Neurodegenerative Diseases at the Systems Level: A Glance at Cognitive, Motor and Metabolic Functioning

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ABSTRACT

Neurodegenerative diseases (NDs) implicate protein aggregation and could impute network dysfunction, neuroinflammation and neuronal loss, among other factors. Changes attributed to a neurodegenerative brain - be it the accumulation of β-amyloid or the formation of neurofibrillary tangles - suggest cognitive, metabolic, and motor deficits. This literature review investigates the correlation between various neurodegenerative diseases at the systems level. Cognitive deficits primarily resulted from protein aggregates, while metabolic dysfunction linked to blood-brain barrier breakdown, damaged gut epithelium, and insulin resistance. Furthermore, motor impairments - seen as initial symptoms in various NDs - were defined by atrophy, autophagy, calcium dysregulation and neuronal reduction. Understanding the physicochemical and molecular changes that affect brain functioning on a systemic level can help provide much-needed information for developing diagnostic and therapeutic strategies.

Introduction

Neurodegenerative diseases affect millions across the world. Statistical studies suggest that dementia patients worldwide could rise to 78 million by 2030 and 139 million by 2050 (World Health Organization, 2021). Anatomic vulnerability, progressive neuronal loss, accumulation of physiochemically misfolded protein aggregates and selective dysfunction are factors that delineate the characteristics of neurodegenerative diseases (Bertram & Tanzi, 2005; Dugger & Dickson, 2017; Kovacs, 2019; Soto & Pritzkow, 2018). Neuronal loss in neurodegeneration is region-specific, and attributed to dysfunctions in metabolic and mitochondrial processes, oxidative stress, changes in synaptic plasticity, and neuroinflammation (Kovacs, 2019; Muddapu et al., 2020; Palop et al., 2006; Singh et al., 2019).

Ageing is a significant risk factor associated with neurodegeneration. Various hallmarks of ageing, such as neuroinflammation, cellular senescence and mitochondrial dysfunction, correlate to the susceptibility of neurodegenerative diseases (Hou et al., 2019; Walker et al., 2019). Astrocyte dysfunction and protein mutations in the central nervous system (CNS) play critical roles in the onset, progression, and resolution of inflammation in neurodegeneration by chronic activation of innate immune responses (Amor et al., 2014; Hill, 2019). Repeated activation is an integral symbol of the ageing process, whereby chronic inflammation and senescence influence the extracellular vesicles to increase the volume of pathogenic proteins. (Hill, 2019; Stephenson et al., 2018).

This literature review compiles existing research to link neurodegenerative diseases at a systems level. It investigates the effects of neurodegeneration on cognitive, metabolic and motor systems across various diseases, including Alzheimer's Disease (AD), Amyotrophic Lateral Sclerosis (ALS), Frontotemporal Dementia (FTD), Huntington's Disease (HD), Parkinson's Disease (PD) and prion diseases.

Cognitive Systems

Cognitive decline is a known symptomatic hallmark across neurodegenerative diseases. Commonly occurring as memory and language dysfunction, cognitive impairments could occur due to changes in β-amyloid levels, grey matter and hippocampal volumes, as well as tau pathologies.

Tau is a microtubule-associated protein that plays a role in axonal transport, helps polymerise and stabilise axonal microtubules and maintains structural integrity (Guo et al., 2017; Pérez et al., 2018). The neuroanatomic distribution of tau plays a crucial role in domain-specific cognitive performance (Bejanin et al., 2017). There are six main isoforms of tau, the splicing of which expresses a 4R:3R ratio of mRNA and protein in a healthy brain (Gao et al., 2018; Hanger et al., 2009). Post-translational modifications such as acetylation, nitrosylation, phosphorylation, and ubiquitination break this 4:3 ratio balance by unregulated tau accumulation, leading to the manifestation of degenerative diseases termed 'tauopathies' - Alzheimer's Disease and frontotemporal dementia being examples of the same (Dugger & Dickson, 2017; Kovacs, 2019).

