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A Brief Review Study on Sthana Sanchyay Avastha (Accumulation) of Alpha- Synuclein Protein in Parkinson's disease – An Ayurvedic Point of View

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ABSTRACT

In Ayurveda, Parkinson's disease is commonly understood as Kampavata. In Ayurveda, Lakshanika Chikitsa is frequently linked to the various phases of the illness, lending meaning to the avoidance of further derangement.But, under the different definitions of Bahukampavata, Snayugatavata, Kaphavruta Vyanavata and Kampavata, the progression of the disease can be understood. As Parkinsonism in Ayurveda is usually treated with better effectiveness Parkinson's disease is a psychiatric condition in which 70% of the presence of Parkinson's disease is compensated. In fact, Parkinson's disease refers to people that have Parkinson's disease without any atypical manifestations and who have essentially regular MRI that excludes all causes of their Parkinsonian symptoms. The key distinction between the two is the influence of the medication on Parkinson's disease and not the other. Parkinson's disease, the second most prevalent neurodegenerative condition after Alzheimer's disease, occurs in around 1 in 1000 individuals in the general population and in 1% of people over 65 years of age via general interventions, drug rehabilitation and surgery, treatment is also mostly directed at avoiding more complications and maintaining the disease.

Keywords: *Parkinson Disease, Kampavata etc.*

Introduction

The first definitive demonstration of a genetic disorder leading to Parkinson Disease was the first connection of Parkinson's disease to alpha-Synuclein, which hence has historical and conceptual significance. While some addressed family exposure to the disorder. A landmark breakthrough was the concrete discovery of a gene defect related to Parkinson Disease in individual families, when it opened the door to a cascade of research exploring the genetic basis of the disease, resulting in more recent genome-wide association studies (GWAS), which have amazingly made a complete circle back to the roots of Parkinson Disease's molecular genetic era;

Parkinsonism is a clinical syndrome that consists of four cardinal signs: Tremor, Rigidity, Akinesia and Postural disturbances.[1] It is also called as the Shaking Palsy or Paralysis agitans. Parkinson's disease is a common cause of the Tremor, Rigidity, Akinesia and Postural disturbances syndrome, but there are numerous other causes which can be considered as the differential diagnosis in Parkinson's disease. Parkinsonism accounts for 80 percent. Specifically, Parkinson's disease refers to people that have Parkinson's disease without any atypical characteristics and who have a basically regular MRI that excludes all sources of Parkinson's symptoms. The key difference between the two is the effect on Parkinson's disease of the modern medication, not the other. Parkinson's disease, the second most prevalent neurodegenerative condition after Alzheimer's disease, occurs in around 1 in 1000 individuals in the general population and in 1% of people over the age of 60. Men are significantly more commonly affected than women because it is due to being present only in males and produced by Substantia Nigra, the brain region affected by Parkinson's, because of a sex gene. The lack of dopamine in the Neostriatum secondary to the loss of pigmented dopaminergic neurons in the midbrain cells of Substantia Nigra is responsible for many of the characteristics of Parkinson's disease. Until clinical characteristics of the disorder evolve, nearly 60 percent of these dopaminergic neurons may have degenerated. There are essentially two forms of Parkinsonism - primary and secondary. Sporadic and hereditary are primary Parkinsonism's. Sporadic is often referred to as idiopathic, and it typically begins in the late middle age and rises with age in occurrence. Mutations in at least six genes, including alpha-synuclein, uchL1, LRRK2, parkin, PINK1, and DJ-1, are frequently due to genetic involvement related to Parkinson's disease.[2] Parkinsonism Plus Syndrome is sometimes

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considered Atypical Parkinsonism. That include Lewy Bodies dementia, Progressive Supranuclear Palsy, Multiple atrophy of the system and Corticobasal syndrome. Progressive conditions are atypical Parkinsonian disorders that appear with any of the signs and symptoms of Parkinson's disease, but normally do not respond well to modern drug therapy. Currently, atypical Parkinsonian diseases are not considered to be inherited. Most cases occur from unexplained causes, although some may be associated with addiction to or damage to long-term medications. Secondary Parkinsonism include Drug induced (antipsychotics, reserpine, tetrabenazine), Infections (post encephalitic infection), Toxins (like Carbon disulphide), Heavy metal (like mercury), brain Trauma, Brain tumours and Liver failure etc.

The Structure and Function of α-Synuclein

The SNCA gene encodes a 140 amino acid protein that does not have a fixed structure in aqueous solutions and hence is the name "Natively Unfolded Protein." However, α-Synuclein forms α-helic structures that attach to negatively loaded lipid, such as phospholipids present in cellular membranes and β-sheet structures at extended incubation times. The protein has three distinct areas:[3] an amino terminus (i.e. residue of 1-60 amino acids) with a lipid-binding motif containing Apo lipoprotein which is required to form amphiphilic helices that give α-helical structures a tendency to bind to membranes;[4] the central hydrophobial structure (i.e. 61-95), the so-called NAC (non-Aβ sheet), which gives the capacity for the β-sheet and the highly-loaded and vulnerable carboxylic terminus[3]

Aim and Objective

The Understanding of *Sthana Sanchyay Avastha* (Accumulation) of Alpha- Synuclein Protein in Parkinson's disease.

