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REVIEW ARTICLE

Role of viruses, prions and miRNA in neurodegenerative disorders and dementia

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Abstract Dementia is known as loss of cellular communications in the brain at a region caused by multi-factorial diseases and pathogenic infections. Approximately eighty percent reported cases of Alzheimer's disease are followed by vascular dementia. The common symptoms of dementia include memory loss, concentration problems, thinking, and language solving situations. Dementia is a multifactorial disease but based on latest research; various reports have been published describing the linkage and role of viruses, prions and miRNAs in neurodegeneration and neurodegenerative disorders resulting into dementia and due to this we selected to review and provide latest information related to dementia. MiRNAs are small non-coding RNAs carrying genetic regulatory information contributing to neurological disorders among human and animals. A prion is an infectious agent made of protein material. Recently, it has been reported that prions play a significant role in signaling processes, resulting in amyloidogenesis and neurological disorders. Viruses attack human immune system and central nervous system and affect classical pathways of neurodegenerative diseases. Comprehensive understandings of the expression profiles and activities of these miRNAs, Prions, Viruses will illuminate their roles as potential therapeutic targets in neurodegeneration and may lead to the discovery of breakthrough treatment strategies for neurodegenerative disorders and dementia. The provided information will further be significant not only in neuro-scientific research, but also in designing and development of management strategies for dementia.

Keywords Viruses · Prions · miRNAs · Neurodegeneration · Dementia

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Introduction

Dementia is not a specific disease, but it is a general and collective term used for loss of memory caused by physical changes in the brain and other mental abilities which interferes the daily life of old age people. Dementia is a symptom of several disorders in the brain. Dementias can be caused by brain cell death, and neurodegenerative disease-progressive brain cell death that happens over time is associated with most dementias. Additionally, dementia is also caused by Pathogenic infections like Prions, virus

infection like HIV, and reversible factors. Currently, it has been a serious challenge and approximately 47.5 million people suffer with dementia globally. There is no specific therapy available to cure dementia. Dementia has been divided into four stages such as mild cognitive impairment, mild dementia, moderate dementia, and severe dementia. In dementia, various symptoms appear such as loss and decline in memory with thinking ability as well as loss of skills to perform basic daily activities. Globally, 60–80% of reported Alzheimer's disease (AD) cases are followed by stroke-induced vascular dementia and known as other most common dementia Alzheimer's disease is the most common type of dementia but there are many other types of dementia such as; dementia with lewy bodies, Cruetzfeldt–Jakob disease (CJD), Down's syndrome, frontotemporal dementia (FTD), Parkinson's disease (PD), Hungtinton's disease (HD), posterior cortical atrophy, vascular dementia, Amyotrophic lateral sclerosis (ALS), Korsakoff syndrome, Traumatic brain injury, and mixed dementia. Many risk factors are involved leading to dementia such as age, family history, Down's syndrome, and mild cognitive impairment. In some cases, dementia or dementia like symptoms can be reversed by many factors such as infections and immune disorders, metabolic problems and endocrine abnormalities, nutritional deficiencies, reactions to medications, subdural hematomas, poisoning, brain tumors, anoxia, and normal-pressure hydrocephalus. Dementia leads to many complications like; inadequate nutrition, pneumonia, inability to perform self-care tasks, personal safety challenges and finally death. In addition to these pathological hallmarks and diagnostic lesions, the AD brain is typified by impaired synaptic function, neuroinflammation, and neuronal loss, which ultimately contribute to the full expression of dementia. Additionally, FTD is also known as a serious neurodegenerative disease of human personality and language and severe atrophy of the frontal and temporal brain lobes. Many other conditions like thyroid problems and vitamin deficiencies are also known to cause dementia symptoms but it can be cured with the passage of time [47]. Pathogenic infections like viruses are known to cause neurodegenerative disorders [53]. Currently, many viruses are also well known to play a significant role in neurodegeneration and neurological disorders disease progression and finally lead to dementia. Viruses are known to have a direct or indirect role in the development of neurological disorders. A viral infection spreads systemically and enters into the immune system as well as another organ. They can severely affect neurons and CNS resulting in development of neurological disorders. There are many viruses reported to be associated with neurological disorders and they are known as Borna Disease Virus (BDV), Cytomegalovirus (CMV), Enterovirus, H5N1, Hepatitis virus, HIV, Herpes Simplex Virus (HSV), Influenza Virus, Picornavirus and West Nile Virus (WNV) [53].

Additionally, prions are also known to cause disease like Creutzfeldt–Jakob disease and leads to dementia. A prion is known as an infectious proteinaceous agent which transfers biological information in both healthy and diseased cells and causes disease like a virus infection. In 1982, the term prion was given by Nobel prize winner Dr. Stanley Prusiner [86]. The prion contains a single protein known as PrP. This protein folded into two different conformations, one is known as normal protein PrP = PrPc and the other is known as diseased protein (PrP = PrPsc − scrapie) and cause deadly neurodegenerative disease in both human and animals [7]. Prion disease is a collective condition affecting the CNS and develops neurodegenerative diseases (NDD) in both humans and animals. Recently, prion has been defined as "proteinaceous nucleating particles" [37, 63, 106, 107]. Generally, a neurodegenerative disease is age dependent and contains filamentous inclusions as major component known as amyloid-β (Aβ), tau and a-synuclein [37, 106]. Based on many published reports and evidence; it is well known that prion and prion-like disease arise from changes in the normal protein conformation into infectious and self-propagating stages and contributes significantly to the emergence of neurodegenerative disease in both human and animals [87, 88]. The role and association of prion in humans and animals NDD are reported in many published papers. The human diseases associated with prion are known as Creutzfeldt–Jakob disease (CJD), Gerstmann–Straussler–Scheinker syndrome (GSS), Kuru, Fatal Familial Insomnia (FFI), FTD, AD, ALS and HD and animal disease are known as Scrapie, Bovine Spongiform Encephalopathy (BSE) and Chronic wasting disease (CWD) [4, 37, 38].

