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REVIEW

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From allegory to conceptualization, hypothesis and finally evidences: Alzheimer's dementia, Parkinson's disease "gut–brain axis" and their preclinical phenotype

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Abstract

Researchers are constantly trying to develop therapeutic targets in neurodegenerative disorders like Alzheimer's dementia and Parkinson's disease. Despite enormous endeavors, there are several unmet needs. Several contradictory pathophysiological basis of neurodegenerative disorders are considered to be one of the most important cause underpinning. "Gut–brain dysbiosis" has been considered as one of the most crucial link to explore. Contemporary researches have suggested similar pathophysiological mechanisms underpinning Alzheimer's dementia and Parkinson's disease. "Gut–brain dysbiosis" may be the missing thread connecting Alzheimer's dementia and Parkinson's disease prior to the expression of their overt clinical phenotype. Recognition of preclinical phenotype of Alzheimer's dementia and Parkinson's disease have much broader perspective as it will help in building robust therapeutics at the earliest. Authors herein critically analyze the pathophysiological basis of Alzheimer's dementia and Parkinson's disease in relationship with "Gut–brain dysbiosis" and also try to search the preclinical phenotype/s of Alzheimer's dementia and Parkinson's disease pivoting around the Freudian hypothesis.

Keywords Alzheimer's disease, Parkinson's disease, Pre-clinical, Gut–brain dysbiosis

Alzheimer's disease (AD) is a neurodegenerative dementia with diverse pathophysiological basis, ranging from genetic associations to amyloid and recently unearthed tau deposition in the brain [1]. Researchers have sought several risk factors like age, female gender, presence of vascular risk factors, addictions, life styles and poor literary level, underpinning AD [2]. In accordance to the current understanding, AD is more appropriately termed as Alzheimer's disease spectrum disorder due to heterogeneity in clinical presentations, pattern of cognitive impairments, genotypes and biomarkers. The predominant clinical phenotypes in addition to "classical AD" are "frontal-variant AD" (dysexecutive/behavioral), "posterior cortical atrophy (PCA), non amnestic AD and corticobasal AD. The chances of having a "variant AD" are higher with a younger age of presentation. Based on the characteristic pattern of brain atrophy, AD can again be typical, limbic predominant, hippocampal sparing, and with minimal atrophy. It has been observed that cognitive decline in AD primarily involves the default-mode network [3]. The most pertinent question remains as to how to detect AD phenotype at the earliest and if there are any clinical predictors [4, 5]. Recent advances in research targeting on these issues have come up with the concepts of minimal cognitive impairments (MCI) and diverse

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biomarkers of AD. Numerous proposed blood and cerebrospinal fluid (CSF) biomarkers to detect AD in early stages (MCI or preclinical stage) have already gained popularity in AD research; and endeavors have started to extrapolate it clinically. It is very much important in clinical practice to identify preclinical AD, or to recognize cognitive and behavioral patterns early, before it becomes clinically overt [6]. However, atypical phenotype and frequent presence of mood symptoms (depression), particularly in older age groups, complicates the scenario. Depression may precede, coincide or follow AD. It is very difficult to differentiate depression, MCI and AD in older age groups, as commonly the history of evolution of symptoms are vague [7–10].

Several laboratory-based tests focusing on biomarkers have already gained popularity; there is an unmet need for determination of subtle preclinical clues, especially in resource poor settings wherein these tests are elusive to the general population due to availability and affordability issues. Previous studies dedicated to recognizing the clinical continuum/spectrum of AD have shown that "personality traits" have a definitive role in clinical prediction of healthy aging as well as AD phenotype; and its modification can be a potential therapeutic target for AD [11–13]. Contemporary researches have shown a probable association between neuroticism and low conscientiousness level with future development of AD [14–18]. Anxiety, depression and obsessive–compulsive spectrum disorders (OCSD) may have an intricate and intriguing relationship with future risk of development of AD. Aligning these evidences in streamline, authors herein try to propose a clinical trajectory of preclinical AD phenotype to clinically overt AD (from neuroticism, OCSD, anxiety, post-traumatic stress disorder, depression and MCI to AD eventually) [19–25]. On the other hand, behavioral and psychological symptoms in dementia (BPSD) are highly prevalent in AD and range from apathy, depression, anxiety, obsessive–compulsive behavior, aggression/agitation, delusions (paranoid usually) to hallucinations, which in turn, impose huge burden and stress on caregivers. The behavioral and psychological symptoms are more common in behavioral variant of frontotemporal dementia, but it is also be found in Alzheimer's dementia [26]. They are further clustered as hyperactivity symptoms (disinhibition, irritability, and aggression/agitation), psychosis symptoms (delusions and hallucinations) and physical behavior symptoms (eating, appetite, sleep behavior and aberrant motor behavior) [26, 27]. Author's concern in this regard is if neuroticism, OCSD, anxiety, depression and cluster 'C' personality traits can be the preclinical AD phenotype. Author's viewpoint in this regard is that there may be some shared pathophysiological basis or modulation (by the above mentioned psychopathologies) of AD pathobiology underneath, which is reflected by the "pure psychological" phenotype of Alzheimer's disease spectrum earlier in life.