Methodology

Parkinson's Disease and It's protein i.e. Alpha – Synuclein Protein related materials were collected from numerous journals, *Ayurvedic* and Contemporary Text Books, Reputed Newspaper Authoritative Websites, Authoritative Literature, Manuscripts, Sanskrit Dictionary, etc.

Clinical Manifestation

The key features are the mentioned including

1. Micrograph
2. Eye twitch reduction
3. Hypophonia
4. Dysphagia
5. Freezing
6. Resting tremors (4-6 cycles per second, pill rolling in nature, on voluntary activity and sleep disappears).
7. Rigidity

The rigidity having two forms i.e.

1. Cogwheel
2. Rigidity of the lead pipe

Lead pipe rigidity across the entire spectrum of motion, with no fluctuations, is sustained resistance to passive movement. The jerky resistance to passive movement as muscles tense and relax is Cogwheel rigidity. The slowness of motion with gradual speed reduction is Bradykinesia. The other non-motor signs are neuropsychiatric symptoms such as depression, depressive disorders, apathy, autonomic disorders such as urinary dysfunction, constipation, sensory symptoms such as discomfort, anxious syndrome, olfactory dysfunction, Sleep disorders such as extreme sleepiness during the day, changes in the REM rhythm and cognitive disability such as dementia in 80% of patients.

To rule out any other factor and validate the diagnosis, examinations should include CT, MRI, PET and Trans cranial Ultrasound etc.[4] For multiple types of Parkinson's, there are different conditions and

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stages specified. Staging is typically conducted by staging Changed (Hoehn and Yahr)[5]. Risks include repeated slips, incapacitation, exhaustion and dementia, postural hypotension, urinary incontinence, constipation, aspiration, are treated in the Allopathic Medicine System is threefold:

1. Physiotherapy
2. Speech therapy
3. Nutrition regulation.

***Ayurvedic* Point of View in Parkinson Disease**

The principle of *DhatuKshaya* and *Avarana* is implicated in the pathogenesis of neurological diseases[6]. Taking the *Lakshanas* seen in Parkinson's disease like *Snayugata* Vata, *Kaphavrutavyana Vata and Kampavata. In Basavarajeeya, Baahukampavata* is described as the tremors on one side of the arm that affect the body's activities and that that give rise to different kinds of discomfort during the day and night. This can be associated with the early stages of Parkinson's disease where unilateral interference along with axial participation occurs. *Snayugata Vata* is described in *Bhava Prakasha* as, "When the deranged *Vatadosha* is located in the tendons, there may be *Shoola, Akshepaka, Kampa, Stambha, Anilaodbhava*". *Swedana, Upanaha, Agnikarma and Bandhana* are recommended to remedy in this condition. This can be related to the stage of disease progression where there is a bilateral involvement with Pull test recovery. The procedure is not meant for *Bahudoshaavasta. Kapavruta Vyanavata* explained in *Charaka Samhita* is interpreted to mean that if *Vyanavayu* is occluded by *Kapha*, there would be heaviness in the body, discomfort in all the joints and bones, and reduced movements or extreme loss of morbidity. This can be understood by analogy to anatomy in Modern science. The main pathology of Parkinson's disease is that substantia nigra pars compact cells tend to die.

This cells make dopamine, which is a hormone and a neurotransmitter (chemical released by neurons to send signals to other cells). Dopamine induces movement, aids in recall, sleep, mood, enjoyable reward, actions and cognition. Dopamine depletion blocks the auto inhibition of acetylcholine production by muscarinic auto receptors, contributing to excessive acetylcholine release, which ultimately prunes the spines of the indirect pathway projection of the striatum neurons and thereby disrupts the flow of input from the motor control centres in the cerebral cortex.[7] In short, the reduction in dopamine contributes to an increase in the proportion of acetylcholine, i.e. they are of an inverse type. Acetylcholine is the neurotransmitter responsible for contracting the muscles, triggering pain responses, regulating endocrine sleep and REM sleep. It therefore contributes to bradykinesia, rigidity, postural disruptions and tremors when the acetylcholine is increased, which are also defined by the Acharya as Gatisanga and *Adhika*. Gatisanga: where the regular work of Vata is obstructed. This can be translated as bradykinesia, rigidity, disruptions. The elevated activity can be considered here, such as tremors. This can be understood under the principle of *Avarana*, where the *Kapha* leading to *Avarana* hinders the direction of *Vyanavata*. In order to cross the blood brain barrier, the dopamine molecule is too polar.[8] Therefore, under those cases, the therapy is L-Dopa, a dopamine precursor that can easily penetrate the blood brain barrier. Initially, *Avaranahara Chikitsa* is performed also in *Ayurveda*, with *Kapikachu* drug being the predominant drug of choice. In *Basavarajeeya, Kampavata* is described and this can be interpreted as the full manifestation of the disease, physically dependent on the patient being bedridden or wheelchair bound.[9]

