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J Neurol Clin Neurosci, ISSN: 2752-809X,
Volume 06

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Intrinsic lrrk2 Parkinson's disease phenotypes using patient specific iPSC-derived models

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Neuroinflammation is increasingly recognized to be a crucial but poorly understood element of Parkinson's disease (PD) pathogenesis and progression. Astrocytes and microglia have inflammatory roles in injury or neurodegeneration. We previously reported that astrocytes derived from LRRK2G2019S (LRRK2) PD patient iPSCs exhibit disease phenotypes including alpha-synuclein (aSYN) accumulation and toxicity to mDa neurons. Here, we sought to confirm these phenotypes in an independent cohort. Second, we asked if LRRK2 microglia exhibit PD phenotypes. We derived astrocytes from three LRRK2-PD patient and healthy control donor iPSCs, and performed immunofluorescence (IF)and RNASeq, and co-culture with mDa neurons. We then derived microglia from this cohort and performed IF and quantitative image analysis (Imaris). Additionally, we used several phenotypic assays (phagocytosis, motility (Incucyte), cytokine analysis (Luminex)) and live imaging (iSIM super-resolution, phase contrast, and holotomography). Here we confirmed LRRK2 astrocyte-neurotoxicity in a new cohort of ISPC lines and show an increased inflammatory profile. In microglia we also identified several phenotypes in LRRK2-PD microglia: aSYN nuclear localization was increased in LRRK2-PD microglia compared to controls whereas abundance of lysosomal receptor involved in chaperone mediated autophagy, LAMP2A, was decreased. We made several observations about the development and cell biology of iPSCderived microglia and functional analyses are underway. LRRK2 mutations perturb the cell-intrinsic cell biology and function of human astrocytes and microglia, including inflammatory tone. Further studies will better define these perturbations as well as the dialog between astrocytes, microglia, and neurons.

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J Neurol Clin Neurosci, ISSN: 2752-809X,
Volume 06

Environmental exposure induced Epigenetic Transgenerational Inheritance of Neurological Disease: Generational Disease Etiology

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Transgenerational effects of environmental exposures of abnormal nutrition, stress, or toxicants significantly amplify the biological impacts and health hazards of these exposures. One of the most sensitive periods to exposure is during fetal gonadal sex determination when the germ line is undergoing epigenetic programming and DNA re-methylation occurs. Previous studies have shown that toxicants (e.g. glyphosate) can cause an increase in adult onset disease such as kidney, prostate, ovary and infertility disease, cancers, obesity and behavior abnormalities. Interestingly, this effect is transgenerational (F1, F2, F3 and further generations) and due to a permanent (imprinted) altered epimutation of the germline. The transgenerational epigenetic mechanism appears to involve the actions of an environmental exposure at the time of sex determination to permanently alter the epigenetic (e.g. DNA methylation) programming of the germ line that then alters the transcriptomes of developing organs to induce disease susceptibility and development transgenerationally. In addition to DNA methylation, alterations in sperm ncRNAs and histone retention have also been observed. A variety of different environmental compounds have been shown to induce this epigenetic transgenerational inheritance of disease including: fungicide vinclozolin, plastics BPA and phthalates, pesticides, DDT, dioxin, hydrocarbons and herbicides like atrazine and glyphosate. Interestingly, exposure specific epigenetic alterations were observed between the specific exposures. Recently we have identified in human's epigenetic biomarkers for parental germ cell transmission of offspring disease states such as infertility, autism and arthritis. The suggestion that environmental exposures and toxicants can reprogram the germ line to induce epigenetic transgenerational inheritance of disease (e.g., neurological abnormalities), is a new paradigm in disease etiology, and indicates generational disease etiology needs to be assessed in the future.

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J Neurol Clin Neurosci, ISSN: 2752-809X,
Volume 06

Case Report: Successful management of internal carotid artery transection secondary to a gunshot wound and subsequent malignant MCA syndrome

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There are over 100,000 strokes each year in the UK. A very small proportion of these can be attributed to gunshot wounds and subsequent surgical intervention. We present a rare case of a 24-year-old male patient admitted to the Emergency Department having sustained a gunshot wound to the left side of his neck. Initial imaging and surgical exploration revealed significant left sided vertebral artery damage and a complete transection of the internal carotid artery. Following damage control surgery (DCS), the patient was admitted to ITU but had an acute neurological deterioration and was found to have suffered malignant middle cerebral artery (MCA) syndrome, requiring an urgent decompressive craniectomy. The patient's NIHSS at this stage was 26. After a prolonged ITU stay and repatriation to a local stroke unit for intensive therapies input, the patient walked out of hospital independently on day 106, with an improved NIHSS of 3. This case report aims to highlight the rarity of an ischaemic stroke, secondary to the damage control surgery required for a near fatal gunshot wound; along with the importance of timely recognition of an acute deterioration following artery ligation. Additionally, it aims to examine the life-saving surgical management of malignant MCA syndrome and in turn the significance of the shared decision making process between clinicians, the patient and family members, due to the high rate of poor functional outcomes following this major surgery.