Tau hyperphosphorylation induces tau missorting from neuronal microtubules to post-synaptic dendrites leading to tau oligomers and neurofibrillary tangles (Kawakami & Ichikawa, 2015; Mazanetz & Fischer, 2007). Hyperphosphorylated tau can set off neuronal dysfunction and cell death, caused by aggregation, microtubule disassembly and loss of cytoskeletal microtubule-stabilising properties (Ferrer et al., 2021; Jadhav et al., 2019).

Changes in tau pathology affect cognitive functioning in neurodegeneration, as seen in Alzheimer's disease, frontotemporal dementia, and Parkinson's disease.

Alzheimer's Disease

Alzheimer's Disease (AD), originally described as "an unusual illness of the cerebral cortex" (Alzheimer, 1907), is characterised by cerebral atrophy and abnormally high β-amyloid levels, as well as the tau-mediated deposition of neurofibrillary tangles and senile plaques (Bertram & Tanzi, 2005; Fu et al., 2018; Guo et al., 2020). Currently affecting over 6 million people in America alone, estimates show that the number of Americans aged 65 or older with Alzheimer's Disease could rise to 12.7 million (Alzheimer's Association, 2022). The Global Burden Disease (GBD) makes AD the 9th most burdensome condition for those over the age of 60 (Alzheimer's Disease International, 2015), evidencing the impact the disease - and attributed global cognitive decline - has on one's quality of life.

Phosphorylation in AD impacts the amyloidogenic pathway (APP) - whose gene, further, has a hypoxia-related pathway - by facilitating APP processing and β-amyloid production (Ferrer et al., 2021; Nalivaeva et al., 2018). Hypoxic conditions can induce changes in the activity and expression of α- and γ-secretase enzymes, causing Aβ accumulation due to deficits in the soluble amyloid precursor protein-α (sAPPα) and soluble acetylcholinesterase (AChE) production (Nalivaeva et al., 2018; Nalivaeva & Turner 1999). β-amyloid accumulation primarily plays a role in the early stages of AD, by promoting the aggregation and spread of tau beyond the tempo-parietal lobes and into the neocortex (Bejanin et al., 2017; Bertram & Tanzi, 2005; Johnson et al., 2016). Individuals with considerably higher levels of amyloid displayed hippocampal atrophy, which is closely associated with verbal and visual episodic memory (Bilgel et al., 2018). Hence, cognitive decline goes hand-in-hand with the inability of the task-irrelevant brain regions to deactivate (Palop et al., 2006).

Region-specific cognitive deficits in AD attributed to grey matter loss, explicated by grey matter atrophy being a consequence of tau pathology (Bejanin et al., 2018; Villeneuve et al., 2015). Neurogranin, a post-synaptic protein, is present in the excitatory neurons and dendrites in the cerebrospinal fluid (CSF), where it plays an integral role in

memory consolidation (Portelius et al., 2015). High concentrations of this protein, as seen in AD, correlates to increased cognitive deterioration and hippocampal atrophy (Kvartsberg et al., 2014; Portelius et al., 2015). Another factor of mild cognitive impairment is the increased abundance of systemic tumour necrosis factor-α (TNF-α), which results in deficits in attentional and working memory function, both of which are affected in delirium (Hennessy et al., 2017). Additionally, cognitive dysfunction, including those in language, visuospatial and executive function, is heavily pronounced in patients with early-onset familial AD (EOAD), where shared biochemical pathways foster the overproduction of Aβ species (Bertram & Tanzi, 2005; Jadhav et al., 2019; Xia et al., 2017). Most cognitive deficits in Alzheimer's Disease are, thus, ascribed to the accumulation and burden of neurofibrillary tangles and tau oligomers.