Apart from viruses and prions, microRNAs are also known to be associated with neurological disorders [20, 69]. miRNAs are ∼ 18–25 nucleotides (nt) long and have essential information for gene regulation and expression in both animals and plants [46]. The existence of miRNA was reported 14 years back, during the study of larval development in the nematode *Caenorhabditis Elegans*. This small non-coding (nc) RNA was discovered by Ambrosa and Tuschl. The involvement of miRNAs in neurological disorders has recently been reported [20, 69]. Recently, some miRNAs have been identified and isolated from CSF and blood serum and provided valuable information about AD diagnosis, and it was further observed that there is no general consensus for their expression pattern, either by up-regulation or down-regulation and provided major challenges in the profiling of miRNAs in the CNS disorders [3, 17, 71]. Approximately 2550 novel miRNAs have been isolated and characterized from humans, but only highly selective miRNA population

appears to be differentially expressed in CNS disorders [3, 71]. The miRNAs are well known to play an important role in gene expression, controlling of aging and disease development but they are not highly selective for their nucleotides sequences arrangement and their abundance and specificity in the tissue and they vary in different population [71]. Molecular biology-based techniques like direct RNA sequencing, RT-PCR, Northern Blot, miRNAs-based microarray helped in the identification of several miRNAs in CNS diseases and currently, around 45 miRNAs altered in the AD have been detected [18, 19, 45, 113]. It has been only about 8 years since the first reports of altered miRNA abundance; speciation and complexity in the human CNS in aging brain and in AD have emerged. Some dominantly inherited cases of AD are caused by mutations in the gene encoding the amyloid precursor protein (APP), the cleavage of which gives rise to Ab. In these cases, dysfunction of APP precedes dysfunction of tau. In contrast, mutations in MAPT, the tau gene, give rise to dominantly inherited frontotemporal dementia and Parkinsonism, with abundant tau inclusions in the absence of Ab plaques. Recent findings have suggested instead that non-cell-autonomous processes play an important part in AD and PD. Inclusions are thought to form in a small number of cells and-given enough time and, perhaps, a genetic predisposition-spread in a deterministic manner to distant brain regions. The prion concept appears to apply to all human neurodegenerative diseases with abnormal protein assemblies, including AD and PD. This has brought unity to the field and changed the way we think about these diseases. It has been known for some time that a seed can template aggregation of the homologous protein [37]. In this review we have provided the latest information about the role of viruses, prions and miRNAs in neurodegeneration and neurodegenerative disorders leading to dementia. Dementia is a widespread disease. The role and linkage of viruses, prions and microRNAs in neurodegenerative disorders leading to dementia are reported well in many published papers from various parts of the world. Currently, the detailed understanding of disease mechanisms, an early disease diagnosis, development of biomarkers and an effective disease treatment is an urgently need.

Types of dementia

Currently, there are many types of dementia has been reported.

A: Alzheimer's disease (AD): AD is the most common form of dementia. It is hallmarked by the loss of neurons in the cerebral cortex and sub-cortical regions and the formation of neurofibrillary tangles and plaques in brain.
B: Dementia with Lewy bodies: This is a neurodegenerative condition linked to abnormal structures in the brain. The brain changes involve a protein called alpha-synuclein.
C: Mixed dementia: This refers to a diagnosis of two or three types occurring together. For instance, a person may show both Alzheimer's disease and vascular dementia at the same time.
D: Parkinson's disease (PD): PD is a neurodegenerative disorder that is characterized by muscular rigidity, resting tremor, akinesia, depression, dementia, olfactory and sleeps disturbances.
E: Huntington's disease (HD): HD is characterized by specific types of uncontrolled movements but also includes dementia.

Additionally, other disorders leading to symptoms of dementia include: Frontotemporal dementia also known as Pick's disease. Normal pressure hydrocephalus when excess cerebrospinal fluid accumulates in the brain. Posterior cortical atrophy resembles changes seen in Alzheimer's disease but in a different part of the brain. Down syndrome increases the likelihood of young-onset Alzheimer's.

Etiologies of dementia

Many factors are known to be associated with dementia. The most important is the progressive brain cell death and neurodegenerative disease, head injury, a stroke, or a brain tumor, among other causes such as cerebrovascular disease prevention of normal blood flow and less oxygen supply to the brain cells. Additionally, an injury leads to brain cell death resulting into post-traumatic dementia. Traumatic brain injury received by sports player also leads to certain dementias appearing later in life. Additionally, dementia is also caused by pathogenic infections like virus infection, Prion disease, and some other factors like medication interactions, depression, vitamin deficiencies, and thyroid abnormalities.

Role of viruses in neurodegenerative disorders and dementia

Viruses are known to infect and play a significant role in neurological disorders. The role and linkage of multiple viruses in neurological disorders have been reported and the most important viruses are known as HIV, HSV, Hepatitis virus, ZIKV and Cytomegalovirus (CMV) [2, 3]. The updated information about the most studied viruses

like HIV, HSV and Hepatitis C Virus and the role of other viruses in dementia are discussed (Fig. 1). Recently, the evidence for the role of viruses as environmental risk factors and supporting a link between viral infection and motor neuron disease for ALS has been published from a new perspective. Viruses have received longstanding attention as potential ALS triggers. But there is a need for multidisciplinary approaches bridging neurology and infectious diseases research to move the field forward in the future [16]. The role and association of CMV, HSV-1 and Epstein–Barr virus with cognitive functioning and risk of AD and dementia in the general population has been recently reviewed and reported [69, 104].

