Chapter 2
Pathophysiological Mechanisms of Brain Disorders

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2.1 Neurodevelopmental Disorders: Etiologies and Management

Autism spectrum disorder (ASD), Attention-Deficit/Hyperactivity disorder (ADHD), and intellectual disability are the most reported neurodevelopmental disorders. These pathologies disrupt normal brain development and affect an individual's emotional, learning, memory, and self-control abilities and diminish the quality of life. The cause of any of these neuropathies is complex as most of them result from a synergy of genetic alterations, and environmental and immunological factors (Fig. 2.1).

2.1.1 Autism Spectrum Disorder (ASD)

2.1.1.1 Synaptic Dysfunction in ASD

One of the most observed disrupted molecular functions in ASD pathology is synaptic dysfunction. Individuals with ASD tend to have more synapses due to disrupted synaptic pruning, abnormal dendritic spine morphology, and dysregulated synaptic transmission during development. This surplus of synapses in the brain results in hyperexcitation of the neurons. The published genomic reports of autistic patients and animal models have reported several genes that are particularly involved

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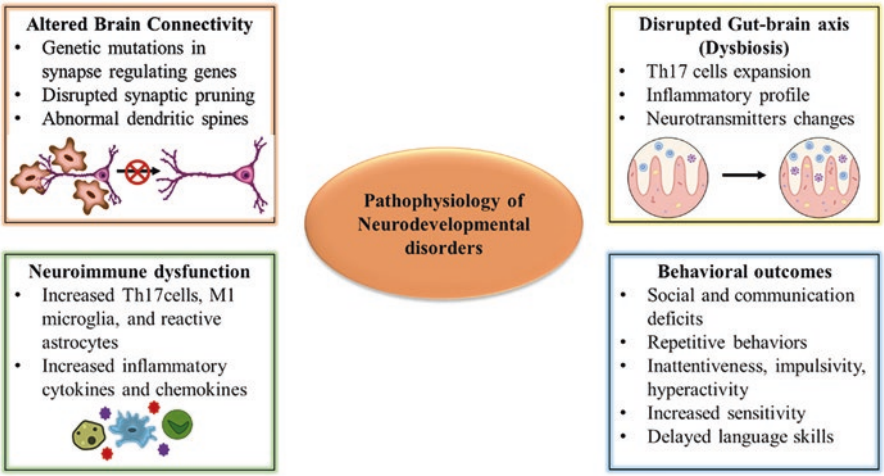

Fig. 2.1 Etiology of neurodevelopmental disorders and phenotypic outcomes: Neurodevelopmental disorders like Autism spectrum disorder or attention deficit hyperactivity disorder share some similar mechanistic changes like altered brain activity, neuroinflammatory profile both in CNS and periphery, and dysbiosis which can lead to disease specific behavioral outcomes like social and communication deficits and repetitive behaviors in autism and inattentiveness, impulsivity, and hyperactivity in case of ADHD

in homeostatic synaptic transmission and diseased conditions, disrupting normal synaptic communication. Normal synaptic function is governed by the synergy between different factors like adhesion molecules, scaffold proteins, ion channels, and neurotransmitter receptors. And some of the genes reported via genomic studies are responsible for keeping in check the expression level of the above-mentioned genes to ensure proper synaptic functioning.

Synaptic transmission is a transcription and translation-dependent neuronal activity, and mutations in many of the transcription factors associated with this translation and transcription processes are reported in ASD. For example, postsynaptic scaffolding proteins (SH3 and multiple ankyrin repeat domains protein (SHANK)), glutamate receptors, chromodomain-helicase-DNA-binding protein 8 (CHD8), and many others. Disorders in any of these synaptic adhesion molecules, neuroligins (NLGNs), scaffolding proteins, or receptors translation or transcription can result in the altered synthesis of synaptic proteins and thus disrupted neuronal plasticity. Changes in the expression of any of these molecular factors can eventually affect the number and strength of synapses leading to alterations in neuronal connectivity [1]. Neuropathological studies in past years have reported that in ASD, abnormal dendritic spine morphology like increased spine density and aberrant structures are observed [2]. Post-synaptic scaffolding proteins Shank1,2 and 3 are encoded by SHANK genes directly in the post-synaptic densities of excitatory synapses. Shank mutations especially Shank3 have been well studied in both humans and its counterpart mutant mice models. Individuals with Shank3 mutations exhibit faulty dendrite development and morphological features along with defective

axonal growth cone mobility. Similar alterations are observed in Shank3 knockout mice together with the reduction in the number of cortico-striatal connections [3]. Shank3 mutant mice display disrupted long-term potentiation due to aberrant synaptic signaling in the hippocampus. Shank2 knockout mice studies have reported defects in excitatory neurotransmission and synaptic plasticity. Shank proteins regulate dendritic spine size, Shank1 overexpression in hippocampal neurons leads to oversized dendritic spines as well as their early maturation. On the other hand, Shank1 deletion results in reduced spine size, thinner PSDs, and weakened synaptic communication [4].

2.1.1.2 Immune Dysfunction and Neuroinflammation in ASD

Immune dysfunction and neuroinflammation have gained the spotlight in the past few years in the field of ASD research. Both patients and animal models have been identified with persistent immune dysregulations. For instance, one of the earliest studies in this field reported 150 differentially expressed genes in ASD individuals compared to controls, 85% of these upregulated genes were involved in the immune response pathways [5]. These changes in the immune landscape occur both in the CNS and periphery, such as ASD patients have more circulating inflammatory Th17 cells, increased M1 microglia (inflammatory) and reactive astrocytes, and their respective signaling pathways. This enhancement in inflammatory molecular signaling pathways in CNS and periphery can affect normal brain functions like synaptic transmission, social behaviors, and other physiological actions [6, 7]. These reactive microglia and astrocytes can lead to increased release of inflammatory cytokines and chemokines such as IL-6 (interleukin-6), TNFα (tumor necrosis factor α), IFNγ (interferon gamma), IL-17 (interleukin-17), and many others. On the other hand, there is a reduction of anti-inflammatory factors like IL-10 (interleukin-10) and TGFβ (transforming growth factor β) [8, 9]. These studies have helped in establishing the diagnosis of immune dysfunction and neuroinflammation via monitoring the levels of inflammatory factors mentioned above as a biomarker tool.