Frontotemporal Dementia

Defined by progressive dysfunction in behaviour, executive function and language (Bang et al., 2015; Bertram & Tanzi, 2005), frontotemporal dementia (FTD) shows post-synaptic dopaminergic failure and cerebral atrophy due to the degeneration of the frontal and temporal lobes and the substantia nigra (Whitwell, 2019). Microscopic findings of the frontotemporal lobar degeneration displayed neuritic threaders and astrocytic plaques in corticobasal degeneration, pick bodies in Pick's disease, and tufted astrocytes in progressive supranuclear palsy (Bang et al., 2015). Neuroimaging findings revealed grey matter losses - associated with cognitive decline - in the gyri, temporal lobe, and parahippocampal entorhinal cortex (Young et al., 2018).

There are two categories within FTD - behavioural (bvFTD) and language. BvFTD is characterised by behavioural compulsions and disinhibitions, while language FTD displays cerebral dysfunction and diverging localisations (Bang et al., 2015; Gorno-Tempini et al., 2011). The semantic variant of language FTD is closely associated with emotional processing and linguistic dysfunction due to bilateral anterior temporal lobe atrophy (Bang et al., 2015).

FTDP-17 and Picks Disease (PiD) are both tauopathies that play a role in the clinical manifestation of frontotemporal dementia (Gao et al., 2018). PiD most commonly manifests as bvFTD with frontotemporal atrophy and is associated with severe neuronal loss (Lin et al., 2019). In the case of FTDP-17, missense and splicing mutations lead to mutations in the coding of the microtubule-associated protein tau (MAPT) gene. Furthermore, as mentioned above, a disturbed 4R:3R ratio can cause neuronal and synaptic dysfunction, leading to behavioural and cognitive deficits, and thus neurodegeneration (Alonso et al., 2004; Gao et al., 2018; Hardy & Orr, 2006).

Parkinson's Disease

Parkinson's Disease (PD) presents itself with Lewy bodies and the loss of dopaminergic neurons in the substantia nigra due to the binding and inhibition of tropomyosin receptor kinase B (TrkB) (Bertram & Tanzi, 2005). Genetic studies have shown an underpinning of extensive tangle pathology due to an association with MAPT (Hardy & Orr, 2006). Leucine-rich repeat kinase 2 (LRRK2) is mutated in PD and contributes to tau pathology either by hyperphosphorylation or by binding to glycogen synthase kinase-3β (GSK-3β) (Kawakami & Ichikawa, 2015).

Cognitive impairments in PD include executive and speech dysfunction and dementia (Fang et al., 2020). Dopamine insufficiency further impairs D2 receptor metabolism in the midbrain-cortex circuits, which cause executive dysfunction (Christopher et al., 2013; Fang et al., 2020). Disturbances in cholinergic pathways, changes in the functional connectivity of the posterior brain regions, and network dysfunction in the default mode, dorsal attention and frontoparietal networks have been evidence of impairments in memory and learning (O'Callaghan & Lewis, 2017). Patients with PD showed deficits in cholinergic neurons and AChE, whereby acetylcholine (ACh) loses its ability to maintain the functional integrity of the central nervous systems and hence induces a cognitive decline in the form of

memory loss and reduced cognitive flexibility (Fang et al., 2020). Therefore, the functioning of the cognitive systems is dependent on the levels of atrophy, neural and synaptic connections, and β-amyloid accumulation.

Motor Systems

Motor deficits relate to those in movement, balance, and coordination. Impairments in motor systems can come about due to various reasons, including, but not restricted to, cellular and molecular pathologies, neuroinflammation, neuronal and synaptic loss, and synucleopathies. We also see converging pathways across various neurodegenerative diseases, proving that gene mutations can occur regardless of protein aggregation and deposition variations.

