Review Article

Parkinson's Disease: A Review of Its Prevalence, Risk Factors and Latest Human's Embryonic Stem Cell Technique for its Treatment

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ABSTRACT

Background: Parkinson's disease is a motor system disorder condition having a negative impression on both the patient's quality of life as well as on their caretakers. The symptoms of the disease emerge due to the loss of certain neurons (which results in the production of dopamine) in the substantia nigra in the mid brain. The four primary symptoms of PD are collectively termed as "TRAP" i.e. trembling or tremors (arms, legs, jaws and face) at rest, rigidity, akinesa and postural instability. As these symptoms turn out to be more prominent, patients may have trouble in their usual walk, talk or completing other simple household tasks. PD affects about 1% of the total population over the age of 60. The exact cause of PD is still unknown yet the researchers are continuously trying to investigate the probable origin of the disease. There are presently no blood or laboratory assessments that have been demonstrated to help in diagnosing periodic PD. Therefore the diagnosis is based on medical history and a neurological scrutiny. Physician's recommendation of brain scans or laboratory tests is usually for the ruling out other diseases.

Objectives: The objective of the current literature review is to highlight the prevalence, causes and evidence based recommendations for the management of early uncomplicated PD. The review also showed the role of human embryonic stem cells to generate dopamine cells which have a similar function and properties like the natural one.

Keywords: Parkinson disease, tremors, trembling, akinesa.

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Introduction

Parkinson's disease is the 2nd most common movement disorder after Alzheimer's disease. It was 1817 when British physicians James Parkinson published a paper on what he called "Shaking Palsy" and described the major signs and symptoms of the disease. More or less after an entire century, etiology of the disease was found to be the loss of dopamine synthesizing neurons in the substantia nigra in mid brain. No exact reasons of PD are known yet however, both genetic and environmental factors play important role in its emergence.[1] Parkinson's disease (PD) is a communal neurodegenerative illness-a synucleinopathy - having a pervasiveness of 160/100 000 in Western Europe expanding to ~4% of the population over the age 80. [2]

Pathology of Parkinson's

Cell loss within the substantia nigra, predominantly distressing the ventral element of the pars compacta, is considered to be the major hallmark of the disease. When an individual with PD dies, this region of the brain has lost 50–70% of its

neurons as compared to a normal individual. The initial reported pathological changes in PD[3] have been detected in the medulla oblongata and olfactory lobe. In first phases, patients are pre-symptomatic. With the disease progression, areas of the midbrain and basal forebrain become involved. Lastly, the pathological variations seem in the neocortex.

Risk Factors of Parkinson's

Genetic Factors: The underlying mechanism of PD is strongly supported by the genetic factors which contribute towards its existence though the genetically persuaded PD constitutes a smaller portion of the cases. Kurosinski *et al.* conducted a study on transgenic mice in order to find out the probable genetic mutation that play role towards the initiation of PD [4]. Another study by Abramov *et al*., presented a model on PD in human.[5] The findings of these studies driven the results towards a conclusion that prevalence of PD is due to certain genes since diverse proteins products relate to it. Kurosinski *et al*. in their work presented that in animal's models, the prevalence of PD is due to the mutation in the gene SYN (A30P & A53T) [6]. A30P and A53T gene mutations results in the formation Lewy bodies of α-synuclein composition (proteins which are abundant in human brain), which are symbols of PD. These mutations also caused dopaminergic neuronal forfeiture (specifically in the basal ganglia of mice and substantia nigra of flies), debility in motor performance, and muscle atrophy. [7]

The censure of the study by Abramov *et al*. was PTEN induced kinase 1, a gene that produces the crucial mitochondrial PINK1 protein.[8] The exact function of this protein is still dubious, however, it has been revealed to explicitly cope with oxidative stress containment in the mitochondria which fuels the process of PD development.

The findings of these studies evidenced that mutation in the genes SYN and PINK1 is the basic cause for the inception of PD. The SYN mutation's consequences are improper α-synuclein folding, dopaminergic neuronal loss, and motor function loss. The PINK1 gene seems to have an altered mechanism that is entangled with the oxidative stress risk factor.

Environmental Factors

Scientists usually have a consensus that maximum cases of PD originate from some combination of "nature" and "nurture" which is a contact between a person's fundamental genetic make-up and his/her life happenings and environmental spotlights. This can be defined as "genetics load the gun and environment pulls the trigger." So we can say that environment holds a comprehensive meaning — that is, it denotes to any and all conceivable causes other than those that are genetic in origin.