Nidana

From the aspects of *Swatantra and Paratantra Vyadhis*, primary and secondary Parkinson's disease can be understood.[10] though the causes are idiopathic, the causes of primary Parkinson's disease can be understood as *Swatantra or Anubandhya Vyadhi. Paratantra or Anubandha Vyadhis* may be known as the secondary Parkinson's disease triggered by secondary causes, as the therapy requires treating the primary cause and not the secondary symptoms.

***Sthana Sanchyay Avastha* of Alpha – Synuclein Protein.**

The hypothesis that enhanced alpha-synuclein protein levels are causative in Parkinson's disease pathogenesis is derived from the familial cases of SNCA multiplication showing a dose-dependent association of alpha-synuclein load to the Parkinson's disease phenotype, the autosomal-dominant

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inheritance trend for point mutations, the concentration of alpha-synuclein in the brain of synucleinopathy. The alpha-synuclein protein levels in substantia nigra are increased with aging and correlate with reduced immunostaining levels (Chu and Kordower 2007).[11]
There is insufficient evidence that in Parkinson's disease brain, there is a generalized abundance of alpha-synuclein protein. In fact, mRNA studies in this regard have been somewhat inconsistent, with some showing a decrease in SNCA gene expression in Parkinson's disease (Dachsel et al. 2007). Obviously, average protein levels in Parkinson's disease brains are not raised, but there is obviously an induction of insoluble elements, including monomeric and oligomeric species. A systematic analysis of many brain regions found that the amount of membrane-associated monomeric alpha-synuclein in Parkinson's disease patients was only modestly increased in substantia nigra, and not in other brain regions.[12]
The rise in membrane-associated alpha-synuclein in sensitive brain regions was stable (Tong et al. 2010). Neurons with the highest levels of expression of alpha-synuclein can, of course, be the most susceptible and succumb early in the disease process, giving their position to glia, thereby misleading the outcomes. Gründemann et al. (2008) conducted laser-capture micro dissection experiments to partially overcome this problem and reported a substantial increase in SNCA expression in surviving PD-derived nigral neurons relative to controls.[13] This rise, however, did not seem unique to SNCA (Gründemann et al. 2008).

Discussion

The *Prakupitavata* contributes to *Dhatukshaya* and manifests as *Ekabahukampa* due to some of the *Nidana* mentioned for *Vatavyadhi*, which is also seen during the initial onset of Parkinson's disease.[14] this can be interpreted as *Nidana* leads to *Vataprakopa* that accumulates in *Rikta Srotas* that leads to *Baahukampavata's Lakshanautpatti*. The possible *Samprapti* leading to Parkinson's disease, given *the Lakshanas of Snayugatavata*, will be that the *Nidana* progresses to *Vataprakopa*, which then goes up to the *Snayusthana*, taking *Snayugatavata's Lakshana*

***Utpatti*.**

The possible *Samprapti* leading to Parkinson's disease, given the *Lakshanas of Snayugatavata*, will be that the *Nidana* progresses to *Vataprakopa*, which then goes up to the *Snayusthana*, taking *Snayugatavata's Lakshana Utpatti*. *Kapha's Avarana of Vyanavata* may be called for the later phases in which postural dysfunction is marked along with body fatigue. Here, the *Nidana* assimilates to bring in *Vataprakopa* to various *Sthanas* leading to *Udhirana* of *Pitta* and *Kapha*. This leads to *Kapha* forming the *Avarana* of *Vyanavata*.[15] Later, this refers to the *Shoshana of Rasadhidhatu* and manifests as *Kaphavruta Vyanavata*. Resting tremors along with being bed ridden or wheel chair bound are characterized by the full presentation of Parkinson's disease. The *Kampavata Lakshanas* can be viewed as the full manifestation of Parkinson's disease, like *Kampa* in the body, contributing to restless nights and leaving the individual emaciated.[16,17,18]
Nidana leads to the *Avastha* of *Dhatukshaya*, where *Vataprakopa* is. That of *Vyanavata* is the *Vriddhi* concerned here.[19,20] This circulates by *Rasayanis*, contributing to *Kampavata's* manifestation.

Conclusion

As the definitive cause of Parkinson's disease is unclear, the purpose of therapy is also to avoid further worsening. The *Lakshanika Chikitsa* is commonly followed with respect to that of Parkinson's disease in *Ayurveda*. Therefore, whenever possible, the appropriate diagnosis should be made and the *Oushadi* and procedures that aid in the same should be followed, bearing in mind our limits.

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