Human immunodeficiency virus (HIV)

HIV infection has been described well and has the significant role in NDD and the development of dementia, known as HIV-associated dementia (HAD). HAD is a sub-cortical dementia insidious beginning. In the early stage of disease, neurologic symptoms including cognitive slowing, forgetfulness, and concentration difficulties, are mild. Gait disturbance is the most common motor symptom, but the problem with hand coordination is also common, as described by impaired handwriting or typing skills. HAD also known as AIDS dementia Complex (ADC) and HIV-Encephalopathy (HIV-E), identified by neuronal degradation, results in progressive cognitive and motor impairments that might lead to a vegetative/mute condition. The manifestations of neurocognitive impairment vary from asymptomatic impairment to dementia. The HIV infection leads to cognitive impairment [84]. It is observed that virus does not enter directly into the CNS. Blood Brain Barrier (BBB) strictly regulates the HIV-1 molecules entry into the CNS. Monocytes help HIV-1 virus to travel into CNS. They have the freedom to cross the BBB and strive in the brain leading to neurodegeneration and HAD [40].

Surprisingly, virus affects Perivascular macrophages (PM) and microglial cells and replicates and produces viral proteins (neurotoxic or infectious proteins). The neurotoxic viral proteins like Tat, Vpr, Nef, Rev, gp120 and gp41 trigger the activation of astrocyte, which results in decreased glutamate uptake and increased glutamate release. This elevated glutamate level causes neuronal bioenergetic disturbances, which results into abnormal synapto-dendritic pruning and leads to neuronal injury. In addition, systemic inflammation and translocation of microbial products lead to activation of microglial and increased chemokines and cytokines production, contributing to neuronal injury [95]. HIV-associated neurocognitive disorder (HAND) is recorded in 30–50% HIV infected individuals [104]. HAD is the most severe indicator of HAND with advanced HIV disease and low CD4 cell counts [5]. Neuronal injury mechanism in HAND might be caused by HIV-1 secreted neurotoxic viral proteins such as Tat, gp120, and Nef that may lead to the activation of pathways like neuro-inflammatory, promote excitotoxicity, block autophagy, oxidative stress, dysregulation of signaling and mitochondrial dysfunction pathways [28]. HAND is further categorized into 3 sub-disorders: (1) ANI (Asymptomatic neurocognitive impairment): an anomaly in 2 or more cognitive abilities with no functional impairment; (2) MND (Mild neurocognitive disorder): a cognitive injury with mild functional impairment; and (3) HAD: a manifest cognitive injury with manifest functional impairment [26]. It was illustrated that Nef protein and nef mRNA are packaged into exosomes that persist in circulation in patients with HIV-HAD. The expression of Nef in target cells may be induced by mRNA and later increase expression and secretion of Aβ and Aβ peptides. An elevated level of the amyloid peptide could lead to cognitive impairment noticed in HAND [55]. The individuals infected with HIV and mild cognitive impairment are more susceptible to dementia and death [42]. The induction of latency and alteration of steamness in brain NPC occurs by HIV-1 infection in multipotent human neural precursor cells (hNPCs), resulting into changed endogenous neurorestoration of the CNS and compounds the severity of dementia in adult neuro AIDS cases. In a recent study, it was suggested that a novel molecular cascade involving miR-155 and TRIM32 leading to HIV-1 Tat-induced attenuated proliferation of hNPCs [27].

Herpes simplex virus (HSV)

HSV-1 is a neurotropic dsDNA virus that generally affects oral and nasal epithelial cells where lytic replication of virus takes place, and thus produces new viral particles. This virus infects sensory neurons and moves towards the trigeminal ganglion by axonal transport. In this trigeminal ganglion, virus particles start a latent infection. In this way, the virus moves to CNS and causes serious neurological disorders. It has been observed that virus exists in the latent phase in numerous elderly brains but reactivates sporadically, such as in the peripheral nervous system, under particular conditions, for instance, stress, immuno-suppression, and peripheral infection, causing collective damage and ultimately the development of AD [50, 66, 83]. (Fig. 1).

Hepatitis C virus (HCV)

HCV is a ssRNA virus that causes serious disease. Even though it is a hepatotropic virus, viral RNA has also been identified in PBMC brain samples with neuro-pathological