To compare various studies conducted regarding the role of environmental factors in the development of PD, a meta-analysis was carried out by priyadarshi et al.[9] The results of this analysis indicated that the people of the rural areas in the world who uses well water as drinking source are at a greater risk to develop PD. But this is not the only reason which contribute towards its development rather some other factors also play pivotal role in its origination.

Pesticides

There are many evidences which show that pesticide contact or exposure is related with an amplified jeopardy for evolving Parkinson's disease. Many animal studies have provided evidence for this, and several studies pertaining to human are at commencement to reveal some specific pesticides and classes of pesticides that may be linked to Parkinson's. Organochlorine insecticides most commonly associated with the disease. Most of these chemicals were banned in the 1970s and 1980s, but because their chemical structures resist breakdown, they can remain in the environment and food chain for an extended time. The organochlorine class includes pesticides like DDT, used for mosquito control, and dieldrin, used for termites. [10]

A study published in 2011 by NIEHS researchers and collaborators at the Parkinson's Institute and Clinical Center in Sunnyvale, Calif., displayed an association between the work-related use of two pesticides, rotenone and paraquat, and People who reported the usage of either pesticide developed the disease 2.5 times more often than nonusers.[11] Rotenone directly inhibits the function of mitochondria while paraquat increases production of certain damaging oxygen derivatives within the cells. People who used other pesticides with a similar mode of action were also more likely to get the disease

Parkinson's Researchers are trying to understand which people, exposed to specific pesticides, are most at hazard of developing Parkinson's. For example, a latest study found that Parkinson's risk from paraquat use was particularly high in individuals missing a certain metabolic enzyme GSTT1. The deficiency of this enzyme is common, so more research is needed to determine if these individuals are more vulnerable to certain pesticides.[12] Other researchers are studying the combined effect of environmental exposures, like pesticides, and genetic susceptibility on Parkinson's risk. Studies conducted by NIEHS-funded scientists at the UCLA School of Public Health have reported that the risk of developing Parkinson's in pesticide-exposed individuals was greater in those who had a gene variation that affected dopamine transport than in those who did not.[13]

Dietary factors

Both in-house investigators and grantees are enduring to discover the role that diet and lifestyle play in the inception, development, and treatment of Parkinson's disease. The quantity of fats a person ingests in his diet is one area under study. Unfortunately, the findings over the years have been inconsistent. However, in a new study, NIEHS researchers and their coworkers revealed that some fats in a person's diet may be related with lower risk for Parkinson's.

A 2013 study found that people who ate a diet high in polyunsaturated fatty acids and low in saturated fat had a lower risk of developing the disease.[14] Although the results prerequisite to be confirmed, they provide additional evidence that it can be beneficial to eat foods high in polyunsaturated fat. Researchers are also exploring the role of vitamin D deficiency in the development of Parkinson's.[15] Vitamin D, which can enter the body through food or sunlight, plays a significant role in maintaining good balance and muscle strength, and in protecting the body from infections and diseases. Researchers are looking into the role that working outdoors may play in reducing the risk of Parkinson's.[16] Another dietary component under study is the possible role of caffeine in the onset and progression of Parkinson's. Animal studies have shown that caffeine can protect the brain's dopaminergic neurons, indicating caffeine may decrease the risk of the disease. Researchers also looked at data from a large sample of older Americans, and found that higher caffeine intake was associated with lower risk of Parkinson's in both men and women.[17] A collaborative study found that coffee consumption may be more protective among individuals with one genotype as compared to individuals with another genotype.[18]

Exercise

Exercise proved to be beneficial for patients with the disease, by improving balance & tumbling depression, and increasing complete life's quality. For an instance, a latest investigation found that tai chi training in patients with mild to moderate Parkinson's improved balance and reduced fall. [19]

Head Injuries

Numerous studies over the years have looked at the role that head injuries might play in Parkinson's disease. This is a practical area to explore, because brain injuries include oxidative stress, inflammation and probable distraction of the blood-brain barrier, all of which could play a subsidizing role in neuronal deterioration and Parkinson's.

Recent studies involving NIEHS researchers further investigated that the association between head injury and Parkinson's may be affected by genetic factors. For example, researchers found that certain variations of a key Parkinson's gene, SNCA, might modify the association between head injury and Parkinson's disease risk. [20]

Air pollution

Researchers are beginning to explore the role that air pollution may play in the evolution and advancement of brain diseases, such as Parkinson's disease. The censure of previous research was on heart and lung maladies, rather than neurodegenerative diseases.

