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An overview on parkinson disease and its pharmacological evaluation methods

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ABSTRACT

Researchers have explored a diversity of clinical and laboratory tests in efforts to differentiate Parkinson's disease patients from a healthy population multi factorial disease known to result from a variety of factors. Age is the principal risk factor; other etiological mechanisms have been identified, including gene mutations and exposure to toxins. Deregulation of energy metabolism, mostly through the loss of complex I efficiency, is involved in disease progression in both the genetic and sporadic forms of the disease. In support to data analysis, a mathematical model of the relevant metabolic pathways was developed and calibrated onto experimental data. Diagnosis of Parkinson disease (PD) and risk factors or early symptoms amenable to population-based screening, systematic review and meta-analysis of risk factors for Parkinson's disease.

Keywords: Parkinson's Disease, Symptoms, Animal Models.

INTRODUCTION

Parkinson's disease (PD) is classically defined by the progressive degeneration of the dopaminergic nigro striatal pathway and by the emergence of rigidity, tremor, and bradykinesia.(1)Staging of brain pathology related to sporadic Parkinson's disease.(2) Parkinson disease is also accompanied by non-motor symptoms, including olfactory loss, cognitive decline, depression and anxiety, which frequently appear in the early stages or even during the pre-motor phase of the disease (3) The rate of cognitive decline in Parkinson disease (4) Non-motor symptoms of Parkinson's disease dopaminergic patho physiology and treatment. Non-motor symptoms of Parkinson's disease dopaminergic patho physiology and treatment.(5,6)

The major pathological hallmarks of Parkinson's disease include the progressive loss of dopaminergic neurons in the substantia nigra pars compacta, a dramatic reduction in striatal dopamine levels and the presence of neuronal proteinaceous aggregates called Lewy bodies [7,8]. Accumulating evidence suggests that a variety of factors, including oxidative stress, mitochondrial dysfunction and apoptosis, are involved in the pathogenesis of Parkinson's disease.[9,10,11,12] Most of our current knowledge on the potential pathogenic and pathophysiological mechanisms of Parkinson Disease derives from innumerable studies conducted, in the past four decades, on experimental models of Parkinson Disease.(13)

The strongest associations with later diagnosis of Parkinson's disease were found for having a first-degree

or any relative with Parkinson's disease relative with tremor, constipation (relative risk, or lack of smoking history , each at least doubling the risk of Parkinson disease. Further positive significant associations were found for history of anxiety or depression, pesticide exposure, head injury, rural living, beta-blockers, farming occupation, and well-water drinking, and negative significant associations were found for coffee drinking, hypertension, non steroidal anti-inflammatory drugs, calcium channel blockers, and alcohol, but not for diabetes mellitus, cancer, oral contraceptive pill use, surgical menopause, hormone replacement therapy, statins, acetaminophen or paracetamol, aspirin, tea drinking, history of general anesthesia, or gastric ulcers. In the systematic review, additional associations included negative associations with raised serum urate, and single studies or studies with conflicting results. The strongest risk factors associated with later Parkinson's disease diagnosis are having a family history of Parkinson's disease or tremor, a history of constipation, and lack of smoking history.

TYPES OF PARKINSON'S DISEASE

Parkinsonian syndromes can be divided into four subtypes according to their origin: primary or idiopathic, secondary or acquired, hereditary Parkinsonism, and Parkinson Plus Syndromes or multiple system degeneration.[(14)]

In recent years several genes that are directly related to some cases of Parkinson's disease have been discovered. As much as this conflicts with the definition of Parkinson's disease as an idiopathic illness, genetic Parkinsonism disorders with a similar clinical course to Parkinson Disease are generally included under the Parkinson's disease label. The terms "Familial Parkinson's disease" and "Sporadic Parkinson's Disease" can be used to differentiate genetic from truly idiopathic forms of the disease.[(15)]

It is classified as a movement disorder. They include multiple system atrophy, progressive supra nuclear palsy, cortico basal degeneration and dementia with Lewy bodies.[(16)] Abnormal accumulation of alpha-synuclein protein in the brain in the form of Lewy bodies, as opposed to other diseases such as Alzheimer's disease where the brain accumulates tau protein in the form of neuro fibrillary tangles.[11] In clinically overlap between tauopathies and synucleinopathies.[(17)]

SYMPTOMS OF PARKINSON'S DISEASE

Parkinson's disease affects movement, producing motor symptoms. Non-motor symptoms, which include autonomic dysfunction, neuropsychiatric problems (mood, cognition, behavior or thought alterations), and sensory and sleep difficulties, are also common. Some of these non-motor symptoms are often present at the time of diagnosis and can precede motor symptoms. [(14)]

MOTOR SYMPTOMS

Four motor symptoms are considered cardinals in Parkinson Disease are tremor, rigidity, slowness of movement, and postural instability.