Parkinson's Disease

Patients with PD depict symptoms typical to such patients, which can include akinesia, bradykinesia, dyskinesia, gait disturbances, and deficits in balance, posture and speech (Magrinelli et al., 2016; Moustafa et al., 2016). The main characteristic of PD is the loss of dopaminergic neurons in the substantia nigra, followed by neuronal degeneration in motor, prefrontal, and sensory cortices (Fu et al., 2018). Similar to ALS, motor dysfunctions in PD can come about due to increased α-synuclein aggregation. Gene mutations can phosphorylate this α-synuclein, which inhibits the necessary process of autophagy and decreases motor function. Genes mutated in Parkinson's Disease include leucine-rich repeat kinase 2 (LRRK2), PARK2 and PRKN. LRRK2 is the leading cause of autosomal dominant forms of PD (Bertram & Tanzi, 2005). Its loss promotes the accumulation of phosphorylated α-synuclein and apoptotic cell death, instigating disturbances in motor functions (Fujikake et al., 2018). In the case of PRKN, the ubiquitination of proteins by ubiquitin ligases sets off mutations in the form of exon deletions and genomic rearrangements, which triggers autophagic cell death and renders neurons vulnerable to cytotoxins, and hence motor deficits (Bertram & Tanzi, 2005).

Studies have shown overlapping pathologies of Parkinson's Disease with AD and ALS. Alterations in the dorsolateral prefrontal cortex and mitochondrial dysfunction can be seen between AD and PD, while ALS and PD show RNA splicing (Arneson et al., 2018).

Amyotrophic Lateral Sclerosis

Amyotrophic Lateral Sclerosis (ALS) is characterised by the atrophy and rapid degeneration of the motor neurons in the brain and spinal cord. Aggregation of α-synuclein is a significant factor responsible for gene mutations that cause motor impairments, such as fatigue and speech dysfunction. Such changes occur due to the activation of calcium-dependent enzymatic pathways and excitotoxicity, leading to synaptic failure (Bertram & Tanzi, 2005; Kiernan et al., 2011). The lack of calcium-buffer proteins can increase the vulnerability of motor neurons following glutamate receptor activation, increasing the risk of neuronal death (Fu et al., 2018).

ALS can present itself with various clinical perturbations - bulbar-onset ALS causes flaccid and spastic dysarthria while limb-onset ALS affects the limb's upper and lower motor neurons (Grossman, 2018; Kiernan et al., 2011). There are two further major subtypes of ALS - primary lateral sclerosis and progressive muscular atrophy (Dugger & Dickson, 2016). Primary lateral sclerosis induces loss of upper motor neurons, causing deep tendon reflexes and spasticity. On the other hand, progressive muscular atrophy is characterised by the loss of the lower motor neurons, leading to fasciculations and fatigue (Grossman, 2018; Kiernan et al., 2011).

ALS pathogenesis begins in the agranular motor cortex and the motor nuclei of cranial nerves. It is believed that the cognitive aspects of the disease worsen with the decline in motor functions (Grossman, 2018; Kovacs, 2019).

Autophagy, which plays the role of regulation of aggregation formation in ALS, mutates superoxide dismutase 1 (SOD1) and TAR DNA-binding protein-43 (TDP- 43) genes and hence degenerates motor neurons (Fujikake et al., 2018). Additionally, the shortage of regulatory t-cells in ALS was also concurrent with neuronal motor death (Stephenson et al., 2018).

Alzheimer's Disease

Motor deficits in AD are seen in the form of bradykinesia, gait and speech disturbances, and tremors (Scarmeas et al., 2004). Different stages of this disease affect varying parts of the brain - Aβ pathology initially affects the neocortical regions and finally the cerebellum and pons, while tau pathophysiology first attacks the basal forebrain, and eventually the occipital lobe and substantia nigra (Kovacs, 2019). The most vulnerable neurons in AD are cholinergic neurons, which disturb motor functions due to their effect on the sensory function regulator acetylcholine (ACh) (Ahmed et al., 2019; Fu et al., 2018; Schirinzi et al., 2018).

Though rare, motor impairments in AD, through various other diseases and pathologies affecting these systems, could be attributed to the presence of the ε4 allele of the apolipoprotein E (APOE) gene (Buchman et al., 2009; Buchman et al., 2014). Additionally, higher left hemisphere and motor cortex atrophy could also contribute to dysfunction in motor processes (Graff-Redford et al., 2021).