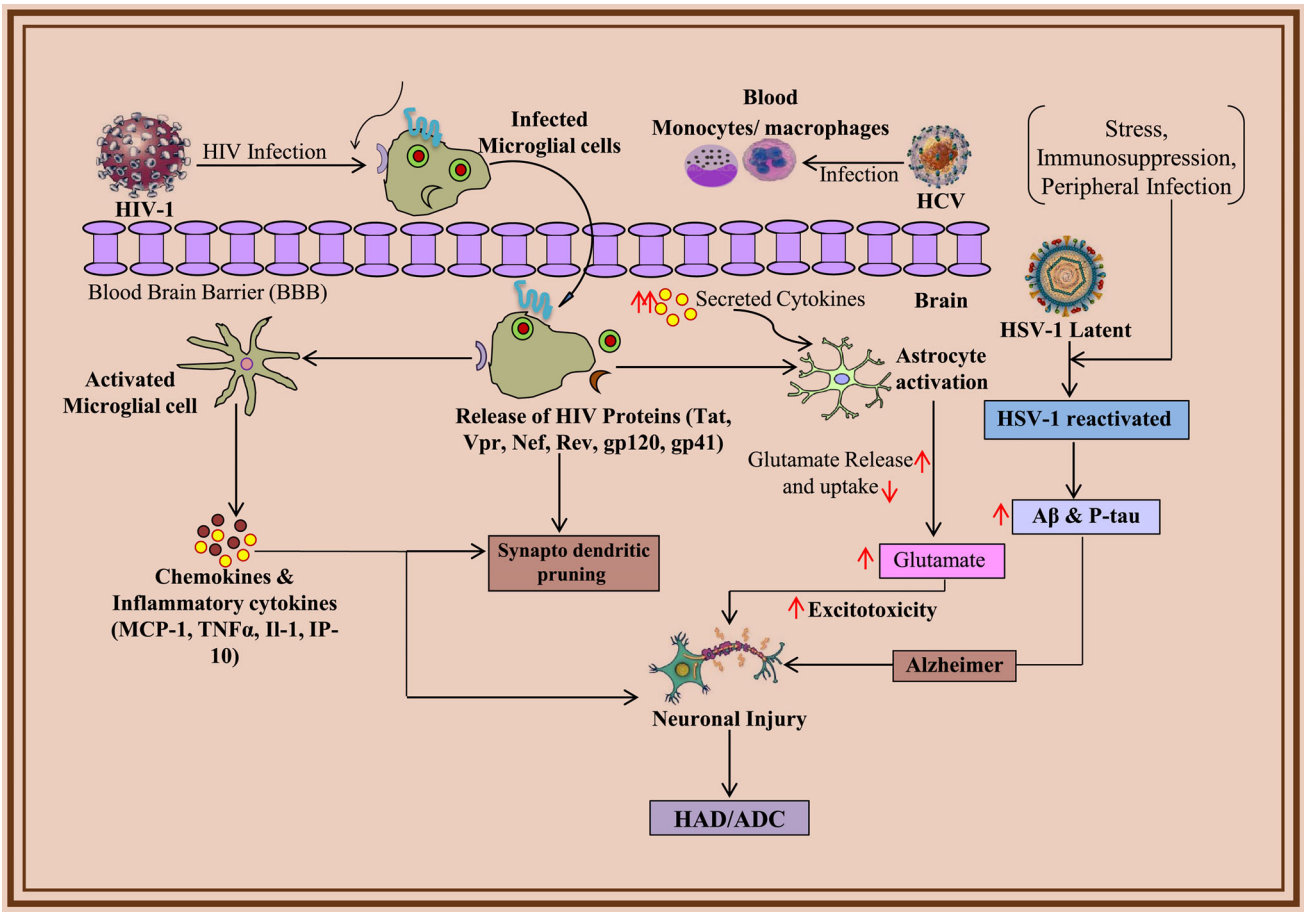

Fig. 1 Virus infection leads to development of neurodegeneration and dementia

abnormalities. Evidence of HCV neuro-invasion is now accumulating [29, 30]. HCV and HIV co-infected patients with a history of prohibited drug use are rapidly increasing. Though, only a few investigations have analyzed the entry of HCV into the CNS and its clinical and neuro-pathological impacts on HIV-infected individuals. For this objective, the distribution of HCV was investigated in the HIV-infected individual brain. The presence of viral RNA detected in CNS by nested PCR was linked with a history of methamphetamine use, substantial ante mortem cognitive impairment and abundant astrogliosis, and less-acute HIV encephalitis [64]. HCV infection also develops chronic inflammation and results in neuropsychological symptoms accompanied by cognitive impairment in AD individuals. Monocytes/macrophages primarily infected by HCV, cross the BBB and subsequently increase the secretion levels of cytokine which causes the excitoxicity in the central nervous system. HCV infections in the brain tend to increase the risk for AD development. Moreover, viremia and HCV infection are correlated with microglial activation and altered cerebral metabolism. HCV-infected elderly patients are stated to have a higher risk of AD, whereas those who have received antiviral therapy have a lower risk for the AD development [16]. Recently the contribution of Enteroviruses (EVs), including poliovirus, coxsackie virus, echovirus, enterovirus-A71 and, enterovirus-D68, to the development of ALS has been suspected as they can target motor neurons, and patients with prior poliomyelitis show a higher risk of motor neuron disease. In a recently published review, the nature of enteroviral infection, including route of infection, cells targeted, and viral persistence within the central nervous system (CNS) and their molecular mechanism of viral pathogenesis and the molecular and pathological features of ALS and the potential role of enteroviral infection in FTD has been provided [111].

Role of prions in neurodegenerative disorders

The role of prions has been shown in neurodegenerative diseases like AD, PD, HD, ALS and other NDD both in human and animals. Neurodegenerative disorders can be developed with the aggregation of misfolded and aberrant

proteins in the CNS and these proteins share prion-like mechanism in the development of NDD [4, 33, 73]. Currently, a strong and dominant hypothesis showed that gain and loss of function is required in prion disease development. Gain-of-function is necessary for disease initiation and spread, but loss-of-function also contributes significantly to the development of NDD [63]. The list of prion diseases in both humans and animals is provided in Table 1. Currently, several studies have indicated that certain misfolded amyloids composed of tau, β-amyloid or α-synuclein can be transferred from cell to cell, suggesting the contribution of mechanisms reminiscent of those by which infective prions spread through the brain. The blocking of a 'prion-like proteinaceous aggregates spreading in brain cells could be a novel putative therapeutic target towards the management of neurodegenerative diseases. The current knowledge about PrP^{C} as a putative receptor for amyloid proteins and the physiological consequences of these interactions has been reviewed [25].