Similar findings have been reported in the maternal immune activation (MIA) and valproic acid (VPA) induced autism mice models. Upregulation of IL-6, IL-17, and TNFα is observed in MIA and VPA mice models both in CNS and periphery [10]. Some reports also provide evidence of infiltration of Th-17 cells from the periphery into the brain along with the migration of IL-1α (interleukin-1 alpha), IL-1β (interleukin-1 beta), TNFα, and IL-6 [11]. This increase in the inflammatory profile of the brain enhances the microglia and astrocyte crosstalk, which can affect blood-brain barrier (BBB) permeability, thus leading to unsupervised communication between CNS and periphery. Maternal autoimmune disorders such as fever or infection or exposure of the mother to external toxins during pregnancy can result in exaggerated immune responses, increasing the risk of ASD in progeny.

One of the well-established mice models to explore ASD pathology from this perspective is MIA, which is created by viral infection molecules (poly(I: C)), bacterial mimics (lipopolysaccharide (LPS)), and some inflammatory cytokines

injection at mid-gestation stage. Treatment of mice with either poly(I: C), LPS, or cytokines disturbs the maternal immune and cytokine profile, such as an increase in IL-6, IL-17, and TNFα levels. These cytokines and inflammatory Th-17 cells can cross the blood-placenta barrier and enter fetal blood, resulting in the alteration of the immune profile of the fetus. These alterations result in the development of ASD phenotypes such as anxiety-like behaviors, deficits in social interactions, and repetitive behaviors [12].

2.1.2 Attention-Deficit/Hyperactivity Disorder (ADHD)

ADHD called hyperkinetic disorder is a persistent neurodevelopmental syndrome that affects 5% of school-age children and 2.5% of adults worldwide [13]. ADHD is characterized by distractibility, inattentiveness, impulsivity, and locomotor hyperactivity. This disorder can enhance the developmental risk for other neuropsychiatric disorders, accidents, and social deficits, which can lead to addictions or educational or professional failures throughout the lifespan of an individual. No single risk factor is associated with the development of ADHD, both genetic and environmental factors together lead to the initiation of this disorder. External factors such as childhood traumas, exposure of the mother to toxins or drugs during pregnancy, and exposure of children to environmental toxins such as lead can trigger ADHD lasting for an individual's life.

2.1.2.1 Genetics of ADHD

Genetics have a strong role in the development of ADHD, about 74% of ADHD cases have mutations at the gene level. Genes impact the onset of ADHD, its persistence, and remission thought the lifespan of an individual. Having said that, reports have also suggested that, living with ADHD individuals can increase their risk of developing ADHD two-ten folds compared to the general population [14]. ADHD occurrence is affected by both stable genetic factors like ADHD-associated genes or the alterations that arise at later time points of an individual's life. Studies have also shown that ADHD shares genetic influences with other neurodevelopmental and psychological disorders including ASD, cognitive impairments, and mood disorders.

Copy number variants (CNVs) such as deletion, insertions, or mutations in the genes have been reported to have a potential connection with ADHD pathology. Some studies have found that a significant number of ADHD cases carry large CNVs of >500,000 base pairs in length compared to non-ADHD individuals [15]. Some of these CNVs occur in genes that encode for neuronal nicotine receptors, key receptors of synaptic transmission in the nervous system. These CNVs also impact the activity of glutamate receptor encoding genes, which are essential for excitatory neuronal activity, and neuropeptide Y encoding gene, this peptide regulates food intake by monitoring signaling in the brain and autonomic nervous system [16, 17].

ADHD cases are presented with lower dopaminergic neuronal functioning (essential for voluntary body movements and a wide array of behavioral processes). ADHD individuals carry mutations for the genes (D4 and D1B) involved in the expression of dopaminergic neurons and the SlC6A3 dopamine transporter. Other genes in ADHD pathology are associated with the dysregulation of the monoamine system include SLC64 (serotonin transporter), HTR1B (gene encoding for serotonin receptor 1B), and SNAP25 (which encodes synaptosomal protein 25) [18, 19]. Some studies also report neuronal structural dysfunction such as neurite outgrowth in ADHD pathology.

2.1.2.2 Environmental Factors in ADHD Pathogenesis

Environmental risk factors are strong contributors to neurodevelopmental disorders, and many of these developmental disorders share the same external causative variables such as alcohol intake during pregnancy, exospore of mother to the toxins or inflammatory substances, difficult childhood, premature birth, or lower birth weight. Traumatic brain injury can increase ADHD risk by 30% [20], and certain infections such as measles or enteroviral infection can lead to an enhanced incidence of ADHD [21].

Animal studies have contributed a lot to our understanding of the association between environmental factors and ADHD. Some of these studies have found a strong correlation between exposure to tobacco or alcohol during pregnancy and ADHD, these external toxins can affect normal CNS development. Prenatal exposure to nicotine is one of the main causative agents of ADHD which can affect early brain development. Nicotinic acetylcholine receptor proteins are expressed early in the brain, indicating their importance in modulating dendrite outgrowth during the developmental phase. Prenatal or perinatal exposure to nicotine can affect neurite growth, influence the glutamate release and uptake by neurons, and may produce changes in the catecholaminergic system (it regulates diverse cognitive, motor, and endocrine functions). Early exposure to nicotine can affect locomotor activity, and impair cognitive functions, principally working memory, reported in human and animal studies [22].

2.1.3 Behavioral Outcomes of ASD and ADHD and Current Therapies

Clinical diagnosis of ASD is based on three main symptoms observed in the individuals i.e., social and communication deficits, repetitive behaviors, and general lack of interest or resistance to change. Along with these main symptoms, there are other behavioral alterations observed in the affected individuals that help in the diagnosis of ASD. For example, avoiding eye contact, reduced interest in children

or people, showing more attention towards toys or objects, increased sensitivity to various stimuli like loud noises, smell, or touch, repetitive movements such as the flapping of hands or spinning in circles, delayed language skills, or repetition of words.

ADHD individuals display three types of core behavioral phenotypes i.e., difficulty in focusing on one thing for a longer time (inattentiveness), exhibiting strange behaviors on sudden urges such as throwing things, talking out in a class, or spending too much money (impulsivity), and restlessness, inability to sit in a place, or climbing when it's not appropriate (hyperactivity). Based on the data collected from the behavioral assessment of the ADHD individuals, the clinician can diagnose the person with one of these ADHD subtypes: predominately hyperactive/impulsive type, in this type a person exhibits the hyperactive or impulsive behaviors for at least six months, but do not meet the criteria for inattention. Predominately inattentive type, an individual must exhibit constant inattentive behavior for six months but do not show hyperactivity for a longer duration, and lastly, combined type, an individual diagnosed with this ADHD type displays both hyperactive and inattentiveness for at least six months, and this is the most common form of ADHD in children [23].

ASD and ADHD management includes psychological counseling, psychoeducational programs, and special schools designed to improve the social and communicative skills, attentive span, and cognitive abilities of individuals. Special education programs and early behavioral therapies can help individuals to acquire communication, self-care, or specific employment skills. Psychoeducational programs are designed to improve cognitive abilities, and social and communication skills. While pharmacological interventions such as psychoactive drugs, anticonvulsants, or antidepressants focus on alleviating one or more symptoms of ASD and ADHD to improve the overall quality of life for the individual.