Frontotemporal Dementia

The behavioural variant of frontotemporal dementia (bvFTD) is most associated with motor dysfunction due to hexanucleotide expansions in the C9ORF72 gene - the mutation of which provokes the formation of motor phenotypes and results in symptoms such as agrammatism and speech apraxia (Dugger & Dickson, 2016; Smeyers et al., 2021; Young et al., 2018).

Neuroimaging studies of corticobasal degeneration have shown atrophy of the primate cerebral cortex containing the supplemental motor area (Bang et al., 2015). Additionally, the increase in the central motor conduction time - a feature of both frontotemporal lobar degeneration and motor neuron disease - was found to be closely associated with the degeneration of the corticospinal tracts and the dysfunction of the upper motor neurons (Burrell et al., 2011; Cairns et al., 2007).

Huntington's Disease

Elucidated by astrocytosis, atrophy of the basal ganglia and neostriatal region, Huntington's Disease (HD) shows degeneration of cortical areas and the expansion of unstable trinucleotide repeats (Bertram & Tanzi, 2005; Goldman et al., 1994; Kovacs, 2019). Neuronal loss in HD is not region-specific but observed across the cerebral cortex (Chi et al., 2018).

Patients with HD have relatively lower levels of the brain-derived growth factor due to the presence of Huntington protein (Ferrer et al., 2000; Macdonald & Halliday, 2001). White lesions observed in the sub-thalamus and the loss of cortical pyramidal neurons are consistent with basal ganglia and cortical atrophy (Macdonald & Halliday, 2001). There is also a correlation between amygdalar volumes and motor dysfunction, whereby decreased amygdalar volume, as seen in HD, relates to increased motor impairments including chorea, dystonia and impaired gait (Ahveninen et al., 2018).

Similar to ALS, calcium regulation and motor functions go hand-in-hand in HD. Certain gene mutations in HD cause calcium leakage from the endoplasmic reticulum, increasing the volume of neuronal store-operated calcium, which is responsible for striated neuronal and synaptic loss causing motor defects (Wu et al., 2018). Furthermore, we can see the shared mechanisms of gain of chromatin organisation genes and loss of oligodendrocyte differentiation genes between AD and HD (Arneson et al., 2018).

Prion Diseases

Prion diseases include converting normal prion protein to its pathogenic form and are classified as acquired, genetic, and idiopathic/sporadic (Dugger & Dickson, 2016). Prion-like mechanisms in neurodegenerative diseases could underlie specific aspects of their phenotypic diversity and help understand therapeutic interventions for misfolded protein aggregates (Frost & Diamond, 2009; Soto & Pritzkow, 2018). One such intervention is the anti-prion concept, which helps delay the onset of disease by generating a conformational strain, and then dissociating seeding from the aggregated product (Diaz-Espinoza et al., 2018; Soto & Pritzkow, 2018).

Axonal transport impairments caused by neuronal reduction in the motor cortex hindlimb area could further worsen disease symptoms, including motor dysfunction relating to gait, movement and speech (Ermolayev et al., 2009). The pathogenic form of prion protein or PrPsc interacts with subunits of the voltage-gated calcium channels (VGCC), increasing subunit accumulation and aberrant VGCC delivery to the synapses, which leads to motor disease (Chiesa, 2015). Motor deficits can, thus, be related to atrophy, autophagic dysfunction, calcium dysregulation, gene mutations, and neuronal loss.

Metabolic Systems

The relationship between the brain and other metabolic organs, such as the gastrointestinal tract and the pancreas, suggests a close link between neurodegeneration and impaired metabolic processes. Understanding these links are integral not only to elucidate the relationship between these metabolic organs but might also help accelerate the treatment of dementia and other neurodegenerative diseases. This section covers two examples: brain function and gut microbiome, and dementia and diabetes.

