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Cognitive Movement Disorders, Gut Dysbiosis and Skin Diseases

Chan Kam Tim Michael*

Specialist in Dermatology, Hong Kong Academy of Medicine, Vice President of Integrative Aesthetic Medicine of Hong Kong, Hong Kong

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***Corresponding author:** Chan Kam Tim Michael, Specialist in Dermatology, Hong Kong Academy of Medicine, Vice President of Integrative Aesthetic Medicine of Hong Kong, 2128, Pioneer Center, 750, Nathan Road, Mongkok, Kowloon, Hong Kong, Hong Kong SAR, China, Tel: 0852-66835651; Email: pioneerskin@hotmail.com

Abbreviations: PD: Parkinson's disease; ENS: Enteric Nervous System; IBD: Inflammatory Bowel Diseases; SN: Substantia Nigra; NMP: Non-Motor Parkinsonism; GI: Include the Gastrointestinal

Opinion

Advances in modern biomedical science and technical research give evidence that Cognitive movement disorders like Parkinson's Disease (PD) may be closely related with gastro-intestinal dysbiosis and the production of internal toxic protein reaching the brain, skin and other organs of the body through the enteric nervous system (ENS) [1-5].Gut especially small intestinal epithelial barrier defects; which primarily function as an important first line physiological, immune and endocrine absorption organ may become aberrant as a result of genetic predisposition and western life style dietary habit. The breaking down of the epithelial cells tight junctions allows diffusions of toxins released froma modern western diet mainly composed of a high content of processed carbohydrate: high sugar and fats ratio relative to low fibres, pollutants like heavy metals, preservatives, pesticides, infections, prolonged antibiotics intake, with a low pH environment into the body circulation.

This loss of epithelial cells cohesion of small bowel termed as "leaky gut" has immense consequences to the understanding and pathogenesis of skin disease, rheumatological disease, inflammatory bowel diseases (IBD), and oral cavity disease, interestingly to some of our brain cognitive disorders like depression, autism and cognitive disease like PD [3]. Though the exact pathogenetic pathways, signaling and control mechanisms is not fully elucidated; factors like malabsorption, autoimmunity with auto antibodies formation to specific organs, inflammation and breaching of the blood brain barrier allowing toxins, cytokines and other inflammatory signals pass into our CNS are strongly suggestive [6]. PD is a complex cognitive movement disorder with non-motor and motor clinical manifestations.The aetiology of PD is multifactorial but genetic predisposition like R1441G mutation, LRRK2 mutation, Parkin and PINK 1 mutation and the neuro toxic effects of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) causing mitochondrial dysfunction are known causations.1,2 Recently, accumulation of a neuronal protein transfers through neuronal synapses from the gut, glial cells and ENSthen deposited in the Substantia nigra (SN) of the basal ganglion of the brain cause gradual dopaminergic neurone cell deaths through apoptosis and inflammation is under active research.There is a gradual depigmentation of the SN in PD observed in control studies due to the loss of neuromelanin. Non-Motor Parkinsonism (NMP) manifestations are diverse but include the gastrointestinal (GI) tract and the skin.

Gut immobility, constipation with the subsequent bacterial overgrowths and dysbiosis of the gut epithelial lining promote absorption of toxins. Helicobacter pylori may play a role in PD. The neuronal protein under intense study is called α- synuclein [7] these proteins are neurotoxic α- synuclein accumulation can cause cell deaths with the formation of Lewy Bodies found in the dopaminergic neurone in the brain. Lewy Bodies are pathognomonic of PD in histopathology α- synuclein and Lewy Bodies are found widely distributed in the ENS of the gut, olfactory bulbs, sympathetic and parasympathetic ganglions, spinal cords, neuronal cells of the brain and skin [8] GI tract motility dysfunction with dysbiosis of gut microbiota interplay with the epithelial glial cells and neurones of ENS that innervate the gut result PD through α- synuclein. Like food allergies in Atopic Dermatitis children, PD patient neuro chemical changes with production of inflammatory cytokines with impairment of intestinal epithelia barrier has been observed. There are also dysregulation and loss of enteric glial cells with formation of α- synuclein.

A positive correlation between gut permeability and deregulation of enteric glial cells and intestinal α- synuclein

has been confirmed in studies. Caffeine ingestion and cigarette smoking reduce small gut inflammation leads to less aggregation of α- synuclein in the ENS, reduce risk of PD. A rostrocaudal gradient of synucleinopathy within the GI tract with submandibular gland and lower oesophagus having the highest density of Lewy Bodies followed by the stomach, small intestine, colon and rectum is evident [1] This rostrocaudal distribution of Lewy Body pathology coincides with vagal innervation from dorsal motor nucleus of the vagus (DMNV) as well as the distribution of dopaminergic neurones in the ENS. Furthermore, peripheral induced inflammation can induce central inflammation and result dopaminergic pathway degeneration [1]. Apart from the gut, NMP also involve the oral cavity with clinic presentations like periodontal diseases, poor oral hygiene, dental problems with loss of teeth and bad breath [9] further research through non-invasive methods like breath test should be employed to look into the changes of microbiota of the oral cavity in PD patients.

A Dual hit theory has been postulated that neurodegenerative process starts in the olfactory bulbs and ENS of the gut following inhalation and ingestion of a neurotropic proteinaceous infectious pathogen; e.g. a prion [10] The neuropathological process that leads to PD seems to start in the upper part of the gut with synucleinopathy throughout the whole GI tract. The ENS, the gut microbiota dysbiosis participate and enhance the active transport of α- synuclein via the vagal nerve to the CNS [11,12] Hence, from top to bottom; the gut, dysbiosis, ENS deposition of α- synuclein and inflammation are closely associated with PD. Maintain a balance intestinal microbiota of the GI tract and its environment may bea primary target in preventing the development of PD. Probiotics and prebiotics administration at relevant time, appropriate dosage and systemic antibiotics may be a possible remedy to correct this disharmony [13] Early stage of NMP is also easily recognisable from the skin. Severe seborrhoea and scarring acne is referred by some as pre-motor features of PD [14]. There is a frequent overlap between patients presented with seborrheic dermatitis and PD. Malassezia globosahas a higher density in PD skin than control subjects.

The skin of PD patients should be carefully scrutinized and examined for melanoma as α- synuclein is also implicated in the pathogenesis of the latter [15,16] Skin biopsies for histological tissue staining for α- synuclein is a promising screening test which can be easily carried out as a minor procedure in an out- patient clinic setting to detect early NMP patient [17,18]. In sum, the GI tract; enteric microbiota; CNS cognitive movement domains, enteric nervous system and skin is an integral part of our body normal physiology as exemplified by clinically unrelated diseases like PD, chronic Atopic Dermatitis, severe acneiform facial eruption and rheumatological conditions like psoriatic arthritis. Understanding the Gut- Nervous system- Cognition-Movement and Skin patho physiological axis not only enlighten us on the pathogenesis of the diseases but mayalso provide new therapeutic insight and management strategy for these distressing conditions.

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