2.2 Neurodegenerative Diseases: Pathophysiology of Neurodegeneration and Resulting Pathologies

Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic lateral sclerosis (ALS), Huntington's disease, and many others fall into the neurodegenerative disorders category. These disorders in general affect the neuronal structure and function, leading to neuronal death, resulting in memory deficits, dysregulated motor coordination, and affecting speech and breathing. These pathologies share a somewhat similar working hypothesis i.e., these diseases arise from the progressive degeneration of neurons, share strong genetic and aging factors, but affect different brain regions (Fig. 2.2).

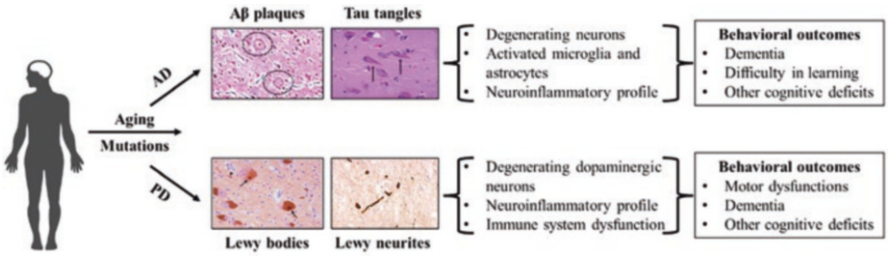

Fig. 2.2 Pathophysiological hallmarks of Alzheimer's disease and Parkinson's disease and behavioral outcomes: Pathological hallmarks of Alzheimer's disease (AD) include deposition of amyloid beta (Aβ) plaques and tau neurofibrillary tangles particularly in the cortical areas which lead to the degeneration of neurons and initiation of inflammatory cascades leading to the associated behavioral outcomes like dementia. Though Parkinson's disease (PD) shares the same concept of degenerating neurons with AD, the affected neurons in PD are mainly dopaminergic neurons in substantia nigra region of the brain. The atrophy of these neurons leads to poor neurotransmission and motor dysfunctions

2.2.1 AD Pathology

AD is an age-associated neurodegenerative disorder, resulting in dementia, affecting approximately 45 million individuals globally, and the fifth leading cause of death worldwide [24]. AD is characterized by two main histopathological hallmarks: amyloid beta (Aβ) aggregation into the extracellular senile plaques, and the formation of intracellular neurofibrillary tangles (NFTs) by hyperphosphorylated tau protein (pTau). One of the well-established mechanisms dysregulated in AD pathology is Aβ accumulation in the brain and how it leads to neuronal degeneration and behavioral outcomes. Recent studies have also identified immune system dysregulation and mitochondrial dysfunction as strong contributors to AD pathology.

2.2.1.1 Genetics and Aβ Pathway

Aβ is a 4kDa downstream molecule of amyloid precursor protein (APP), widely produced in the brain by both neuronal and non-neuronal cells. APP in homeostatic conditions is catalyzed by two proteolytic enzymes, β-secretase (β-APP- cleaving enzyme-1 (BACE1)) and γ-secretase subsequently, generating Aβ fragments. Pathomechanistic studies indicate that dysregulation in the production of Aβ and its clearance from neurons leads to Aβ dyshomeostasis, resulting in amyloid protein misfolding and aggregation into the neuronal senile plaques. Neuroimaging studies have identified a gradual spreading of Aβ plaques in the brain, senile plaque accumulation initially starts in cerebral regions and spreads from there to the brainstem and lower brain regions. This spreading phenomenon can explain the different phases observed in AD pathologies such as the pre-clinical stage in which Aβ continues to accumulate in the same brain areas and the clinical stage in which protein

plaques start spreading to the other brain regions, leading to behavioral outcomes [25].

AD pathology has a strong correlation with genetic mutations in the genes responsible for Aβ homeostasis in the brain, particularly in early-onset AD (EOAD). Genome-wide association studies (GWAS) of EOAD have identified mutations in the APP gene and presenilin 1 and 2 (PSEN1 and PSEN2), these genes govern Aβ synthesis and removal in the brain. In mouse models of EOAD, a mutation in any of these genes result in dysregulation of Aβ homeostasis, leading to misfolded proteins, aggregated plaques, and their buildup in the brain parenchyma. EOAD accounts for 1% of all AD cases, and most of these incidences have reported mutations in the above-mentioned genes. These studies of one-gene-one mutation-one misfolded protein further strengthen the Aβ hypothesis of AD pathology [26].

In LOAD, which is late-onset AD, no causal relation is observed so far between genetic mutations and AD pathology, but several genetic risk factors have been suggested to increase the susceptibility of LOAD development. And many of these genetic factors are linked to the homeostasis of Aβ in the brain such as APP, PSEN1, and PSEN2 responsible for Aβ expression, apolipoprotein E family (especially APOE4) involved in Aβ trafficking, and genes responsible for Aβ degradation. Several genes associated with LOAD pathogenesis are involved in other processes as well which can contribute to AD pathogenesis such as inflammatory and immune responses, cellular trafficking, lipid metabolism, cholesterol transport, endocytosis, and ubiquitination (mechanisms crucial for protein clearance) [27].

Current studies have found a synergy between Aβ aggregation and tau tangles formation, it is observed that Aβ might functions as a facilitator of tau dyshomeostasis, including tau protein misfolding, accumulation in tangles, spreading to the different areas, and associated neuronal degeneration. Most of the studies have identified tau markers as drivers of neurodegeneration and cognitive impairments in AD, suggesting that Aβ pathophysiology might trigger downstream pathways such as tau-spreading and tau-induced toxicity [28]. AD mouse models also show that modulation of tau accumulation in the brain irrespective of Aβ plaques levels can result in reduced neurodegeneration and cognitive deficits [29]. Similar findings have been observed in *in-vitro* studies, such as treating healthy neuronal cultures with AD cortex-derived Aβ oligomer results in neuronal dystrophy and tau hyperphosphorylation. However, no pathology is observed if tau is knockdown before the treatment with Aβ oligomers [30].

2.2.1.2 Neuro-immune Crosstalk in AD Pathology

Recent studies in identifying the critical significance of glial cells in particular and the immune system in general coupled with human genetic studies in AD led to rediscovery and re-evaluate the importance of the immune system in AD pathology. AD *in-vitro* and mice models studies also provide evidence that neuroinflammation is one of the key pathogenic events occurring in AD etiology [31]. Microglia, also known as immune cells of the brain are chief cells involved in the clearance of cellular waste, metabolic by-products, and protein debris. Many experimental AD

mouse model studies have reported that microglia tend to surround Aβ plaques and tau fibrils, to prevent further spread and phagocytosed them. Microglia may aid in reducing the overall Aβ brain burden by facilitating the removal of Aβ and tau.