A 2012 NIEHS workshop brought researchers from across the country together, to look at what is known about outdoor air pollution and brain health. [21] The researchers called for more studies to find how air pollution affects brain health, with the eventual goal of identifying early indicators of disease and developing methodologies for prevention and interpolation.

Nicotine

Cigarette smoking has a no of serious effects on human health but regardless of this, a large number of studies have steadily recurded that smokers have a lower incidence of Parkinson's disease than nonsmokers.

The reason for its occurrence is ambiguous, but is likely related to the fact that nicotine interacts with receptors to protect dopamine neurons. Nicotine has also been shown to be neuroprotective in animal models. NIEHS researchers observed from a large study to see if they could determine the characteristics of smoking behavior that reduced Parkinson's risk. They found that consistent smokers were at lower risk of Parkinson's among smokers.[22] NIEHS researchers are also investigating whether genetic factors modify the associations between smoking and Parkinson's disease.[23]

Clinical Diagnosis of PD

The clinical finding may often look straightforward. An alteration of handwriting with micrographia (abnormally small, cramped handwriting, or the progression to continually smaller handwriting) is frequently an initial feature. A loss of arm swing on one side is also an early and useful diagnostic feature.

A reduced sense of smell is, however, worth asking about since this may be one of the first symptoms in early PD.[24] With the disease progression, hypophonia, dribbling of saliva (from reduced swallowing) and damage of postural reflexes may advance. Non-motor complications of the disease often become more bothersome with the disease developments. It is helpful to probe about symptoms of depression which happens in ~40% of PD patients.

Treatment

Unfortunately, no proper treatment for Parkinson's disease is discovered yet, but there are drugs that can slow it down, and deep brain stimulation can improve symptoms of Parkinson's in certain patients.

Dopamine Replacement Therapies (Examples: Levodopa/Carbidopa): Levodopa/Carbidopa is widely recognized as the most effective treatment for motor symptoms of the disease. In most patients, Levodopa/Carbidopa considerably progresses movement and permits them to function comparatively in a normal way, probably in the beginning stages of the disease. Because Parkinson's disease worsens over time, increased doses must be taken to manage symptoms as they progress.

Dopamine Agonists (Pramipexole, Ropinerole, Bromocriptine): Dopamine agonists are those drugs that do not transform to dopamine in the brain rather they mimic the effect of dopamine. Several dopamine agonists have been in use for years, still new dopamine agonists have been developed that attempt to better accomplish side

effects. Dopamine agonists can be used alone or in combination with Levodopa/Carbidopa

MAO-inhibitors (Selegiline, Rasagilene): MAO-inhibitors impede an enzyme that play role to breaks down Levodopa, thus extending its action. MAO-inhibitors are used alone or in combination with Levodopa/Carbidopa.

COMT-inhibitors (Entacapone, Tolcapone) : Catechol O-methyltransferase (COMT) inhibitors allow a larger amount of Levodopa to reach the brain, as a result raising dopamine levels there. They help in providing a more stable and continuous source of Levodopa, which makes its beneficial giving effects which are long lasting and manage off times better. They are used in unification with Levodopa/Carbidopa.

Role of Surgery in PD [25, 27]

The use of surgery in PD antecede over 50 years. In the early 1950s, patients principally those with severe tremor would be referred for ablative surgical procedure. With the addition of levodopa, surgical procedures lost their popularity. With the extensive recognition of levodopa-induced complications encouraged health care professionals to reenter the area of surgical involvement. Initially, this focused on lesion surgery usually in the form of pallidotomy which was exposed to be fruitful mainly for levodopa-induced dyskinesias.

An additional expansion came with the introduction of stimulators. This involved high-frequency deep brain stimulation (DBS) of distinct brain areas. The procedure most commonly carried to reduce bradykinesia, tremor and rigidity. This can produce very histrionic benefit. The operation is technically difficult, but in experienced hands the risk of adverse events is low. However, the infrastructure and support team required to assess, carry out and monitor patients limits the availability of this form of treatment.

Major Breakthrough in PD Treatment

Human embryonic stem cells - ancestor cells that have the potential to become any cell of the body - are a promising source of new dopamine cells, but they have shown problems in their attachment. Now, a revolutionary study from Lund University in Sweden reveals "it is possible to get human embryonic stem cells to yield a new generation of dopamine cells that act like natural dopamine cells when transplanted into the brains of rats."