Brain Function and Gut Microbiome

The gut microbiome is responsible for various immunological and pathophysiological functions, such as regulating host metabolic pathways and the development and functioning of the brain (Kho & Lal, 2018; Wang et al., 2018). The gut-brain axis connects the brain to the gut, where the vagus nerve facilitates communication between the cognitive domains of the brain and the gastrointestinal tract with the help of microbial metabolites (Carabotti et al., 2015; Petra et al., 2015). Alterations in the bidirectional communication between the brain and the gut in response to various stresses manifest as gut-brain disorders (Martin & Mayer, 2017).

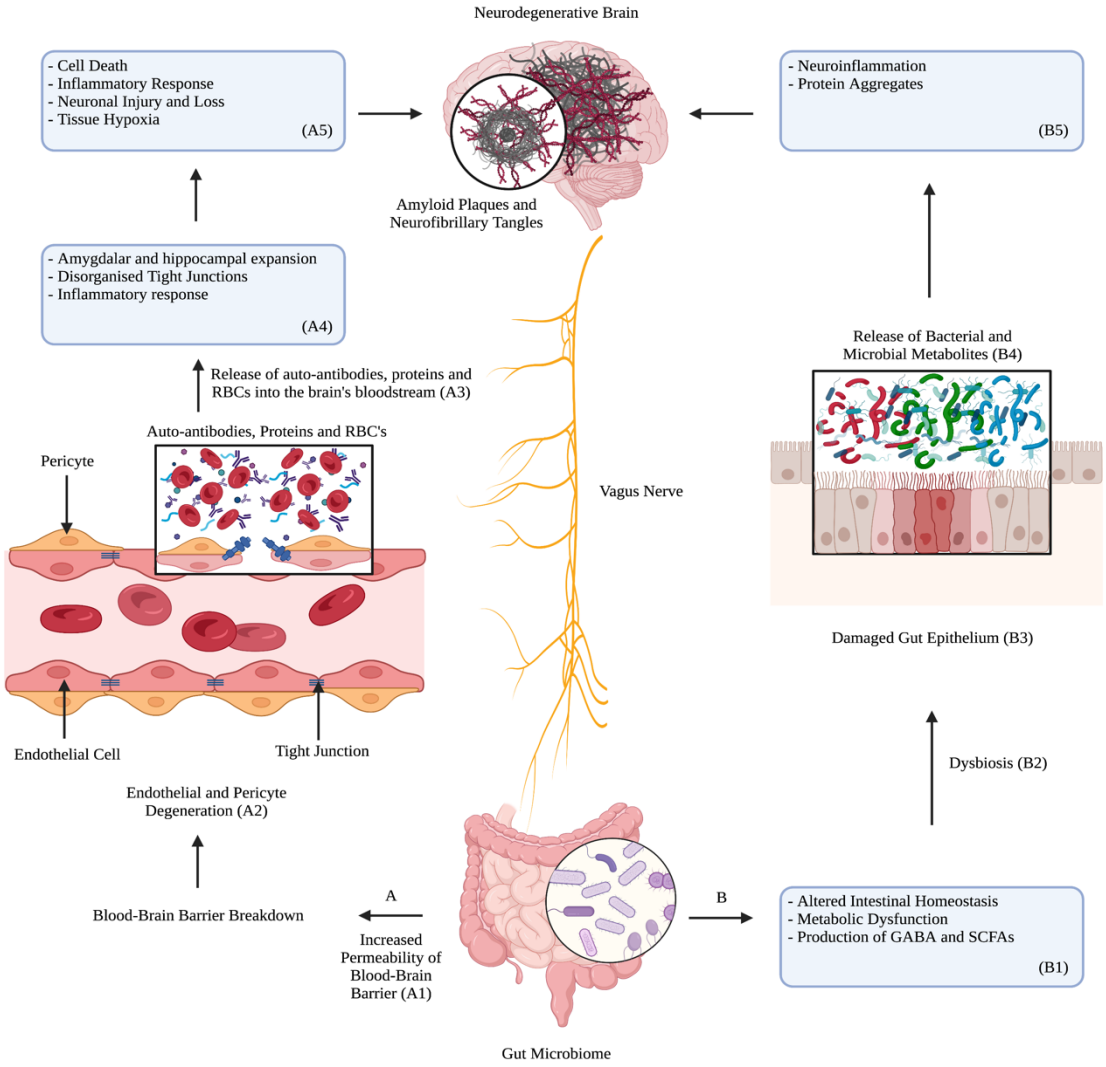

Figure 1. Brain and gut microbiome relation. The presence of microbiota can affect brain function by the breakdown of the blood-brain barrier (BBB) (A) and by damaging the gut epithelium (B), both of which induce neurodegeneration due to the release of toxins into the blood flow. A. Increased permeability of the BBB (A1) over time leads to its breakdown due to endothelial and pericyte degeneration (A.2). This causes the tight junctions to break and neurotoxins such as auto-antibodies, proteins, and RBCs to leak into the brain's bloodstream (A.3). The presence of these toxins results in changes such as amygdalar and hippocampal expansion (observed in a mouse model of adult microbiota-deficient mice), disorganised tight junctions and inflammatory responses (A.4), all of which lead to cell death and neuronal injuries contributing to neurodegeneration (A.5). B. Microbiota alters homeostatic and metabolic processes, facilitating the production of GABA and short-chain fatty acids (B.1). This is followed by the process of dysbiosis (B.2), which damages the gut epithelium (B.3). It allows metabolites to be released into the bloodstream (B.4), causing neuroinflammation and protein aggregation in the brain (B.5). (Created with BioRender.com)

Increased blood-brain permeability is a direct impact of the gut microbiota (Fig 1 A1). This increased permeability can be causal for many reasons, one of them being microglial activation - prolonged neuroinflammation can