The prion and prion protein (PrPc)

A prion is a proteinaceous infectious agent which causes neurological disorders in human and animals. Human prion disease is also known as transmissible spongiform encephalopathy (TES). Prion contains only one protein known as PrPc which plays a significant role in NDD in both human and animals. Currently, many proteins like Aβ, α-synuclein, TAR and copper zinc superoxide dismutase are known to behave like prion proteins in NDD like the AD, PD, FTD and motor neuron diseases [4, 51, 85]. The key role of PrPc is to protect and maintain the health of neurons, regulate neurotransmission and prevent excitotoxicity in the brain. The normal protein structure contains only alpha-helices, while pathogenic form PrPsc (sc = scrapie) contains only beta-sheets. Devastating effect can be observed on the CNS after the misfolding of PrPc to PrPsc protein and soluble oligomers formation takes place after the aggregation of abnormal prions in the cells and due to accumulation of these abnormal prions inside neurons, programmed cell death, as well as seizures and seizure-like symptoms in the diseased individuals, occur [11]. The PrPsc can avoid the pathway for their clearance and aggregate into cells and they may propagate from one cell to another, from one individual to another and between species [4, 63].

Prion disease

Prion diseases are incurable neurological disorders that produce a wide range of devastating symptoms in humans and several mammals. The unusual type of self-replicating microbe can initiate prion disease [72, 88]. In prion disease, the normal cellular prion protein (PrPc) gets misfolded and becomes pathogenic and propagates further in the neighboring cells and tissues and can infect other organisms. Currently, three forms of prion disease are reported in human beings and they are designated as sporadic, genetic and acquired [4]. Approximately 1.5 million per year mortality rate has been reported due to the most frequent Sporadic CJD (sCJD) [59]. Globally, only 5–15% cases of genetic prion diseases have been reported which occur due to the mutation in prion protein gene (PRNP) located on human chromosome 20. BSE and Kuru are included in acquired prion diseases with only 2–5% disease

Table 1 Types of Prion disease in both human and animals

Types of disease	Types of host	Pathogenesis
Kuru	Humans	Infection through ritualistic cannibalism
Iatrogenic Creutzfeldt–Jakob disease	Humans	Infection from prion-contaminated HGH, medical equipment, etc.
Variant Creutzfeldt–Jakob disease	Humans	Infection from bovine prions
Familial Creutzfeldt–Jakob disease	Humans	Germline mutations in the PRNP gene
Gerstmann–Sträussler–Scheinker syndrome	Humans	Germline mutations in the PRNP gene
Fatal familial insomnia	Humans	Germline mutations in the PRNP gene
Sporadic Creutzfeldt–Jakob disease	Humans	Somatic mutation or spontaneous conversion of PrPc to PrPsc
Sporadic Fatal insomnia	Humans	Somatic mutation or spontaneous conversion of PrPc to PrPsc
Scrapie	Sheep	Infection
Bovine spongiform encephalopathy	Cattle	Infection or sporadic
Transmissible mink encephalopathy	Mink	Infection with prions from sheep or cattle
Chronic wasting disease	Deer, elk	Infection
Feline spongiform encephalopathy	Cats	Infection with prion-contaminated bovine tissues or MBM
Exotic ungulate encephalopathy	Greater kudu, nyala, oryx	Infection with prion-contaminated MBM

incidence rate globally [4]. The symptoms of prion disease (sporadic, genetic and acquired) include cognitive and executive dysfunction, language, and memory impairments [63, 76]. The widespread of amyloidogenesis can be induced by Aβ peptide prion-like aggregates [88, 101]. Recently, it has been reported that prion can serve not only as Aβ receptors but also to spread amyloid neurotoxicity and finally this prion reaches to the brain and plays a significant role in AD-like signaling processes leading to amyloidogenesis followed by neuro-inflammation and synaptic degeneration [15, 44, 88].

Alzheimer's disease (AD)

The role of prion in the AD is known but the equilibrium of toxic gain of function versus loss-of-function is unclear and it may be involved in different steps in different brain regions [63]. Similar disease pathology has been observed in both AD and prion diseases and many reports documented that the physical, biochemical and genetic interactions of AβPP and PrPc occur during cell and organism physiology and disease development [60, 97]. It has been proposed that PrPc acts as receptor/mediator of Aβ toxicity and contributes significantly to AD [60]. Aβ oligomers and misfolded tau have prion-like properties. The interaction of PrPc occurs in many CNS proteins like AβPP and tau and develops NDDs like an AD, PD and FTD [63]. The interaction of PrPc and AβPP results into loss of normally folded PrPc and disruption of AβPP physiology which finally leads to progression of prion disease. The PrPc can potentially modulate the mechanism of AD pathogenesis and prion disease by regulating the AβPP metabolism. The level of PrPc significantly reduced in AD patients at early stage of prion disease suggests that loss of PrPc plays a significant role in sporadic AD progression [110]. Both the AD and prion disease share many similarities and the interaction study of AβPP and PrPc will provide a valuable information to develop novel therapies for both AD and prion disease [63].

Parkinson's disease (PD)