Tremor is the well-known symptom. It is usually a rest tremor: maximal when the limb is at rest and disappearing with voluntary movement and sleep. It affects to a greater extent the most distal part of the limb and at onset typically appears in only a single arm or leg, becoming bilateral later. Frequency of Parkinson Disease tremor is between 4 and 6 hertz (cycles per second).

Bradykinesia (slowness of movement) Bradykinesia is commonly a very disabling symptom in the early stages of the disease. [(18)] Clinical evaluation is based in similar tasks such as alternating movements between both hands or both feet. Bradykinesia is not equal for all movements or times. It is modified by the activity or emotional state of the subject, to the point that some people are barely able to walk yet can still ride a bicycle. [(14)]

Rigidity is stiffness and resistance to limb movement caused by increased muscle tone, an excessive and continuous contraction of muscles. The combination of tremor and increased tone is considered to be at the origin of cogwheel rigidity.[19] Rigidity may be associated with joint pain; such pain being a frequent initial manifestation of the disease.

Postural instability is typical in the late stages of the disease, leading to impaired balance and frequent falls,[20]and secondarily to bone fractures.[5] Up to 40% may experience falls and around 10% may have falls weekly, with number of falls being related to the severity of Parkinson Disease.[5]

NON MOTOR SYMPTOMS

Cognitive impairment, bradyphrenia, tip-of-the-tongue (word finding) phenomenon. Depression, apathy, anhedonia, fatigue, other behavioural and psychiatric problems. Sensory symptoms: anosmia, ageusia, pain

(shoulder, back), paresthesias Dysautonomia (orthostatic hypotension, constipation, urinary and sexual dysfunction, abnormal sweating, seborrhoea), weight loss. Sleep disorders (Rapid Eye Movement behaviour disorder, vivid dreams, daytime drowsiness, sleep fragmentation, restless legs syndrome).

ENVIRONMENTAL FACTORS

Implicated agents include insecticides, primarily chlorpyrifos and organo chlorines [23] and pesticides, such as rotenone or paraquat, and herbicides, such as Agent Orange.[21][22][24] Heavy metals exposure has been proposed to be a risk factor, through possible accumulation in the substantia nigra; however, studies on the issue have been inconclusive.[21]

Parkinson Disease traditionally has been considered a non-genetic disorder

ANIMAL MODEL

In vivo (animal) models, in particular, have not only provided (and are still generating) invaluable information, but also the possibility of testing innovative therapeutic approaches they aim to reproduce the pathological and behavioural changes of the human disease in rodents or primates by using pharmacological agents (neurotoxins) that induce the selective degeneration of nigrostriatal neurons. These toxins can be administered either systemically or locally, depending on the type of agent used and the species involved. (25)

MPTP ADMINISTRATION

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP-hydrochloride) was dissolved in 0.9% solution of NaCl (2 mg/ml) and administered intraperitoneally in four doses of 10 mg/kg each, at one hour intervals, to a total dose of 40 mg/kg. After crossing the blood–brain barrier (BBB), MPTP is transformed by monoamine oxidase B into its active metabolite, 1-methyl-4-phenylpyridinium ion (MPP+) (Fig. 1), which is then carried by the dopamine (DA) transporter (DAT) into dopaminergic neurons of the substantia nigra pars compacta (SNpc), where it blocks mitochondrial complex I activity. MPTP causes a 3,4-dihydroxyphenylalanine (l-DOPA) responsive parkinsonian syndrome, characterized by all of the cardinal symptoms of Parkinson Disease.