Furthermore, Aβ can lead to the priming of the microglia to the inflammatory type, these primed microglia also known as activated microglia, secret pro-inflammatory factors, increasing the inflammatory load of the brain. Moreover, dysregulation of microglia phagocytic activity can increase the Aβ accumulation, as primed microglia fail to clear the accumulated protein plaques and neurofibrils. Both human and animal studies have reported an abnormal increase in the levels of TNFα, by activated microglia, neurons, and astrocytes, and Aβ triggers its release. TNFα is reported to stimulate γ-secretase activity, increasing the Aβ production, which further increases TNFα release, thus working in a vicious loop. In mice models of AD, blocking the TNFα pathway resulted in the reduction of activated microglia and Aβ accumulation [32].

Parallel to microglial activation, the human postmortem brain, and animal model studies have reported that astrocytes tend to surround Aβ, and become reactive like microglia [33]. These reactive astrocytes release a plethora of pro-inflammatory molecules such as interleukins, nitric oxide, complement system components, and many other cytotoxic elements [34]. Human and rodent studies have also suggested the presence of Aβ plaques in the astrocytes, reflecting the phagocytic ability of astrocytes to engulf and phagocytize Aβ [35].

2.2.2 Parkinson's Disease (PD)

PD is the second most common progressive neurodegenerative disease primarily distinguished by motor system dysfunction i.e., it affects muscle movements, control, and balance. PD progresses for 10-15 years before the manifestation of clinical signs and symptoms, making the early diagnosis challenging. As age progresses, non-motor or autonomic symptoms of PD start to appear such as anxiety, depression, dementia, and sleep issues. Aging is the greatest risk factor for the development of PD, and apart from aging, genetic and environmental factors are also major initiators of PD pathogenesis. PD shares several aspects of pathology with other neurodegenerative disorders linked to alpha-synuclein (αSyn) aggregation such as synucleinopathies. The main histological features of PD is Lewy bodies (intracellular inclusions (LBs)) that are aggregated αSyn in the neuronal cell bodies and Lew neuritis (LNs) and dopaminergic neuronal loss in substantia nigra [36].

2.2.2.1 Pathophysiology of PD

Genetics of PD: About 5-10% of PD cases are due to mutations in the specific genes associated with PD, these mutations may not lead to the PD onset but can increase the risk of the disease onset and progression combined with environmental and age factors. Both autosomal dominant and autosomal recessive mutations have been

reported in PD patients, at least 11 genes have been identified to be associated with autosomal dominant phenotype and 9 genes with autosomal recessive traits. The risk of developing PD increases by 20–30 folds if the mutation is present in any of the associated genes. Autosomal dominant genes include SCNA, PARK3, UCHL1, EIF4G1, RICE3, and many others, among which the most common mutations are observed in SCNA. Genes associated with autosomal recessive phenotype are PRKN, PINK1, ATP13A2, and PARK7, including several others [37, 38].

Studies of familial forms of PD have identified mutations in SCNA, that are responsible for the αSyn expression, mutations result in the overexpression of αSyn, a pathological hallmark of PD. Human postmortem brain studies have suggested that mutations or duplications in the SCNA gene are sufficient to cause PD or Lewy body dementia. Macroscopically speaking, mild frontal cortex atrophy and distinctive histological changes are observed in substantia nigra pars compacta (SNpc) and locus querulous of the PD brain. Almost all the reported cases present with dopaminergic neuronal degeneration in SNpc and loss of noradrenergic neurons in locus calculus. This neuronal damage can lead to denervation of the nigrostriatal pathway (dopaminergic signaling pathway that connects SNpc with striatum), which is critical for the movement. Denervation of this pathway leads to diminished dopamine levels in the striatum, which is cardinally responsible for the motor deficits observed in PD [39].

Lewy body pathology: LBs are the inclusion bodies of abnormally aggregated proteins inside the nerve cells formed during the PD pathology. The pathological characteristic of PD is the development of unchecked accumulation of αSyn in neuronal cell bodies, that aggregate to form LBs, resulting in the dystrophy of neuronal projections both in axons and dendrites accompanied by cellular loss. In PD and other synucleinopathies, αSyn is abnormally phosphorylated, acquires an amyloid-like filamentous structure, and forms clumps of LBs. Several mechanisms have been proposed for this structural transformation of αSyn into an amyloid phenotype, among which the phosphorylation at serine 129 is mostly observed in reported cases and animal studies [40]. Apart from αSyn serine subunit phosphorylation, dysfunctional post-translational modifications of αSyn have also been seen such as ubiquitination or C-terminal truncation [41].

LB is mainly comprised of αSyn along with other proteins such as heat shock proteins, tau, ubiquitin, proteasomal and lysosomal elements, and many others [42]. αSyn apart from individually contributing to PD pathology has been documented to interact with other proteins in the brain and affect several molecular pathways. One such protein is tau; exaggerated levels of hyperphosphorylated tau in the striatum of both PD and PD-induced dementia patients are observed in postmortem studies [43]. This has been backed by animal model studies as well, which also report that increasing the αSyn levels can trigger the hyperphosphorylation of tau both *in-vivo* and *in-vitro* [44, 45]. Moreover, GWAS found a strong link between MAPT (gene encoding tau protein) and PD onset and progression risk. αSyn is reported to interact with Aβ; in a subgroup of PD patients, αSyn associated Aβ aggregates are deposited in the cortical regions. Moreover, PD patients with cognitive symptoms seem to have a widespread accumulation of tau tangles and Aβ plaques [46].

Neuroinflammation in PD: Whether neuroinflammation independently triggers PD or it is the consequence of PD pathology is still debatable. But postmortem brain studies have identified dysregularities in the immune system of the brain in particular and of the whole body in general. These studies have reported an increased number of activated microglia, complement system, peripheral T lymphocyte infiltration, and subsequent release of proinflammatory cytokines by these cells, especially in the SNpc and striatum of patients with PD [47, 48]. PD rodent model studies have reported that diminishing the microglial activity pre- and post-neurotoxic insult with minocycline significantly reduces the dopaminergic neuronal death in the SNpc, suggesting that microglia-triggered neuroinflammation might be responsible for the neuronal degeneration [49, 50]. On the other hand, evidence also shows that αSyn can trigger microglia activation into inflammatory phenotype, initiating the inflammatory processes. *In-vitro* studies have shown that αSyn treated primary cortical cultures mediate microglial activation in a dose-dependent manner [51].