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J Neurol Clin Neurosci, ISSN: 2752-809X,
Volume 06

What is intensity and how can it benefit exercise intervention in People with Stroke (PwS) - a rapid review of the literature

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Stroke is one of the major causes of chronic physical disability in the UK, typically characterised by unilateral weakness and a loss of muscle power and movement quality. When combined with pre-existing comorbidities such as cardiac and diabetic disease, it results in reductions in cardiovascular fitness, physical activity levels, functional capacity and levels of independence in day to day living. High intensity training protocols have shown promising improvements in fitness and function for People with Stroke (PwS). However, it remains unclear how intensity is defined, measured and prescribed in this population. Further, we do not know what the optical outcome measures are to capture the benefits of intensive exercise. A rapid review of the literature was undertaken to provide an evidence synthesis that would provide more timely information for decision making (compared with a standard systematic review). Electronic databases were searched (including Medline, PubMed, CINHAL and Embase for studies from 2015 to 2020. These were then screened by title and abstract for inclusion if they were a) specific to adult PwS and b) were high intensity exercise interventions. Eligible studies were critically appraised using the MMAT. Seventeen studies were selected for review, fifteen primary research studies and two literature reviews. Sixteen of the seventeen studies were high quality. Nine of the primary research studies used bodyweight supported treadmills to achieve the high intensity training threshold, four used static exercise bikes and two used isometric arm strengthening. Five of the primary research studies had the aim of increasing walking speed, five aimed to increase cardiovascular fitness, three aimed to improvement to brain activity and two investigated the changes in muscle strength. Although only one study gave a clear definition of intensity, all studies clearly defined the high intensity protocol used, with most (15 out of 17 studies) clearly describing threshold periods of high intensity activity, followed by a rest or active recovery periods (of varying times. All of the studies reviewed used outcomes specific to body structure and function (ICF domains), with fewer included outcomes relating to activity and only three outcomes relating to participation. There is a clear lack of definition and understanding about intensity and how thresholds of intensity in this population are used as an intervention. There is also an inconsistency into the appropriate methods to assess and provide a training protocol based on that assessment. It remains unclear if high intensity training impacts the desired body system, given the diverse issues PwS can present with, from a neurological, muscular, cardiovascular, functional and psychosocial perspective. Future work needs to establish a clearer understanding of intensity and its impact on exercise training on multiple body systems in PwS.

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Molecular Pathogenesis and Neuroinflammation in Parkinson Disease beyond Alfa-synuclein

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Various mechanisms play an essential role in the pathogenesis of Parkinson's disease, including a disruption of the cellular energy balance (mitochondrial dysfunction) and oxidative stress and disruption of protein breakdown (lysosomal and proteasomal dysfunction). The protein α-synuclein plays a central role in the pathogenesis of Parkinson's disease and is involved in many intracellular functions or their disruption in Parkinson's disease. A number of important cellular processes are inhibited by aggregated α-synuclein. The disruption of these processes, in turn, leads to increased aggregation of α-synuclein. Therefore, protein misfolding, aggregation, and accumulation of aggregated α-synuclein is a key feature of Parkinson's disease. In the course of the disease, there is an inflammatory reaction in the brain (neuroinflammation), in which mainly microglial cells are involved. The exact triggers of neuroinflammation are not known. However, it is known that aggregated α-synuclein and neuromelanin are able to activate microglia. In the course of neuroinflammation, there is a change in the expression of toll-like receptors (TLR) on the microglial cells. Hence, in Parkinson's disease, both the aggregation of proteins, primarily α-synuclein and one that occurs during the course of the disease play a role in neuroinflammation with microglial activation in the brain of Parkinson's patients playing a role in the pathogenesis of the disease.

