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Stem Cell-Based Therapies for Parkinson's Disease

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Description

Recent news of an impending clinical cell transplantation trial in Parkinson's disease using parthenogenetic stem cells as a source of donor tissue have raised hopes in the patient community and sparked discussion in the research community. Based on discussions held by a global collaborative initiative on translation of stem cell therapy in Parkinson's disease, we have identified a set of key questions that we believe should be addressed ahead of every clinical stem cell-based transplantation trial in this disorder. In this article, we first provide a short history of cell therapy in Parkinson's disease and briefly describe the current state-of-art regarding human stem cell-derived dopamine neurons for use in any patient trial. With this background information as a foundation, we then discuss each of the key questions in relation to the upcoming therapeutic trial and critically assess if the time is ripe for clinical translation of parthenogenetic stem cell technology in Parkinson's disease. Stem cell-based therapies for Parkinson's disease (PD) are rapidly moving towards clinical trials. Several academic and industry efforts are well under way to produce dopaminergic neurons from stem cells under conditions compliant with use in patients. In December 2015, a press release announced a Phase I/IIa trial in PD using a parthenogenetic stem cell source, resulting in widespread excitement about stem cell therapy for PD in traditional print media, social media and especially in the PD patient community(1).

The Clinical Symptoms of Parkinson's Disease

In this review, the clinical features of Parkinson's disease, both motor and non-motor, are described in the context of the progression of the disease. Also briefly discussed are the major treatment strategies and their complications.Parkinson's disease is a slowly progressing neurodegenerative disorder, causing impaired motor function with slow movements, tremor and gait and balance disturbances. A variety of non-motor symptoms are common in Parkinson's disease. They include disturbed autonomic function with orthostatic hypotension, constipation and urinary disturbances, a variety of sleep disorders and a spectrum of neuropsychiatric symptoms. This article describes the different clinical symptoms that may occur and the clinical course of the disease [1].

Parkinson's Disease (PD) is a progressive multi-system neurodegenerative disease affecting people mainly in later years of life. It is the second most common neurodegenerative disease worldwide with incidence and prevalence on the rise along with changing population demographics (Pringsheim et al. 2014). The prevalence of PD in industrialised countries is generally estimated at 0.3% of the entire population and about 1% in people over 60 years of age (De Lau and Breteler 2006).

The prevalence increases with advancing age both for men and women with no decreases at higher ages (De Rijk et al. 1997). In Europe, the prevalence at ages 85–89 has been reported as 3.5% (Clarke and Moore 2007).

The disease has distinctive neuropathological brain changes. There is formation of abnormal proteinaceous spherical bodies called Lewy bodies and a spindle- or thread-like and, in part, branching Lewy neurites in the somata of the involved nerve cells, beginning at defined induction sites and advancing in a topographically predictable sequence within the nervous system (Braak et al. 2004). Braak et al. (2003) have mapped PD into six neuropathological disease stages. In the pre-symptomatic stages of the disease (stages 1–2), the inclusion bodies are confined to the medulla oblongata/pontine tegmentum and olfactory bulb/anterior olfactory nucleus. With progression of the disease, substantia nigra and other nuclei of the midbrain and forebrain become affected (stages 3–4). It has been suggested that patients develop clinical symptoms of the disease at this stage. In the end stage (stage 5–6), the process enters the neocortex with a wide variety of clinical manifestations (Braak et al. 2004). The degeneration of dopaminergic nigrostriatal neurons with Lewy bodies is regarded as the primary neuropathological correlate of motor impairment in Parkinson's disease, but glutamatergic, cholinergic, GABA-ergic, tryptaminergic, noradrenergic and adrenergic nerve cells may show similar damage in their cytoskeleton (Braak and Braak 2000). The clinical symptoms of PD are usually defined by the motor disturbances, but there may be disturbances in several other functions of the nervous system. The symptoms are generally categorized into motor and non-motor symptoms, and some of the symptoms may be provoked or aggravated by the dopaminergic treatment [2]. Parkinson's Disease (PD) is a heterogeneous neurodegenerative disorder that affects an estimated 10 million sufferers worldwide. The two forms of PD include familial and sporadic, and while the etiology of PD is still largely unknown, the condition is likely to be multifactorial with genetic and environmental factors contributing to disease genesis. Diagnosis of the condition is attained through the observation of cardinal clinical manifestations including resting tremor, muscle rigidity, slowness or loss of movement, and postural instability. Unfortunately, by the time these features become apparent extensive neurological damage has already occurred. A cure for PD has not been identified and the current therapy options are pharmaceutical- and/or surgical-based interventions to treat condition symptoms. There is no specific test for PD and most diagnoses are confirmed by a combination of clinical symptoms and positive responses to dopaminergic drug therapies. The prevalence and incidence of PD vary worldwide influenced by several factors such as age, gender, ethnicity, genetic susceptibilities, and environmental exposures. Here, we will present environmental factors implicated in sporadic PD onset. By understanding the mechanisms in which environmental factors interact with, and affect the brain we can stride toward finding the underlying cause(s) of PD [3].

Although the identification of a marker for diagnosis and for disease progression (preferably one that is non-invasive, affordable and accessible) is of utmost importance, concepts like Quality of Life (QoL) are also very important in chronic diseases, such as PD, for which a cure does not exist . Improving patient QoL and identifying factors that lead to caregiver burden are very important aspects of the management of PD. In particular, the role of the principal caregiver in PD is very important because caregiver burden generates poor care

and, in the long term, leads to patient institutionalization. Specifically, identifying the changes experienced by PD patients and their caregivers in their QoL and degree of burden, respectively, over time, as well as factors that may predict these changes, in order to carry out a proper intervention, should be a priority. Well-designed, longitudinal prospective studies are key. Access to a population with a high proportion of patients who have been assessed comprehensively and rigorously, without screening bias, is highly valuable for both cross-sectional analysis and prospective follow-up. This is especially relevant for studying populations affected by a neurodegenerative disease, given that these patients are expected to develop different complications that we could identify and analyze[4].

Management of Parkinson's Disease (PD) is complicated due to its progressive nature, the individual patient heterogeneity, and the wide range of signs, symptoms, and daily activities that are increasingly affected over its course. The last 10–15 years have seen great progress in the identification, evaluation, and management of PD, particularly in the advanced stages. Highly specialized information can be found in the scientific literature, but updates do not always reach general neurologists in a practical and useful way, potentially creating gaps in knowledge of PD between them and neurologists subspecialized in movement disorders, resulting in several unmet patient needs. However, general neurologists remain instrumental in diagnosis and routine management of PD. This review provides updated practical information to identify problems and resolve common issues, particularly when the advanced stage is suspected. Some tips are provided for efficient communication with the members of a healthcare team specialized in movement disorders, in order to find support at any stage of the disease in a given patient, and especially for a well-timed decision on referral [5]

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