Genetic studies suggest a strong association between immune system components and PD; studies have reported human leukocyte antigen (HLA) class II region (a key molecule of the immune system) dysregulation and PD onset risk [52]. Moreover, based on recent research, PD patients are also screened for a pro-inflammatory immune profile i.e., enhanced levels of inflammatory components of the immune system are considered to be associated with accelerated motor system dysfunction and severe cognitive impairment [53]. Epidemiological data suggests a reduced PD risk in individuals taking the non-steroidal anti-inflammatory drug ibuprofen on regular basis [54].

2.2.3 Common Behavioral Alterations in AD and PD and Current Medications

The main symptoms of AD include memory loss or dementia which is usually one of the first symptoms to appear. PD phenotype is characterized by different stages depending on the signs and symptoms that are observed in the affected individuals i.e., motor, and non-motor abnormalities. Hand and muscle weakness leading to slower movements also called bradykinesia, tremors, rigidity or stiffness, unstable gait, drooling, and difficulty in swallowing (dysphagia) are generalized motor dysfunctions observed in the motor stage of PD. While the non-motor stage of PD shares similar phenotypic outcomes as observed in AD such as cognitive deficits e.g., difficulty in learning or remembering new information, trouble in carrying out daily life activities like self-care, sleep disturbances, difficulty reading, speaking, walking, anxiety, depression, trouble recognizing familiar faces like friends and family, and many others.

Currently, no medication exists for the complete cure of AD, but available medications slow down the progression of pathology and help with behavioral problems

observed throughout the disease. There are four medicines from two classes of drugs currently prescribed to AD patients: cholinesterase inhibitors which include donepezil, rivastigmine, and galantamine used to treat mild to moderate AD symptoms, and NMDA antagonist memantine for the treatment of AD moderate to severe symptoms. Medications currently prescribed to PD individuals are majorly targeting to improve the dopamine levels in the brain, and the most commonly used drug is levodopa which increases the available dopamine levels in the brain and can ease some of the motor symptoms. Apart from medication, rehabilitation such as physical therapy and exercise can help improve the motor symptoms in the individuals, e.g., improved mobility, gait, flexibility, strength, and quality of life. Occupational therapies are also recommended for patients, the idea of which is to engage people in activities related to daily life and enhance their health and quality of life.

2.3 Neuropsychiatric Pathologies: Recent Mechanistic Findings and Treatments

Neuropsychological diseases/disorders fall in the wide spectrum of mental illnesses that mainly target our emotional states and result in anxious behaviors, depression-like symptoms, mood issues, social deficits, and poor quality of life. The most common diseases in this category are anxiety, depression, bipolar disorder, and schizophrenia. Anxiety, depression, and bipolar disorder share several similar phenotypes and to some extent similar pathophysiology and will be discussed together in the coming section (Fig. 2.4).

2.3.1 Pathophysiology of Neuropsychiatric Disorders

2.3.1.1 Disruption of Neuronal Circuitry in Anxiety, Depression, and Bipolar Disorder

The generalized hypothesis addressing the changes in the brain circuitry in depression and anxiety hypothesizes that there is a dysfunction in the brain areas responsible for governing emotional and cognitive functions. Disruption of neural circuitry involving the amygdala and hippocampus is reported to have a critical role in the onset and progression of anxiety i.e., people who suffer from anxiety tend to show higher activity in the amygdala in response to emotional stimulus. Following the research on individuals through infancy to adolescence has provided the evidence that nucleus accumbens of these individuals are more sensitive when it comes to making decisions compared to other people [55]. Structural MRI studies of depressive patients indicate a reduction in the thalamus, basal ganglia, hippocampus, and prefrontal cortex (PFC), and some other studies have also reported this reduction in the amygdala and anterior cingulate cortex [56]. Meta-analysis across a variety of

experimental paradigms found a generalized hypoactivity of dorsal PFC, temporal cortex, insular cortex, cerebellum, and hyperactivity in the thalamus, visual cortex, and anterior PFC associated with depression [57].

The neurogenic model of the bipolar disorder suggests that emotional circuitry in bipolar disorder consists of two substructures i.e., the ventral system (main regulator of emotional behaviors) comprised of the amygdala, insular cortex, ventral striatum, and ventral anterior cingulate cortex, and dorsal system consisting of the hippocampus, dorsal anterior cingulate cortex, and some other parts of the prefrontal cortex. This neurogenic model suggests that in the case of bipolar disorder, generalized hyperactivity is observed in the ventral system while dorsal system activity is diminished. Bipolar disorder is distinguished by the episodes of mania and hypomania; the former encompasses elevated mood levels often called psychosis, abnormally energetic, happy, and irritable, and later covers the episodes of severe depression, suicidal thoughts, and self-harm. Reports have suggested that manic episodes in bipolar disorder are associated with the overactivity of right vPFC and depressive episodes are linked to the under activity of left vPFC [58].

2.3.1.2 Neuroinflammation as a Driving Force in Neuropsychiatric Pathologies

A well-established triggering mechanism in the pathology of anxiety, depression, and bipolar disorder is the development of neuroinflammation. Studies have suggested that during these diseases, microglial phenotypic remodeling occurs in the brain, and the proliferation of proinflammatory phenotype i.e., M1 is increased. These M1 microglia increase the synthesis and release of inflammatory molecules such as IL-6, IL-1β, TNFα, IFNβ, and many others [59]. Microglia also secrete chemokines to facilitate the peripheral immune cells, particularly IL-1β producing monocyte infiltration into the brain, thus exacerbating the ongoing inflammation [60]. There is evidence reporting that sterile inflammation (inflammation occurring in the absence of microorganisms) can affect neuronal functioning, resulting in the release of damage-associated molecules (DAMPs) which are then recognized by microglia and can result in the activation of inflammatory cascades [61]. Anti-inflammatory factors such as TGFβ, IL-2, IL-10, and neurotrophic factors are severely diminished in both humans and animal model studies [62].

There is a generalized shift in the immunological responses in the individuals affected by anxiety, depression, or bipolar disorder, these patients tend to have higher levels of circulating inflammatory Th17 and Th1 cells, along with their immune profiles demonstrating increased expression of proinflammatory cytokines. These cells and factors can cross the compromised BBB and enter CNS to further contribute to an ongoing inflammatory cascade. Neuroinflammation affects the proper functioning of the hypothalamic-pituitary axis also called the HPA axis, which is the main axis that monitors the stress and energy levels in the body and regulates the activities of the hypothalamus, pituitary, and adrenal glands. Studies have provided evidence that neuroinflammation interferes with the serotonin levels

in the brain, as affected individuals have lower levels of serotonin both in the brain and circulation.