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Neurodegenerative Disorders and botanicals as therapeutics in Indian system of medicine

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Neurodegenerative disorders are the neural impairedness in the aged & old people or a result of injury to the head is young people which primarily remain unnoticed until manifestation of disease in form of visible sign and symptoms or the ischemic changes in the radio diagnostics. Parkinson's disease (PD) is a complex multi-system, neurodegenerative disease. Though predominantly perceived as a motor disease, it also has debilitating non- motor features, which are frequently missed and not treated. Major treatment goals are to increase striatal dopamine levels with precursor-substitution and/or reduce its breakdown. As the disease progresses, a steady increase in the dose of levodopa is inevitable. However, higher doses cause motor complications of dyskinesia and dystonia and compromise medical treatment. Indian system of medicine offers a natural source of levodopa - the seeds of Mucuna pruriens L which have a long-standing safe use in the condition. Its clinical studies have shown pharmacokinetic profile distinct from synthetic levodopa, which is likely to reduce the untoward motor complications. Additionally, its seed extracts have shown neuroprotective benefits which are unrelated to levodopa. Medicinal plants used in Ayurveda have been subjected to exploratory studies with promising early results in the condition. Effects of medicinal plants Withania somnifera (L.) and Curcuma longa (L) in Parkinson's disease related models have been documented beneficial. We have also shared a shortlist of medicinal plants most likely to be useful in management of specific features of the disease such as cognitive decline, mood disorders, risk of osteoporosis amongst others. Medicinal plants like Mucuna pruriens (L.) and Withania somnifera (L.) have been used in traditional Ayurvedic medicine to manage neurodegenerative diseases like Parkinson's disease.

Aim: The aim of this article is to share the role of Ayurveda's insights, traditional usage and contemporary investigations for translational, integrative applications to manage Idiopathic Parkinson's Disease. Materials and methods: High impact journals for Parkinson's diseases, traditional textbooks from Ayurveda as well as relevant clinical and para clinical studies with botanicals are selectively incorporated to evolve the aforesaid translational application.

Conclusion: Ethnopharmacological relevance and contemporary understanding and existing therapeutic gaps can be filled by making use of Ayurveda with its medicinal plants and treatment approaches, can strengthen the therapeutic armamentarium of PD to improve clinical outcomes, if these leads are systematically further investigated by well-designed longer-term studies.

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J Neurol Clin Neurosci, ISSN: 2752-809X,
Volume 06

Improving outcome in subclinical manifestations of Neuronal Degeneration and Parkinson's Disease

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The neuropsychological aging changes are evident on the functional level in form of cognition and memory impairment due to changes in neurotransmitters and various receptors. Many older adults suffer with a decline in attentional abilities. Whereas the deficit in orientation is an initial and common symptom. The recent research suggests that normal aging is usually not associated with significant declines in orientation, a mild deficit, though, may be a part of normal aging. A significant decline in orientation may point to underlying Parkinson's disease. The measures to retard cognitive decline with aging may help in improving the outcome for Parkinson's disease patients. Studies of cognitive reserve link the specific biological, genetic, and environmental factors that make one person susceptible to cognitive decline. Certain factors and measures appear to delay the cognitive decline associated with the aging process. Some of these are specific, such as, high level of education, staying intellectually engaged in mental activities and maintaining social and friendship networks, and underline the importance of regular intellectual exercise. Whereas other non-specific factors that delay the aging process, like maintaining a healthy diet, including omega-3 fatty acids, and protective antioxidants may help in improving the outcome in Parkinson's disease. A low to moderate alcohol intake may stimulate the areas related to cognitive function and appears to improve cognitive decline. But it should be remembered that the elderly people are also sensitive to the toxic effects of alcohol on the brain. A regular physical exercise aiming for fitness in general, is a measure to keep healthy, including cognitive health. It increases the executive functioning and reduces the aging-related expected decline of white and grey tissue density. At individual level, the healthy lifestyle that reduces cardiovascular risk, will also benefit the brain. Optimal medical care in this context, offers a protection in terms of cognitive decline with help of anti-hypertensives, antiplatelet, and lipid lowering agents. The calorie restriction (CR) is needed to be mentioned as a tool to prevent or slow down aging process, cognitive decline, and outcome in underlying Parkinson's disease with subclinical manifestations The CR appears to protect the brain against aging and neurodegeneration through increased activities of plasma membrane redox enzymes (PMRS) like NADH-ascorbate free radical reductase, NADH-quinone oxidoreductase 1, NADH-ferrocyanide reductase, NADH-coenzyme Q10 reductase, and NADH-cytochrome c reductase and antioxidants like α-tocopherol and coenzyme Q10. The age-related increases in PM lipid peroxidation, protein carbonyls, and nitrotyrosine are attenuated by CR. Further, CR has been shown to lower the rate of production of free radicals by mitochondria and to protect cells against oxidative stress. The CR has been proven to reduce metabolic rate and oxidative stress, improves insulin sensitivity, and alters neuroendocrine and sympathetic nervous system function. CR, thus, appears to attenuate age-related deficits in brain function and protect neurons and may help outcome in neurodegenerative diseases including Parkinson's disease.

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