induce phagocytosis, causing loss of blood-brain barrier (BBB) permeability (Haruwaka et al., 2019). Certain neurotoxic proteins could also affect permeability. TNF-α is one such protein responsible for increased BBB permeability, as it suppresses the expression of tight junction proteins (Takechi et al., 2017).

The blood-brain barrier (BBB) regulates reliable neuronal signalling and facilitates communication between the central and peripheral nervous systems (Abbott et al., 2006; Rhea & Banks, 2019). Defined by the breakdown of tight junctions and release of neurotoxins into the blood flow (Fig 1 A3), BBB breakdown is characterised by endothelial and pericyte degeneration and generation of autoantibodies (Fig 1 A2) (Sweeney et al., 2018). These neurotoxins such as free iron generating reactive oxygen species, plasma proteins such as fibrin and plasmin, and RBC-derived haemoglobin, cause inflammatory responses and neuronal injuries leading to neurodegeneration (Fig 1 A4 and A5) (Montagne et al., 2017). The accumulation of albumin, in particular, leads to oedema and hence tissue hypoxia due to reduced blood flow (Montagne et al., 2017; Sweeney et al., 2018).

The gut epithelial cells maintain gut homeostasis by regulating host immune responses (Okumura & Takeda, 2017). The presence of microbiota sets off a chain reaction, thereby disturbing homeostatic and metabolic processes and producing GABA and short-chain fatty acids (SCFA) (Fig 1 B1). Gut dysbiosis, then, exacerbates the pathological state of the neurotoxins and neurotransmitters, damaging the epithelial cells in the gut barrier (Fig 1 B3) and promoting the release of bacterial and microbial metabolites into the bloodstream (Fig 1 B4) (Conte et al., 2020).

Neurodegeneration caused by gut microbiota is thus attributed to the release of neurotoxins into the brain bloodstream by BBB breakdown and gut epithelial damage. However, intestinal microbiota induces Aβ aggregation and ageing in AD, further setting off the neurodegenerative process (Kowalski & Mulak, 2019).