2.3.1.3 Gut-Brain Axis in Mood Disorders

Gut-brain axis and microbiota have garnered much attention in the last few years, as how the changes in the intestinal microbiota during stress conditions modulate behavioral responses and vice versa. Studies have found that microbiota-free rats and specific pathogens-free rats exhibit increased anxiety and depression-like behavior, particularly through the overactivation of the HPA axis. On contrary, studies have shown that *Lactobacillus and Bifidobacterium* can reduce cortisone levels and reverse the HPA regulation [63]. Intestinal microbiotas can synthesize and secrete several neurotransmitters as *Lactobacillus* subspecies produce acetylcholine, *Candida, Streptococcus, Escherichia coli,* and *Enterococcus* can synthesize and release serotonin, and *Bacilli and Serratia* secrete dopamine. Literature reports that lower levels of dopamine, and increased kynurenine/tryptophan plasma ratio are associated with depression resulting due to disrupted tryptophan metabolism. Germ-free rats administered with microbiota from depressed patients showed a similar trend of increased kynurenine/tryptophan ratio and reduced dopamine levels. Studies are reporting a reduction in the levels of serotonin in germ-free mice and rats particularly in males, pointing to the potential role of microbiota in keeping the balance of several neurotransmitters in the body [64]. Apart from neurotransmitters, the microbiota is also reported to influence the expression of neurotrophic factors such as brain-derived neurotrophic factor (BDNF), which is essential for neuronal cell growth, differentiation, and maturation. Intestinal microbiota, especially *Bifidobacterium* and *Lactobacillus* can increase the BDNF levels in the hippocampus. Similarly, levels of BDNF are reported to be reduced in germ-free mice [65] (Fig. 2.3).

2.3.2 Disease Management and Therapeutic Interventions

Anxiety is characterized by panic, extreme nervousness, uncontrollable thoughts, repeated thoughts of traumatic experiences, inability to stay calm, trouble with sleep, cold or sweaty hands, nausea, muscle tension, and heart palpitations. Major symptoms of depression include anhedonia (feelings of sadness), abnormal eating habits such as eating too much or too little, difficulty in concentration, not enjoying the things that used to give joy, easy irritation, frustration, headaches, and stomachache. Bipolar disorder symptoms include changes in energy levels such as low energy and general tiredness, irritability, lack of motivation, suicidal thoughts, problems with concentration, increased sleeping, and changes in appetite.

Though neuropsychiatric diseases are curable, relapse of the disease can happen at any stage. The management of these diseases involves medication,

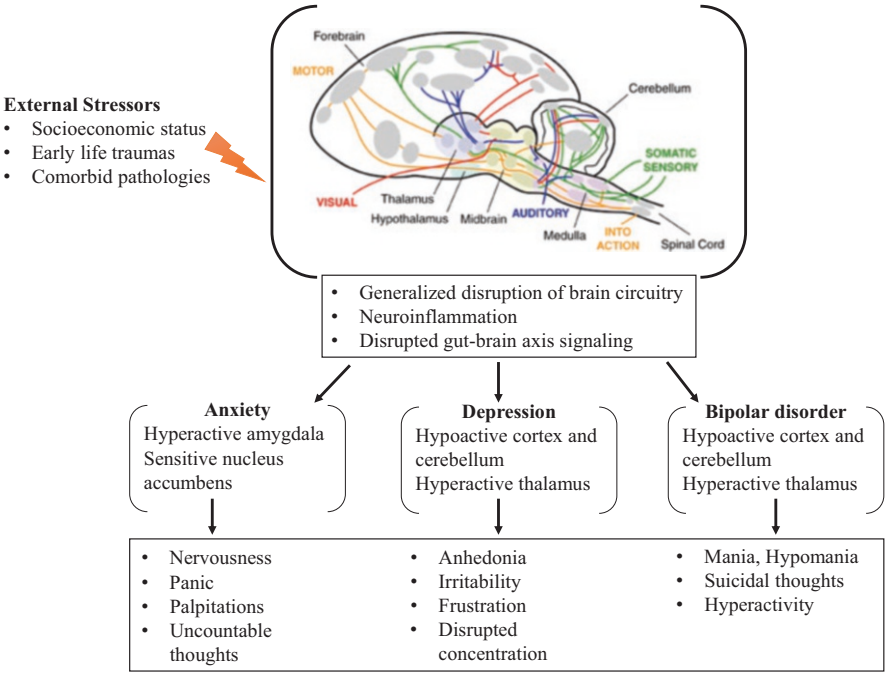

Fig. 2.3 Pathogenesis of neuropsychiatric disorders and their respective phenotypic outcomes: Generalized disruption of brain circuitry is observed in neuropsychiatric disorders along with changes in the immune profile of brain and periphery and alterations in gut-brain axis communication. These changes lead to disease specific behavioral outcomes

psychotherapy, and counseling. Commonly prescribed medicines are anxiolytics such as benzodiazepines, which can alleviate anxiety and panic, and antidepressants, and beta-blockers which can help with physical symptoms like palpitation, shaking, or trembling. Psychotherapy is recommended and essential for these individuals, it helps affected individuals in thought processing, and emotional management, and aid in developing coping skills. Regular exercise and getting enough sleep have proven to alleviate some of the symptoms and overall improve the life and health quality of individuals.

2.4 Traumatic Brain Injuries and Their Management

Traumatic brain injury (TBI) or intracranial injury, is an injury to the brain caused by external blunt traumas or physical force. TBI can be categorized based on the severity of the injury i.e., mild TBI also called concussion to severe TBI, also the injury can be penetrating or closed or affect a specific part of the brain. TBI can result in several signs and symptoms e.g., limitation of physical activity, cognitive

and emotional abnormalities, and social and other behavioral changes, and the TBI outcome can range from complete recovery of the individual to permanent disability or death. Causes of TBI are all environmental and external such as gunshot wounds, falls, assaults, vehicle collisions, or domestic violence.

2.4.1 Mechanisms of TBI Progression

TBI pathology is generally categorized into primary and secondary brain injury. The damage that occurs at the time of trauma falls in the category of primary injury and includes compression, stretching, or tattering of brain tissue or blood vessels. After days or weeks of the initial trauma, a complex cascade of intracellular processes and biochemical alterations are observed, called secondary injury. Secondary brain injury complications are the main cause of death in a large population of people killed by brain trauma. The secondary brain injury complications include disruption of BBB integrity which results in the infiltration of peripheral system components into the brain both regulatory and inflammatory resulting in alterations, and in most cases causing inflammation in the brain. Reactive oxygen species (ROS) and free radical levels are elevated in the brain after TBI, which further contribute to an ongoing inflammatory insult. Elevated serum levels of several molecular factors such as IL-1β, IL-6, and CCL2 are reported in patients after TBI. These cytokines and chemokines can cross the damaged BBB and enter the brain, where they can lead to the priming of microglia and astrocytes to their activated state, resulting in further synthesis and release of inflammatory substances by these cells [8].