PD is a serious disorder of CNS characterized with the accumulation of protein in the form of Lewy bodies and neurites. The formation of Lewy bodies occurs by the autocatalytic conversion of phosphorylated and ubiquitinated forms of α-syn aggregate [68]. Recently, it has been shown that this disease has strong linkage with prion disorder. The Lewy bodies and Lewy neuritis are observed in the substantia nigra pars compacta (SNc) neurons and CNS of PD patients. Point mutations in both the a-synuclein and PrP genes resulted in PD and prion diseases. In both PD and Prion diseases reactive gliosis, protein deposits followed by neuronal death occur [81]. Based on genetic and pathologic research, protein accumulation and cell death in PD could be a result of prion disorder. The prion disease occurs when the normal form of PrPc protein converts into PrPsc. To provide the linkage of prion disease to PD, the transmission of Lewy bodies into grafted SNc cells was performed and results showed that a-synuclein in b-sheet-rich conformation can be transported from one cell to another in PD patients. Based on autopsy results, Lewy bodies were found in the grafted embryonic mesencephalic neurons in the PD patients which further confirm that α-syn has prion-like cell-to-cell transmissibility [65]. In another study, recombinant α-syn fibrils were injected in the substantia nigra, the striatum or the entorhinal cortex of wild-type mice which initiated propagation of phosphorylated α-syn, affecting different brain regions directly or indirectly. These results strongly support the transmission and spread of α-synuclein in neighboring brain cells through axonal transport [75]. The α-synuclein behaves like a prion and PD could be a prion disorder. Due to the mutation in *MAPT gene* and the tau gene, the formation of filamentous tau inclusions occurs in the brain, causing PD and developing dementia [79]. It is well known that PrPc and a-synuclein adopt an α-helical-rich conformation under physiological conditions and the misfolded protein can covert further and acquire wild type b-sheet configuration and may transmit to neighboring cells and promote neurodegenerative disorders. The pathological form of PrP (PrPsc) displays a predominantly β-sheet conformation at C-terminal region and resistant to proteolytic degradation [4, 39, 81].

Creutzfeldt–Jakob disease (CJD)

CJD was described in 1920 by German neurologist Hans Gerhard Creutzfeldt and the name Creutzfeldt–Jakob was given by Alfons Maria Jakob. This is an incurable, fatal neurodegenerative disorder caused by a prion. This is the most common human prion disease but believed as the rare disorder and found in one out of every one million people/year. The most important symptoms include loss of memory, paranoia, psychosis anxiety, and depression, changes in personality, hallucinations and finally progressive dementia. The normal prion protein folds into infectious protein and accumulates in a larger amount in the affected cells and can spread to neighboring cells, leading to disruption of neuronal cell function and cell death [6]. CJD has two forms designated as familial (fCJD) and (sporadic form: sCJD). The rapid brain tissue degeneration occurs in CJD and brain develops holes and forms kitchen sponge-like texture. Recently, it has been reported that some hormones get contaminated with PrP prion, resulting in iatrogenic CJD [92]. Additionally, it is known that the transplantation of PrP prion contaminated dura mater in

CJD patients significantly increased the Ab plaques and cerebral amyloid angiopathy (CAA) [32].

Amyotrophic lateral sclerosis (ALS)

ALS is a serious neuromuscular disease in which central and peripheral motor neurons are affected by the prion-like spread of misfolded proteins. The symptoms include weakness, muscle paralysis and finally, death occurs due to respiratory failure [41, 53]. The important mutations observed in the superoxide dismutase-1 (*SOD1), TARDBP, C9ORF72, FUS* genes, and bone morphogenetic protein modifier genes resulted in increased susceptibility. Approximately, 150 mutations were observed in SOD1 related to the development of familial ALS [105]. In ALS, the substantial loss of functions and prion-like propagation of SOD1 misfolding occurs [63].

Huntington disease (HD)

HD was initially described by Charles Oscar Waters in 1841, later detailed description was given by George Huntington in 1872, and finally, it was designated as Huntington's disease (HD). This is an inherited brain disorder causing cell death in both men and women equally. As the disease progresses, the body movement becomes jerkier and the mental ability declines, resulting in dementia [22, 31]. Unlike other neurodegenerative diseases, HD is inherited. HD has recently been classified as a prion-like disease [88]. In the wild-type huntingtin protein, $\sim$ 35 glutamine residues are found at N-terminal region. The spontaneous aggregation occurs in the expanded polyglutamine repeats of the huntingtin in cultured cells and this shows that it could be the prion [90].

Role of miRNAs in neurodegenerative disorders

MicroRNAs (miRNAs) bind to the 3′-UTR of mRNA and lead to gene expression and suppression. MicroRNAs (miRNAs) play a key role in modifying the physiological and pathophysiogical progressions of neurodegenerative disorders. The significant up-regulation of miR-21 was observed in the human and monkey brain with HIV associated dementia and SIV encephalitis. The novel role of miR-21 was identified and reported as potential signature and crucial effector of HIV induced neuronal dysfunction and neurodegeneration. In a recent study, the expression levels of miR-196a were increased in a mouse model of spinal and bulbar muscular atrophy (SBMA) [99, 112]. Recently, the role of mir30-hSNCA was examined in hSNCA gene silencing in vivo and positive effects with AAV-mir30-hSNCA on forelimb behaviour and SNDA neurons were observed [56]. There are abundant miRNAs in CNS where they show specific expression platform and perform biologically essential functions like synaptic plasticity and neural plasticity. They are involved in the indirect regulation of neurodegeneration by controlling the proliferation and autonomous rejuvenation of neural stem cells. Several neurodegenerative disorders lead to dysregulation of miRNAs which finally culminates in neuronal cell death. Recently, dysregulated miRNAs and their role in several neurological disorders explored in many neurological disorders like AD, PD, ALS and HD opened a new avenue for the development of new treatment and management strategy. The miRNA expression profiling leads to the recognition of signature molecules related to detection, prognosis, staging and progress of reaction for the treatment of NDD. Most of the research efforts have been undertaken in the last few years using the invertebrate model system, but they still require further verification by using an animal model. Last decade has shown progression in the establishment of circular miRNAs as a potential biomarker in the diagnosis of NDD. The types of miRNAs and their profiling in many NDD are listed in Table 2. Recently a review has been published mainly focusing on the role of MicroRNAs as novel drug targets and biomarkers for neurodegenerative disorders like AD, PD and HD and their role in other neurological disorders including traumatic brain injury and status epilepticus [49, 89].