Diabetes and Dementia

Observations from statistical studies show that diabetic patients have a greater rate of cognitive decline and a higher risk of future dementia (Cukierman et al., 2005; Strachan et al., 2011). Cerebral amyloid angiopathy, impaired glucose tolerance and oxidative stress contribute to neurodegeneration through Aβ and TNF-α formation, autophagic impairment and GSK-3β activation (Biessels et al., 2006; Jellinger, 2013).

Neuroimaging studies have shown that grey matter loss in Type 2 diabetes mellitus (T2DM) was highest in regions of the anterior, cingulate, medial frontal, and medial temporal lobes, all of which are incredibly susceptible to neurodegeneration in Alzheimer's Disease (Moran et al., 2015). Other observational studies have also shown the association between higher blood glucose levels and reduced average thickness in these vulnerable regions in AD (Wennberg et al., 2016).

Insulin resistance is an integral characteristic of AD and T2DM (Chatterjee & Mudher, 2018). On binding to the insulin receptor, insulin then activates tyrosine and the insulin receptor substrates, promoting AKT activation and GSK-3β phosphorylation by the phosphatidylinositol-3-kinase (PI3K) (Avila et al., 2012; Chatterjee & Mudher, 2018). This phosphorylated GSK-3β further hyperphosphorylates tau, leading to neurofibrillary tangle formation (Avila et al., 2012). Hyperglycemia elevates the level of advanced glycated end products (AGE), which is associated with cognitive deficits in AD due to increased Aβ aggregation (Chatterjee & Mudher, 2018; Li et al., 2013; Moreira et al., 2003). Additionally, post-mortem studies of senile plaques in dementia evidenced the presence of metabolic oxidised products closely related to hyperglycaemia, which can also contribute to chronic cognitive deficits (Cukierman et al., 2005).

Autophagy is the process of self-induced lysosomal degradation, which plays a role in the degradation of misfolded proteins in neurodegeneration (Fujikake et al., 2018; Glick et al., 2010). Oxidative stress initially damages intracellular organelles and affects autophagic clearance, following the accumulation of autophagosomes and hence Aβ and tau oligomers over more extended periods (Chatterjee & Mudher, 2018; Jung et al., 2011). Insulin resistance also plays a role in autophagic dysfunction.

Synaptic dysfunction and neuroinflammation are other characteristics of neurodegenerative diseases, accredited by the effect of T2DM on Aβ and tau pathologies. Hyperinsulinemia promotes synaptic dysfunction by increasing insulin concentration, thereby decreasing the impact of the Insulin Degrading Enzyme (IDE) responsible for Aβ regulation (Chatterjee & Mudher, 2018; Son et al., 2016). On the other hand, hyperglycaemia activates the nuclear factor kappa-light-chain enhancer B (NF-κB) and releases TNF-α, which triggers neuronal apoptosis, neuroinflammation, and tissue damage (Jaeschke et al., 2004).

Conclusion

Various neurodegenerative diseases are implicated by deficits in cognitive, motor and metabolic functioning. The investigation facilitated the study of these systems in such diseases and described their effects through a literature review. By virtue of understanding the deficits brought about by dysfunction across various systems, this study portrays that atrophy, gene mutations, neuroinflammation, changes in grey matter, neuronal connectivity and protein levels all affect the cognitive, motor and metabolic abilities of the individual.

While limitations to the study relate to changing deficits with disease progression, overlapping symptoms across systems, varying aetiologies across diseases, this analysis can provide information which could be useful to future studies compiling data to further the development of therapeutic interventions in neurodegenerative diseases. This study may also provide insight into the importance of neuroimaging, and how it can be a valuable tool to track cognitive, motor and metabolic outcomes.

Acknowledgements

This review article has been written under the guidance and mentorship of Dr. Gonca Bayraktar, neuroscientist and research associate at the University of Cambridge, England, United Kingdom.

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Figure 1 created with BioRender.com . Blood-Brain Barrier adapted from “Blood Brain Barrier (simple longitudinal)” by BioRender.com (2022). Retrieved from https://app.biorender.com/biorender-templates .

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