The dysregulation in the neurotransmitter system particularly glutamate levels and transmission are reported as well, for instance, studies have found excessive synthesis and release of glutamate resulting in the excitotoxicity of the neurons [66]. Changes in the neuronal membrane potential leading to hyperexcitation of cells due to increased sodium and calcium ions influx are reported. Mitochondrial bioenergetics are also disrupted, resulting in the excessive release of free radicals and ROS. Physical injury to the neurons can also take place i.e., neuronal death due to the disconnection of axons from their cell bodies [67]. Ischemia, hypoxia, edema, or intracranial pressure are also observed in TBI patients. Intracranial pressure may arise due to hemorrhage, due to which blood supply to the brain is diminished, resulting in ischemia. On the other hand, too much pressure in the skull can lead to the crushing of the brain by the skull, resulting in brain herniation or death [68] (Fig. 2.4).

2.4.2 TBI Management and Therapeutic Interventions

The common signs of TBI are behavior or mood changes, memory problems, seizures, headaches, nausea, dizziness and fatigue, sleep problems, and slurred speech. All the cognitive, social, and other behavioral alterations along with changes in the

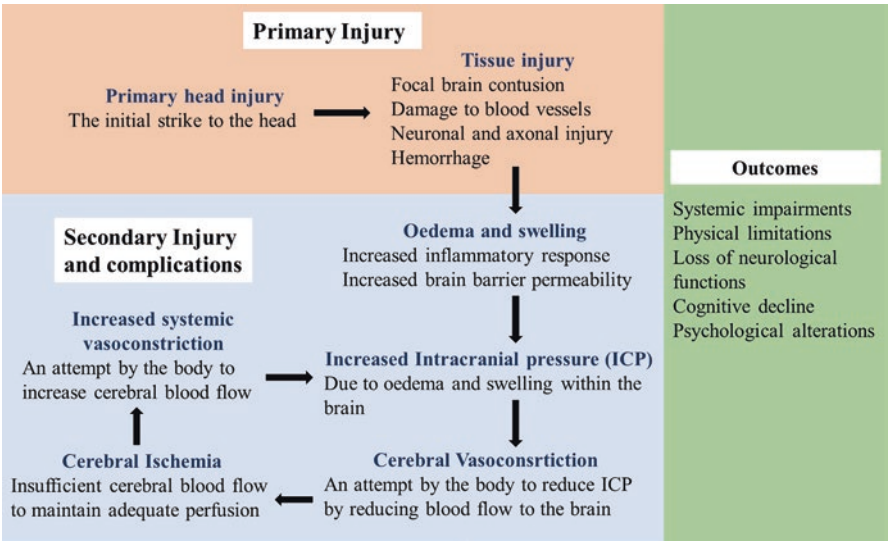

Fig. 2.4 Traumatic brain injury pathogenesis: Following blunt trauma to head also called primary head injury or primary injury can result in blood vessels or neuronal which is then followed by secondary injury. Secondary injury is the set of physiological alterations happening in the brain and systemically, which can lead to various phenotypic outcomes

proper functioning of other systems are the result of secondary brain injury complications. TBI is manageable, and individuals with TBI are usually recommended for counseling to address the cognitive and emotional problems, and rehabilitation including physical, occupational, and speech therapy to address the physical limitations resulted due to TBI. Surgery is often done, if there is internal brain bleeding to prevent the further pooling of the blood and to reduce brain swelling. Complete rest is advised for days to weeks till the individual is capable of self-care and management of professional and occupational activities. In case of physical disability, continuous physical therapy is recommended, and follow-ups are done.

2.5 Stroke, Classifications, and Its Management

A stroke or brain attack occurs when the blood supply to the brain is restricted or diminished due to blood vessel blockage or bursting. As the brain is entirely dependent on the blood supply for its nutrition and oxygenation, stroke can cut off both nutrition and oxygen supply which can result in the death of the surrounding nerve cells. Depending on the site of the stroke, both pooling and lack of blood supply can affect the specific functions, for example, one of the most common symptoms of stroke is contralateral paralysis, meaning if the brain is affected on the right side, it will result in the paralysis of the left side of the body and vice versa. High blood pressure and cholesterol levels, excessive tobacco intake, diabetes, end-stage renal

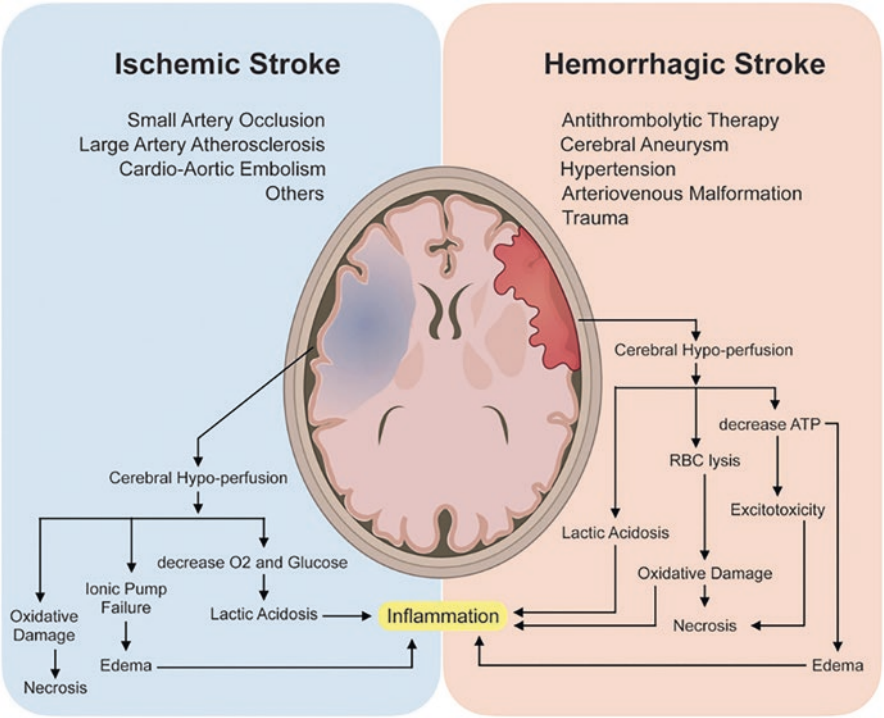

Fig. 2.5 Pathophysiology and Mechanism involved in Ischemic and Hemorrhagic stroke: Adapted from Peng and Jiang, 2022 from Figure 1. Mechanistic alterations taking place in ischemic and hemorrhagic strokes involve cerebral hypo-perfusion leading to lower oxygen supply to the brain. This reduction in the oxygen supply can switch the cellular metabolism from aerobic to anaerobic, resulting in the lactic acid accumulation which can directly damage the neurons and glial cells. Changes in ionic pumps, ecotoxicity, oxidative damage, and edema all lead to inflammatory responses further exacerbating the pathology

disease, or previous transient ischemic attack are the main contributing initiators of stroke (Fig. 2.5).