Long back in 1908, Sigmund Freud described anankastic personality disorder (anankastic PD) to illustrate the psychological issues of mental guarding, checking, rigidity, frugality, parsimonious attitude, lack of generosity, obstinacy in certain category of people. Freud compared these traits to constipation/holding of stool and termed it as "anal retentive behavior" in his "psycho-sexual" developmental model [28–31]. Anankastic PD was later renamed as obsessive–compulsive personality disorder (OCPD) by Diagnostic and Statistical Manual III Revised version (DSM-III-R) and later in DSM-IV, it was grouped under "Cluster C" personality trait. Allegorical conceptualization of the term anankastic PD by Freud now has much wider implication, as it might be the missing thread to amalgamate OCPD, OCD, and their association with constipation and AD in later life [32–34]. This raises the question that if Freud had really conjectured the "gut–brain dysbiosis" as one of the most important pathophysiological basis of several neurodegenerative (like AD and PD) and psychiatric disorders or if it was a pure allegorical categorization/nomenclature [35–38, 38, 39, 39]. There has been a paradigm shift in the understanding of pathophysiological basis of Parkinson's disease (PD) after the conceptualization of "gut–brain dysbiosis" as one of the most important patho-biological link. The gut dysbiosis results in excessive stimulation of the innate immune system and can lead to systemic inflammation. As a result, alpha-synuclein misfolding may be commenced from activation of enteric neurons and enteric glial cells. Furthermore, the bacterial proteins cross-reacting with human antigens may influence the adaptive immune system. The aggregation and propagation of enterically derived alpha-synuclein is probably the inceptive pathophysiological steps that can later result in the development of PD with its characteristic motor and non-motor symptoms [40–43]. Contemporary research has shown the association of OCPD and OCD with Parkinson's disease [44–47]. Constipation is one the prominent non-motor symptom of Parkinson's disease that needs further attention after "gut–brain dysbiosis" and has effectively been proposed and proven to be the most important patho-biological link [48–51]. Parkinson's disease is characterized by motor rigidity, bradykinesia, resting tremor and postural instability. However, decreased cognitive flexibilities, executive difficulties, visuospatial dysfunctions and delayed information processing speed (IPS) are the most important facets of cognitive disabilities among the various cognitive domains affected in Parkinson disease dementias (PDD). Obsessive–compulsive behavior is considered to be one of the most common

behavioral issues beside depression, anxiety, impulsivity and disinhibition in Parkinson's disease. Constipation is one of the most common non-motor symptom of PD beside anosmia and depression [42, 52–56].

Conclusion

Authors herein try to align these pieces of evidence and connect the dots to figure out the preclinical trajectory of Parkinson's disease and its relationship with "gut–brain dysbiosis" and the "rigid" personality (OCPD) trait, OCD and constipation. Recognition of preclinical phenotypes of AD and PD can greatly augment the understanding of the pathophysiology and offer therapeutics at the earliest. "Gut–brain axis" has already been proven to be the most important patho-biological linkage between AD and PD. It may be intriguing to speculate that the shared clinical continuum of OCPD, OCD, depression, anxiety, "Cluster C" personality traits and constipation are the preclinical phenotype, connecting AD and PD. So did Freud anticipate this entire spectrum while describing "anankastic personality disorder", which was the earliest clue of brain–gut crosstalk later, proved to be "gut–brain dysbiosis"?

Abbreviations

AD	Alzheimer's disease
PCA	Posterior cortical atrophy
MCI	Minimal cognitive impairments
CSF	Cerebrospinal fluid
OCSD	Obsessive–compulsive spectrum disorders
BPSD	Behavioral and psychological symptoms in dementia
Anankastic PD	Anankastic personality disorder
OCPD	Obsessive–compulsive personality disorder
DSM-III-R	Diagnostic and Statistical Manual III Revised version
PD	Parkinson's disease
IPS	Information processing speed
PDD	Parkinson disease dementias

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