At the PMG Conference 2018, Dr Sarah Mason (University of Cambridge) presented a talk entitled “*Cell transplantation research into Huntington’s and Parkinson’s diseases”,* outlining the pathological and clinical features of each, and current treatments for both, before expanding on what cell replacement therapies are and how they have been used in trials for Parkinson’s and Huntington’s diseases to date.

Huntington’s and Parkinson’s diseases are both progressive, neurodegenerative disorders involving the basal ganglia, categorised largely by the effect they have on movement. Huntington’s disease predominantly affects the caudate and putamen of the basal ganglia, which primarily mediate motor function and certain executive cognitive functions in addition to involvement in the reward system (Malenka, et al., 2009). Outputs from this region are mainly composed of medium spiny neurons, described as GABAergic neurons, which have inhibitory action at receptors; the loss of these neurons gives rise to the hyperkinetic motor effects (Siegel & Sapru, 2014). Dr Mason described the resultant symptoms, which include: changes to saccadic eye movements; unusual posturing; wide gait; poor balance; choreic movements; difficulty swallowing; and slurred speech. In contrast, Parkinson’s disease affects a different part of the basal ganglia; the pars compacta of the substantia nigra, the most prominent function of this region being motor function. The loss of dopaminergic neurons in this region leads to a reduction in dopamine in the striatum (Siegel & Sapru, 2014); giving rise to a variety of symptoms. Symptoms highlighted during the talk were: stooped posture; rigidity; flexed elbows and wrists; trembling of extremities; shuffling; short-stepped gait; slightly flexed hips & knees; reduced arm swinging; forward tilt of trunk; and masked facial expressions.

Symptoms of the two diseases are not restricted to motor function. Non-motor symptoms can include sleep abnormalities; hallucinations; depression, anxiety and apathy; and cognitive problems. Combinations of these symptoms often cause a significant impact on a patient’s everyday life and, crucially, on their independence. Unfortunately, there is currently no disease modifying therapies; therefore treatment heavily relies on pharmaceuticals (and deep brain stimulation, in the case of Parkinson’s) which have associated side effects and decreased "usefulness" over time. As such, finding long-term management for these problems is greatly needed to improve the quality of life of these patients.

Cell transplantation is the key novel, experimental approach discussed by Dr Mason.  It aims to replace lost neurons in Parkinson’s and Huntington’s disease by replacing the dead cells with healthy ones to restore functional loss that resulted. It was highlighted that this form of therapy works best for certain conditions or disease, where:

* there is a focal loss of a defined set of neurons
* the affected neurons have a relatively non-specific modulatory actions
* the function of the neurons doesn’t depend on precise and complex patterned connectivity

Previously the source of tissue for cell transplantation had been from ventral mesencephalic tissue taken from donor embryos of terminated pregnancies.  The tissue is homogenised for transplantation, then injected into required regions of the basal ganglia along with immunosuppressant’s to reduce the risk of rejection (Angot, et al., 2010).

Clinical Trials

Dr Mason gave an overview of several clinical trials, and corresponding results, that has been carried out so far.  The first trial for cell transplantation in Parkinson’s disease began in 1987 in Sweden which was an “open label study” involving a 15 patient cohort with variable results, however, 2 patients did show positive effects.  Double-blind controlled clinical trials have since been carried out in Parkinson’s disease with mixed results; a 34 patient trial published in 2003 concluded that based on their results, “foetal nigral transplantation currently cannot be recommended as a therapy for PD” (Olanow, et al., 2003), whereas a 40-patient trial published in 2001 concluded that by using human embryonic dopamine neurons, grafts did survive in patients and some positive results were seen in younger patients (Freed, et al., 2001).

The first trials for Huntington’s disease began in the late 1990s, Dr Mason tells us that there have been 7 open-label studies worldwide and have helped to establish the safety, feasibility and tolerability of cell transplantation in Huntington’s disease - however she reports that the efficacy results are much less conclusive than for Parkinson’s.  In certain patients, Huntington’s “dots” (pathologies) were visible in the grafts after time and so gives rise to the question; what allowed it to transfer into the healthy tissue?

Overall, Dr Mason explained that it is possible to successfully graft transplanted cells which survive, however functional restoration is not consistently observed in all patients.  There are several factors that could influence the outcome of these grafts, such as: tissue survival, protocols for preparing the tissue, variation in the source tissue supplied to each patient, and different patient populations for example age, severity of disease, rate of progression, other treatment patient may be undergoing related to disease and lifestyle.  It can be difficult to determine which aspects are most influential and whether this would differ from patient to patient. TRANSEURO is a research consortium consisting of experts that include clinicians, scientists, industrial partners, ethicists and patient representatives. Their principal objective is to “develop and efficacious and safe treatment methodology for patients suffering from Parkinson’s disease using cell based treatments” (TRANSEURO, 2017).  In the talk, their work was described as the next generation, and some examples of the work they are carrying out were given. They are trying to answer questions about how certain factors influence the treatment; “Are there some patients who are more likely to benefit and less likely to experience side-effects from cell replacement therapies?” this is being assessed by reviewing all current data from existing trials for patient meeting a certain criteria; another example “Does the way the tissue is prepared influence the efficacy of the trials and the likelihood of side-effects?” this currently has 11 patients that has undergone a new approach and are being followed up.

One of the key limitations discussed, regarding the foetal tissue approach, concerns the ethics surrounding sourcing and using foetal tissue and whether the supply is sustainable.  In an attempt to address these problems, alternative sources have been explored. We were told of Human Embryonic Stem Cell (hESC) - derived dopaminergic cells that have been developed, these cells have now reached the stage of being ready for clinical trials.

Myself and colleagues found the talk very interesting and thought provoking; although not directly related to my work at the wheelchair service, we do see a lot of patients with life-limiting conditions and so it was interesting to see an alternative approach to treatment.  The reasoning behind finding alternative treatments for Parkinson’s and Huntington’s diseases described in the talk was largely centred on improving quality of life of patients. Working in posture and mobility services we are constantly trying to improve a patient’s quality of life, whether that be through clinical assessment and equipment provision, modification and adaptation, postural management, and by identifying areas where a need is not met.  We try and achieve this by improving independence and reducing the impact on a patient’s everyday life, a shared goal with cell transplantation therapies.

Thank you to Dr Mason for delivering this talk that allowed me to see potential interventions that lie outside my usual field of work, and therefore I may not have seen.  Personally, it demonstrated how important research can be in trying to improve patient treatment. Unfortunately we don’t always get time or funding to get involved in research - but it has encouraged me to question more when there is a need not met or where there may be opportunities for further work.

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