Alzheimer's disease (AD)

AD is the most general stage of prime degenerative dementia. Clinico-pathological examinations indicated a long preclinical stage of the disease. In the last few years, the report about the altered expression and regulation of miRNAs in AD has been published. Altered miRNAs profiling has been widely observed in brain tissue samples or cell cultures but little information is available regarding circulating miRNA in AD [35, 43, 45, 108]. Schipper et al. in 2007, studied the possibility of miRNAs as a biomarker in AD. By using microarray technology, the higher expression of miRNAs was observed in peripheral blood mononuclear cells (PBMCs) taken from AD individuals [96]. A recent study based on next generation sequencing (NGS) observed that 12 miRNAs signature could differentiate between AD with 93% accuracy as compared to control group [62]. Using Nanostring technology, Kumar et al. [58] observed a unique 7 miRNAs signature sequence in plasma which can differentiate AD patient with normal control with 95% accuracy. In a separate study, miRNAs in cerebro spinal fluid (CSF) by qRT-PCR observed lower expression of hsa-miR-27a-3p in AD patients [93]. Cogswell et al. [20] also conducted the miRNAs study from CSF

Table 2 Circulating miRNAs for various neurodegenerative disorders

miRNAs	Sample	Approach	Method	NDD
Increased expression of miR-34a and miR-181b	PBMC	miRNA profiling	Microarray	AD
Reduced expression of miR-27a-3p	CSF	miRNA profiling	qRT-PCR	AD
60 miRNAs differentially regulated between the different Braak stages, including Let-7 family members	CSF	miRNA profiling	qRT-PCR	AD
Elevated levels of miR-146a and miR-155	CSF	Candidate miRNA	Microarray	AD
Significant increase in miR-9, miR-125b, miR-146a, miR-155	CSF	Candidate miRNA	Microarray	AD
12-miRNA signature:	Peripheral blood	miRNA profiling	NGS	AD
7-miRNA signature:	Plasma	miRNA profiling	Nanostring	AD
Elevated levels of let-7b	CSF	Candidate miRNA	qRT-PCR	AD
miR-15a associated with amyloid plaque score	Plasma	Candidate miRNA	Microarray	AD
miR-29a/b, miR-181c, and miR-9 down-regulated	Serum	Candidate miRNA	qRT-PCR	AD
Increased levels of miR-34c	PBMC	Candidate miRNA	qRT-PCR	AD
Circulating brain-enriched miRNAs: “miR-132 family” and “miR-134 family”	Plasma	Candidate miRNA	qRT-PCR	AD
18 significantly under-expressed miRNAs	PBMC	miRNA profiling	Microarray	PD
miR-1, miR-22-5p and miR-29 distinguish non-treated PD from healthy subjects	Total Peripheral Blood	miRNA profiling	qRT-PCR	PD
miR-16-2-3p, miR-26a-2-3p, miR30a differentiate treated from untreated patients	Total peripheral blood	miRNA profiling	qRT-PCR	PD
miR-331-5p upregulated	Plasma	miRNA profiling	qRT-PCR	PD
miR-1826, miR-450b-3p, miR-626, and miR-505	Plasma	miRNA profiling	Microarray	PD
16 miRNAs (including miR-16, miR-20a and miR-320) modified in patients pre-DBS	Leukocytes	miRNA profiling	NGS	PD
8 miRNAs (miR-451, miR-1275, miR-328, miR-638, miR-149, miR-665 and miR-338-3) significantly up- or downregulated	Leukocytes	miRNA profiling	Microarray	ALS
Expression of ALS-specific miRNA inflammatory signature	Monocytes	miRNA profiling	Microarray	ALS

by qRT-PCR and same expression pattern were observed in both CSF and brain tissue for miRNAs of AD individuals. Lukiw et al. [2, 70] identified miRNAs associated with inflammatory signaling pathway and reported that miR-146a and miR-155 are plentiful in AD CSF samples. Another group study identified miR let-7b which activates TLR 7 and causes neurodegeneration from CSF samples of AD patient [61]. Circulatory miRNA (miR-15a) were obtained from plasma and found to be significantly associated with amyloid plaques serum for the pathological diagnosis of AD [8], and down-regulation of miR29a/b, mir-181 c and miR-9 in serum was also observed [36]. It is well reported that amyloid β (Aβ) level is directly regulated by SPT by post transcriptional regulation of various miRNAs known as miR-137, miR-181c, miR-9 and miR-29a/b 39 and it is believed that SPT could be an important target for AD diagnosis. The miR-34 family is another important miRNA implicated in the AD and affects two signalling pathways: Bcl-2 for cell survival/apoptosis and SIRTI de-acetylation for p53 or neuro-protective

signalling. The increased level of miR-34c in both PBMC and plasma in the AD as compared to control was observed [9]. Plasma miRNAs biomolecules were also reported for mild cognitive impairment, an intermediate stage between normal aging and AD (dementia) [24, 98]. Two sets of miRNAs (miR-132 family consisting of miR-128 and miR-134) have 79% and 100% specificity. Their study also matched with the separate longitudinal study which identified miRNAs and MCI in many infected individuals at asymptomatic conditions 1–5 years before diagnosis. The miR-132 family contains miR-128/miR-491-5p, miR-132/miR-491-5p and miR-874/miR-491-5p, while miR-134 family contains miR-134/miR-370, miR-323-3pmiR-370 and miR-382/miR-370 [98]. Recently, the role of miRNA in the AD and their therapeutic potential have been presented on the activities of ten miRNAs in biological pathways involved in the AD pathogenesis [78].