Study leader Malin Parmar, associate professor in Lund's Department of Medicine, and co-workers reported their results in the journal "Cell Stem Cell". The team states that the novel cells show all the properties and functions of the dopamine neurons that are vanished in Parkinson's disease, and the possibly infinite supply sourced from stem cell lines unbolts the door to clinical application. In their work, the researchers carried out experiments in rat models of Parkinson's disease. For making a rat model of Parkinson's, research workers devastated the dopamine cells in one portion of the rat's brain. The experiments showed that dopamine cells synthesized from embryonic stem cells of the human, behaved like native dopamine cells just after their transplantation into the rat's brain. [28]

Conclusion

Though the exact reason of PD leftovers unidentified, there are three dominant suppositions in literature. Research has revealed that there is a discrete connection between environmental toxin exposure and the onset of PD. However, this needs to be further scrutinized to know an underlying relationship. Genetic mutations in the SYN and PINK loci have finally been shown to lead to PD. Further studies need to be conducted to determine the causes of these mutations in humans. Degeneration due to oxidative stress is a new line of research that is also proving to be fairly promising. Deficiency of MTH1 seems to be strongly connected with an increase in ROS

formation. Recently human's embryonic stem cell technique is proved to be more successful for the treatment of PD.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Hassan S, Alex B, Angela C, Raynarth L. Causes of Parkinson's disease: Literature Review. JPRLS 2011; 1(1): 5-7
2. National Institute for Health and Clinical Excellence. Parkinson's Disease: Diagnosis and Management in Primary and Secondary Care. London: NICE; 2006. (http://guidance.nice.org.uk/CG35).
3. Braak H, Bohl JR, Müller CM, Rub U, Tredici KD. Stanley Fahn Lecture 2005: The staging procedure for the inclusion body pathology associated with sporadic Parkinson's disease reconsidered. Mov Disord 2006;21: 2042-2051.
4. Kurosinski P, Guggisberg M, Götz J. Alzheimer's and Parkinson's disease – overlapping or synergistic pathologies? TRENDS in Molecular Medicine 2000; 8(1): 41-43
5. Abramov AY, Gegg M, Grunewald A, Wood NW, Klein C, Schapira AHV. Bioenergetic Consequences of PINK1 Mutations in Parkinson Disease. PLoS ONE 2011; 6(10): 1-9.
6. Kurosinski P, Guggisberg M, Götz J. Alzheimer's and Parkinson's disease – overlapping or synergistic pathologies? TRENDS in Molecular Medicine 2000; 8(1): 41-43
7. Kurosinski P, Guggisberg M, Götz J. Alzheimer's and Parkinson's disease – overlapping or synergistic pathologies? TRENDS in Molecular Medicine 2000; 8(1): 41-43
8. Abramov AY, Gegg M, Grunewald A, Wood NW, Klein C, Schapira AHV. Bioenergetic Consequences of PINK1 Mutations in Parkinson Disease. PLoS ONE 2011; 6(10): 1-9.
9. Priyadarshi A, Khuder SA, Schaub EA, Priyadarshi SS. Environmental Risk Factors and Parkinson's Disease: A Metaanalysis. Environmental Research Section A 2001; 86: 122-127.
10. Goldman SM. Environmental Toxins and Parkinson's disease. Annu Rev Pharmacol Toxicol 2014; 54: 141-164.
11. Tanner CM, Kamel F, Ross GW, Hoppin JA, Goldman SM, Korell M, Marras C, Bhudhikanok GS, Kasten M, Chade AR, Comyns K, Richards MB, Meng C, Priestley B, Fernandez HH, Cambi F, Umbach DM, Blair A, Sandler DP, Langston JW. Rotenone, paraquat, and Parkinson's disease. Environ Health Perspect 2011; 119(6):866-872.
12. Goldman SM, Kamel F, Ross GW, Bhudhikanok GS, Hoppin JA, Korell M, Marras C, Meng C, Umbach DM, Kasten M, Chade AR, Comyns K, Richards MB, Sandler DP, Blair A, Langston JW, Tanner CM. Genetic modification of the association of paraquat and Parkinson's disease. Mov Disord 2012; 27(13):1652-1658.