2.5.1 Classification of Stroke and Their Pathophysiology

2.5.1.1 Ischemic Stroke

In ischemic stroke, a diminished blood supply to some parts or a particular part of the brain is observed, which results in the damage and death of that tissue and dysfunction of that area. Primarily, four causes can lead to ischemic stroke: blockage of a vessel by a locally formed clot (thrombosis), impairment of a blood vessel by a clot formed somewhere else in the body (embolism), a generalized reduction in the blood supply to the brain (hypoperfusion), and the presence of a blood clot in cerebral veins resulting in cerebral venous sinus thrombosis. One of the main initiating

factors in stroke is atherosclerosis i.e., the buildup of fats, cholesterol, and other substances inside and outside of the arterial wall. This build-up of substances in and around the arterial wall can lead to the tightening of the blood vessels, thus disrupting the normal blood flow to the brain. In addition to this, atherosclerosis can lead to the formation of multiple blood clots (emboli) by fragmenting the larger atherosclerotic plaques (emboli infarction) [69].

As the brain is fully dependent for its nutritional supply on blood flow, this disruption due to blocked vessels leads to diminished energy levels in the brain, shifting the neuronal metabolism from aerobic to anaerobic. Anaerobic metabolism produces less energy and releases lactic acid as a by-product, which is a neuronal irritant and can potentially destroy the cells and disrupts the homeostatic acid balance of the brain. And the area affected as a result of this ischemic cascade is known as the ischemic penumbra. This shift of cellular metabolism towards the anaerobic can result in the initiation of interrelated processes and pathways that can result in cell injury and death. For example, neuronal injury can result due to abnormally elevated levels of glutamate (excitatory neurotransmitter). Glutamate concentration outside the cells is kept normally low by uptake carriers, their activity is driven by the ion gradient concentration established across the membrane (particularly of sodium). Oxygen and glucose are the main mediators powering ion pumps and keeping the gradients across the neuronal membrane, but during stroke pathology, poor oxygen, and glucose supply lead to the loss of this ion gradient. This loss of transmembrane ion gradients reverses the activity of glutamate transporters, resulting in higher extracellular glutamate levels, thus excitotoxicity and eventually neuronal death.

2.5.1.2 Hemorrhagic Stroke

Hemorrhagic strokes make up 13% of all the reported cases of stroke. Hemorrhagic strokes have two subclasses based on the site of bleeding i.e., rupturing of an artery leading to blood pooling and flooding in the brain (intracerebral hemorrhage) and subarachnoid hemorrhage. In subarachnoid hemorrhage, bleeding happens outside the brain but still within the skull, precisely in the meninges. Both Intraparenchymal hemorrhages which is the accumulation of blood within the brain tissue and intraventricular hemorrhage which is the pooling of blood in the brain ventricles can result in intracerebral hemorrhage.

Hemorrhagic strokes may occur due to alterations in the architecture of the brain vessels, such as cerebral amyloid angiopathy in which amyloid beta plaques deposit inside the blood vessels and meninges of the brain, abnormal connection between the arteries and veins of the brain (cerebral arteriovenous malformation), and intracranial aneurysm that is dilatation or ballooning of the blood vessels due to weakness in the walls of a cerebral artery. Moreover, hemorrhagic strokes often cause specific symptoms, for instance, a severe form of headache known as thunderclap headache results due to subarachnoid hemorrhage. Hemorrhagic stroke can result in both primary and secondary brain injury. For instance, tissue injury can occur due to compression of the surrounding areas from expanding hematoma, this developing

pressure can affect the blood supply to the affected area resulting in the loss of blood supply and leading to infarction. In addition, blood released by hemorrhage is reported to have direct toxic effects on the brain tissue and vasculature, and not only this, pooling of blood and cutting off of local blood supply result in secondary brain injury by initiating inflammatory cascades. This inflammatory response is pronounced in several hemorrhagic types but particularly in intracerebral hemorrhage. The inflammatory response in intracerebral hemorrhage is characterized by the activation and accumulation of immune system components, both in the brain and periphery. Intracerebral hemorrhage allows the infiltration of peripheral immune cells such as leukocytes and macrophages and their mediators into the brain, which lead to the activation of local immune cells, microglia as well as astrocytes. The infiltrated cells and activated microglia and astrocytes further contribute to ongoing inflammatory insult by releasing proinflammatory mediators such as IL-1β, TNFα, IL-6, and IFNγ [70].

2.5.2 Stroke Management and Current Therapeutics

The first few hours of stroke are critical in managing the following outcomes. In ischemic strokes, definitive treatment is targeted to remove the blood vessel blockage by breaking the blood clot by thrombolysis (by medication) or removing it mechanically by thrombectomy (surgical removal of clots from cerebral arteries). Aspirin also known as a blood thinner and recombinant tissue plasminogen activator (to break down the clots) is reported to have beneficial effects in patients. In cases when a larger portion of the brain is affected, hemicraniectomy i.e., the temporary surgical removal of the skull from one side of the brain to reduce the intracranial pressure is done. Patients with hemorrhagic strokes are monitored for blood pressure, and their oxygenation and blood sugar levels are kept at optimum. In some patients, accumulated blood is removed by surgical interventions to reduce the compression of the surrounding tissue and increased pressure. Stroke rehabilitation is aimed to improve the quality of life for the patients affected by stroke and includes medications, routine follow-ups with clinicians, psychotherapies, physical therapies to aid individuals to return to their normal physical activities, occupational therapies, speech-language therapies, and orthotics (which is the designing of devices to support neuromuscular and skeletal system of the affected individuals).

2.6 Conclusion

This subunit highlighted already established structural changes, molecular alterations, and cellular contributions in various neurological disorders. The recently published reports and literature discussed in this chapter shed light on how diversified diseases can be even if they fall into the same category such as neurodegenerative

disorders. The structural and molecular findings discussed have helped a lot in designing various diagnostic tools and therapeutics, though for many disorders a complete cure does not exist yet. But these studies highlight the importance of a pathophysiological understanding of the disease, to design better tools for timely diagnosis and medication for timely treatment.

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