Parkinson's disease (PD)

PD is a neurodegenerative disorder affecting millions of people globally. PD leads to defective motor function as a reduction of dopamine producing brain cells. The symptom includes stiffness, tremors, slow and impaired balance, anxiety, depression, and dementia. Environmental acquired risk factors and genetic factors are established as a risk factor for this disease [80]. Mutations in the α-synclein gene (SNCA) and leucine-rich repeat kinase 2 (LRRK2) are responsible for the late onset, while Parkin (PARK2) and PTEN induced putative kinase (PINK1) are oncogenes DJ1 (DJ1) responsible for early onset [21]. The neuropathological features including cellular inclusions known as Lewy bodies, identified by protein biomolecules, provided conflicting results, therefore, the identification of circulatory biomarkers like miRNAs has immense remedial prospective; however, it is still in infancy and open research opportunities are available to explore new miRNAs and their role in PD [48]. In a study based on the application of microarray approaches, researchers determined the expression profile in PMBC of 19 patients with 13 controls; and total 18 miRNAs were identified with significantly lower expression [74]. In another study, qRT-PCR results showed that the expression of miR-1, miR-22-5p, and miR-29 in peripheral blood differs in PD from healthy individuals. While expression of miR-16-2-3p, miR-26a-2-3p and miR30a also differs among treated and control groups [48]. The profiling of miRNA from the plasma of PD patients has also been conducted by another group using qRT-PCR and miR-331-5p was identified as up-regulated significantly [13]. Additionally, miR-1826, miR-450-3p and miR-505 were identified from 32 patients and 32 controls conducted by another group [13, 57]. By using next generation sequencing analysis in total leukocytes, 16 miRNAs were observed to be changed significantly in PD patients containing miR16, miR20a, and miR-320 as compared to control group [100].

Amyotrophic lateral sclerosis (ALS)

ALS is another serious neurological disorder with symptoms like muscular weakness, atrophy, paralysis and respiratory failure affecting neurons responsible for voluntary movements. Various types of studies are being conducted to identify biomarkers for ALS using CSF and blood samples up to protein level [103], but due to lack of satisfied results, more studies are also being conducted to explore miRNA as a possible biomarker for ALS. Recently, the profiling of total 911miRNAs from leukocytes of ALS patients using microarray technology was performed and only 8 miRNAs were observed to be significantly up and down regulated as compared to control [23]. One parallel study identified a profile containing an inflammatory signature of around 56 miRNAs which was considerably affected in CD14 + CD16 monocytes and they can be used as ALS biomarker [12]. Although these two studies were executed by similar technical methodologies, the number of dysregulated miRNAs found in leukocytes and monocytes is not overlapped and comparable [12, 23].

For the other neurological disorders like HD and FTD, little information is available based on circulating miRNAs in plasma or serum. Interestingly only one miR-34b was observed to be up-regulated in response to Huntingtin (mHTT) mutant indicating the role of miRNA-34b as a biomarker of HD [34]. There is a little concordance between these miRNAs both for precise disease as compared to various NDD. There is an urgent need for the more detailed investigation to be considered for the miRNA as a diagnostic biomarker. The therapeutic potential against HD was investigated by reducing the expression of HTT using RNA interference (RNAi), and approximately 45% reduction of rhesus HTT expression was observed in the mid- and caudal putamen and the partial suppression of wild-type HTT expression is well tolerated in the primate putamen. Based on these results, it is possible that RNAi could be a novel strategy for HD therapy [77]. The level of virus-specific RNAs (vsRNAs) or miRNAs was found to be very high in the exterior of cells of their origin CSF and blood serum [2].

Concluding remarks

Based on the latest information, now it is known that the viruses, prions and microRNAs are associated with neurological disorders leads to emergence of dementia stages. Currently, no treatment is available to control the

progressive neurodegenerative diseases. Discovery of miRNAs elaborated the knowledge and understanding of post transcriptional gene regulation in NDD [3, 91]. Data available so far indicate that miRNAs profiling study in AD and other NDD suffer from poor consensus, which is the main concern. Many difficulties are still present in considering these miRNAs as biomarkers for neurological disorders. There is an urgent need of more detailed investigation to consider these miRNAs as a diagnostic biomarker. There is an urgent need to understand the role of other RNA or DNA based helper viruses in promoting and intensifying the action of miRNA. Most importantly, there is an urgent need to understand the potential spread of miRNA information from cell to cell, tissue to tissue, and between species [10, 54, 82, 94]. The generated additional information during the last few years will provide new perspectives for designing and development of an effective therapeutic and disease management strategy. The understanding about the prion and NDD has reached an advanced stage. *In-vitro* studies about the prion and associated NDDs have elucidated multiple aspects of neurological disorders which are found to be very useful in designing and development of an effective therapeutics and disease management strategies. The complexity of gain-versus loss-of PrPc functions in prion diseases should be further examined and requires strong support based on detailed research work [63]. The role and linkage of prion in NDDs have been reported and the generated information contributed significantly towards the understanding of neurological disorders. More detailed studies are urgently required about the progression of prion diseases and this information will play a strong and valuable role in the designing and drug development strategies for NDD. The recent information showed that prion-like propagation of misfolded protein states is not limited to the prion protein [52, 106]. It is well known that amyloidogenic proteins or peptides, like Aβ, α-synuclein, tau, huntingtin, can also spread from cell to cell or can be transmitted from animal to animal or human to animal in a prion-like fashion to cause NDD [1, 7, 101, 106, 109]. Both AD and prion disease share many similarities and the interaction study of AβPP and PrPc will provide valuable information in developing novel therapies for both AD and prion disease [63]. Based on the above and recent literature, there is still more detailed information required about the role of viruses, prions and miRNAs in neurological disorder. The identification of specific miRNAs can be used as candidate diagnostics biomarker and development of future therapeutics. The detailed understanding of involved mechanism of virus infection, prions and microRNAs in neurological disorders and dementia disease development will help in management and design and development of an effective treatment plan.

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