly awaited.

In the meantime there are lessons to be learned from the results pouring in from MSC trials for other diseases. One issue turning up is the remarkable variation in outcome from trial to trial and lab to lab. Going forward, scientists agree that it will be crucial to distinguish various MSC populations, in terms of their tissue of origin, biomarkers, response to different inflammatory conditions, as well as functionality across different laboratories, animal models and individuals. This knowledge will help researchers to design better clinical trials, taking into account many more known factors that

could impact MSC performance.

Learning more about neural stem cells (NSCs)

In 1992, Canadian researcher Samuel Weiss at the University of Calgary kindled great excitement in the field when he and his colleagues isolated a store of neural stem cells in the adult mammalian brain. These are present in very small numbers, as if in reserve, and much current research since then has been devoted to figuring out how to coax these cells into repairing the brain after injury. Weiss' work also showed that adult neural stem cells (also called neural precursor cells) in mice are active throughout life and can generate all three kinds of brain cells in vivo in response to injury: neurons (transmit electrical impulses), astrocytes (a type of support cell) and oligodendrocytes (cells that add a protective myelin cover to nerve fibres to increase their conductivity). These discoveries opened the door to the possibility of repairing neurological damage by transplanting neural stem cells or their progeny. More recently in 2013, work from the Fehlings laboratory demonstrated that injecting neural precursor cells into the injured brain and spinal cord could induce significant remyelination of nerve fibres lacking the insulation layer due to a genetic mutation.

In theory, two main strategies underpin the exploration of neural stem cells and the cells they make as potential therapies. The first type of repair is called 'endogenous', meaning inside the body. The idea here is to stimulate stem cells that are already present in the brain to heal damaged tissue. The other repair strategy is called 'exogenous', meaning outside the body; this approach harnesses the power of stem cells from donor tissue and cells. Exogenous stem cells are first harvested from donors and then manipulated in the lab prior to being transplanted. The harvested stem cells can be purified, expanded in number and differentiated into the type of cell required to repair damaged tissue.

Scientists are still optimizing pre-clinical studies on the utility of NSCs for CP. For example, they are trying to identify drugs that can optimally trigger expansion of NSCs in individuals, as well as better ways to expand or treat them in the laboratory before implanting them back into the individual. The method that works best in animal models uses exogenous NSCs, expanding them and injecting them directly into the animal's brain. In vivo, NSCs commonly differentiate down a single pathway to specialize into one of three cells of the nervous system (neurons, astrocytes or oligodendrocytes); research suggests that this might be skewed towards oligodendrocyte differentiation with perinatal versus adult transplants. Gene therapy is also being tested by investigators in the hope that inserting growth factors into NSCs will increase their capacity to protect damaged neurons in animal models of injury.

Scientists are continuing to learn about NSCs from studying other diseases and although they show much promise, their application to CP is not without challenges. First and foremost, they must be deemed safe for clinical use in humans and as yet there are still concerns (albeit increasingly minimal) over potential tumour formation or transplant rejection. Once safety concerns are addressed, timing and dosage must be optimized. In the case of exogenous transplantation, the ideal number of cells and location of delivery must also be determined. Additionally, as with all exogenous cell transplants, strategies to enhance survival must also be utilized. The transition from 'bench' to 'bedside' is challenging, yet the exciting work being undertaken suggests that stem cells as a therapy for CP and other neurodegenerative diseases is a realistic goal.

Future Challenges

At the same time that preliminary stem cell trials for CP are unfolding, scientists agree that more work needs to be done to address the long list of challenges that present themselves at the basic research level. For example, they are still trying to understand more about how best to grow and differentiate stem cells in vitro and how to stimulate the small number of brain-resident stem cells in vivo.

Transplantation studies in animal models have shown some benefits but the exact mechanism of action of the stem cells is still somewhat nebulous as not many of the transplanted cells actually go on to survive. Mechanisms that may account for a stem cell effect include their ability to promote blood vessel formation, differentiate into support cells of the brain (astrocytes or oligodendrocytes), increase survival of brain cells, or block the spleen's normally inflammatory response to injury – depending on the type of stem cell utilized.

Another important issue that delays research progress is the lack of good animal models for CP. Because there are so many ways to acquire CP damage and because symptoms reveal themselves in such different ways, it is difficult

to develop animal models that can cover all of the varying symptoms associated with the broad “CP” diagnosis. While a number of different animal models of acute brain injury or motor deficiency are being used as cross-disciplinary research, very few of these models mimic the type of chronic injury that would be observed in CP in humans. Researchers are therefore prioritizing the development of better animal models of CP that will provide a more accurate landscape on which to test the different candidate stem cells.

Lastly, it is currently unknown how many stem cells will produce the most benefit, what timing after injury to transplant them, or where and by what method they should be administered to produce optimal results. These are but a few of the many issues being addressed in the lab. The ongoing results should help to design better, more targeted clinical trials that safely assess the potential of stem cells for treating individuals with CP.

Overall, discoveries in stem cell and CP fields are advancing at a pace; with the first clinical trials underway, we could see real world results in the next several years. It is, therefore, essential that scientists, clinicians, policymakers, families and individuals with CP work together to maintain the iterative dialogue necessary to successfully move this strategy forward from bench to bedside.

Web Resources

Readers may wish to peruse the recommended sites or review the selected reading list below for more information about the application of stem cells to treat CP.

- EuroStemCell: <http://www.eurostemcell.org/factsheet/cerebral-palsy-how-could-stem-cells-help>
- The Fehlings Laboratory for Neural Repair and Regeneration: DrFehlings.ca
- NeuroDevNet: <http://www.neurodevnet.ca/>
- Ontario Federation for Cerebral Palsy: <http://www.ofcp.ca/>
- National Institute of Neurological Disorders and Stroke: http://www.ninds.nih.gov/disorders/cerebral_palsy/cerebral_palsy.htm

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