13. Ritz BR, Manthripragada AD, Costello S, Lincoln SJ, Farrer MJ, Cockburn M, Bronstein J. Dopamine transporter genetic variants and pesticides in Parkinson's disease. Environ Health Perspect 2009; 117(6):964-969.
14. Kamel F, Goldman SM, Umbach DM, Chen H, Richardson G, Barber MR, Meng C, Marras C, Korell M, Kasten M, Hoppin JA, Comyns K, Chade A, Blair A, Bhudhikanok GS, Webster Ross G, William Langston J, Sandler DP, Tanner CM. Dietary fat intake, pesticide use, and Parkinson's disease. Parkinsonism Relat Disord 2013; 20(1):82-87.
15. Evatt ML, DeLong MR, Kumari M, Auinger P, McDermott MP, Tangpricha V; Parkinson Study Group DATATOP Investigators. High prevalence of hypovitaminosis D status in patients with early Parkinson disease. Arch Neurol 2011; 68(3):314-319.
16. Kenborg L, Lassen CF, Ritz B, Schernhammer ES, Hansen J, Gatto NM, Olsen JH. Outdoor work and risk for Parkinson's disease: a population-based case-control study. Occup Environ Med 2011; 68(4):273-278.
17. 9 Liu R, Guo X, Park Y, Huang X, Sinha R, Freedman ND, Hollenbeck AR, Blair A, Chen H. Caffeine intake, smoking, and risk of Parkinson disease in men and women. Am J Epidemiol 2012; 175(11):1200-1207.
18. 0 Hamza TH, Chen H, Hill-Burns EM, Rhodes SL, Montimurro J, Kay DM, Tenesa A, Kusel VI, Sheehan P, Eaaswarkhanth M, Yearout D, Samii A, Roberts JW, Agarwal P, Bordelon Y, Park Y, Wang L, Gao J, Vance JM, Kendler KS, Bacanu SA, Scott WK, Ritz B, Nutt J, Factor SA, Zabetian CP, Payami H. Genome-wide gene-environment study identifies glutamate receptor gene GRIN2A as a Parkinson's disease modifier gene via interaction with coffee. PLoS Genet 2011; 7(8):e1002237.
19. 2 Li F, Harmer P, Liu Y, Eckstrom E, Fitzgerald K, Stock R, Chou LS. A randomized controlled trial of patient-reported outcomes with tai chi exercise in Parkinson's disease. Mov Disord 2013: doi:10.1002/mds.25787 [Online 29 December 2013.
20. Goldman SM, Kamel F, Ross GW, Bhudhikanok GS, Hoppin JA, Korell M, Marras C, Meng C, Umbach DM, Kasten M, Chade AR, Comyns K, Richards MB, Sandler DP, Blair A, Langston JW, Tanner CM. Genetic modification of the association of paraquat and Parkinson's disease. Mov Disord 2012; 27(13):1652-1658.
21. Block ML, Elder A, Auten RL, Bilbo SD, Chen H, Chen JC, Cory-Slechta DA, Costa D, Diaz-Sanchez D, Dorman DC, Gold DR, Gray K, Jeng HA, Kaufman JD, Kleinman MT, Kirshner A, Lawler C, Miller DS, Nadadur SS, Ritz B, Semmens EO, Tonelli LH, Veronesi B, Wright RO, Wright RJ. The outdoor air pollution and brain health workshop. Neurotoxicology 2012; 33(5):972-984.
22. Hawkes CM. Diagnosis and treatment of Parkinson's disease. Anosmia is a common finding. BMJ 1995;310:1668. No abstract available Erratum in: BMJ 1995: 311, 129.
23. Gross RE, Lozano AM. Advances in neurostimulation for movement disorders. Neurol Res 2000;22:247-258.
24. Limousin P, Krack P, Pollack P, et al. Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med 1998;339:1105-1111.
25. Volkmann J, Allert N, Voges J, et al. Safety and efficacy of pallidal or subthalamic nucleus stimulation in advanced PD. Neurology 2001;56:548-551
26. Chen H, Huang X, Guo X, Mailman RB, Park Y, Kamel F, Umbach DM, Xu Q, Hollenbeck A, Schatzkin A, Blair A. Smoking duration, intensity, and risk of Parkinson disease. Neurology 2010; 74(11):878-884.
27. Gao J, Nalls MA, Shi M, Joubert BR, Hernandez DG, Huang X, Hollenbeck A, Singleton AB, Chen H. An exploratory analysis on gene-environment interactions for Parkinson disease. Neurobiol Aging 2012; 33(10):2528 .e1-6.
28. http://www.medicalnewstoday.com/articles/285069.php. 7/11/2014.