ROTENONE

Rotenone (Fig. 1) is a flavanoid found in the roots and stems of several plants and used as a broad-spectrum pesticide. (5) Being highly lipophilic, rotenone easily crosses the BBB and, unlike MPP+, does not depend on DAT to enter dopaminergic neurone. Once in the cell, rotenone blocks complex I activity, causing massive formation of reactive oxygen species (ROS), and inhibits proteasome activity, thereby generating proteolytic stress

6-HYDROXYDOPAMINE (6-OHDA)

Mechanism of action of 6-OHDA is substantially related to its pro oxidant properties. Once in the neuron, 6-OHDA accumulates in the cytosol and undergoes prompt auto-oxidation, promoting a high rate of hydrogen peroxide formation. As an additional mechanism, 6-OHDA can accumulate in the mitochondria, where it inhibits complex I activity. (25) The rats were anesthetized with chloral hydrate (350mg/kg, i.p.) and fixed in a Stereotaxic instrument. Lesions were made by injecting 6-OHDA (20 μg in saline containing 0.1% AA) into the left MFB (left medial forebrain bundle) at the coordinate: A, −2.5; L, −2.0; V, −8.5 mm, from bregma using a 5μL Hamilton syringe at a rate of 1 μL/min [26]. The sham animals were injected vehicle only (0.1% AA-saline) at the same coordinate. After injection, the syringe was left in place for an additional 5min before being slowly retracted. 6- OHDA and sham rats were housed one week for further experiments.

Behavioral Studies are done one week after injection of 6-OHDA, animals were subjected to behavior testing, which were, respectively, spontaneous locomotor activity test, rota rod test, narrow beam test, and apomorphine-induced circling test.

Glutamate-Induced Oxidative Stress

In vitro protection against glutamate-induced oxidative neuronal cell death— To investigate the effect of formulations on oxidative stress-induced neuronal cell death. The PC12cells are cultured in F12K with L-glutamine (292 mg/l) medium containing 5% fetal bovine serum, 15% equine serum, 100 U/ml penicillin, and 100 mg/ml streptomycin in a 5% CO2 humidified atmosphere at 37 °C. PC12 cells are incubated in 96-well micro plates (2×105 cells / well in 100 µl) for 24 h. The cells are then pretreated with various

formulations for 6 h, and treated with 250 μM H2O2 for 1 h or 200 μM 6-OHDA for 24 h at 37 °C, respectively. The controls are exposed to the same solvent. [27]

IN-SILICO METHOD

Slice preparation

Mice were anaesthetized with halothane and immediately killed by decapitation. The brain was rapidly removed and placed in ice-cold carboxygenated (95% O2 and 5% CO2) cutting-solution (glycerol-containing artificial cerebrospinal fluid (G-ACSF)) containing (in mM): NaCl, 125 mM; KCl, 2.5 mM; KH2PO4, 0.3 mM; NaHCO3, 26 mM; $CaCl_2$, 2.4 GLC, 10 mM; MgSO4, 1.3 mM; at 300 mOSM. The olfactory bulbs and cerebellum were removed and the rest of the brain sliced using a vibrating microtome (Leica VT1000SH) in order to make 300- mm thick coronal slices. During slice preparation, the tissue was always maintained immersed in 4uC ACSF. Each slice was delicately transferred to a Petri dish continuously perfused with oxygenated ACSF. After preparation, brain slices from both mice were allowed to recover for about 30 min. Finally, the vial contained the pooled extracts was micro centrifuged at 21 000 g and 4uC for 5 min. The supernatant was then filtered in a syringe with a 0.2 mm filter (Millipore) and stored at 280uC until LCMS analysis. [28]

TREATMENT OF PARKINSON'S DISEASE

Antiparkinsonian agents are a group of drugs that are primarily used in the treatment of the neurodegenerative disorder, Parkinson's disease (PD). In PD the nigrostriatal dopamine pathway is severely compromised and the antiparkinsonian agents work to counteract the defective dopamine pathway or modulate supporting chemical pathways. Drugs aimed at the reduction of the dopaminergic deficit (L-DOPA, monoamine oxidase B and catecol-O methyl transferase inhibitors, dopamine agonists) remain the main stay of symptomatic therapy of PD [29]. However, development of side-effects, such as motor fluctuations and dyskinesia, limits drug effectiveness during the course of treatment [30]. These side-effects, in particular dyskinesia, are thought to be due to pulsatile DA receptor stimulation which strictly reflects plasmatic L-DOPA concentrations during advanced stages of the disease [30,31].The most common antiparkinsonian agent used for the treatment of PD is levodopa, the precursor to dopamine. Other antiparkinsonian agents include dopamine receptor agonists, catechol-o-methyl transferase inhibitors (COMTIs), monoamine oxidase B inhibitors (MAOIs), anticholinergics, and amantadine.

CONCLUSION

Review and analysis of all risk factors of Parkinson disease and its screening in primary care and reports give assessment of the evidence, magnitude of association for the numerous proposed risk and early disease factors of PD, and helps to understand better their contribution to the risk of Parkinson's Disease.

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