

Epigenetic and Therapeutic Analysis of various Neurological Disorders

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Abstract

Neurological disorders are diseases of the central and peripheral nervous system. In this Review, It has been analysed epigenetic changes present in neurological diseases and discussed its therapeutic potential. The article has reviewed advances and considers approaches that may provide hope for alleviation of the disorders. This also reviews in this supplement focus on the neurobiology of a variety of these diseases of the central nervous system (CNS), including epilepsy, Alzheimer's disease (AD), Parkinson's disease (PD) and multiple sclerosis (MS).

Keywords: Neurology; Epigenetic; Therapeutic; Drug; Disorders

Introduction

Neurological disorders are diseases of the central and peripheral nervous system. Neurology is a medical specialty dealing with this system. Specifically, it deals with the diagnosis and treatment of all categories of disease involving the central, peripheral and autonomic nervous systems, including their coverings, blood vessels and all effector tissue, such as muscle. These are the diseases of the brain, spine and the nerves that connect them.

These disorders include epilepsy, Alzheimer disease and other dementias, cerebrovascular diseases including stroke, migraine and other headache disorders, multiple sclerosis, Parkinson's disease, neuroinfections, brain tumours, traumatic disorders of the nervous system such as brain trauma and neurological disorders as a result of malnutrition [1]. Various Neurological disorders have been displayed in Figure 1.

Hundreds of millions of people worldwide are affected by neurological disorders: For example, 50 million people have epilepsy; 62 million are affected by cerebrovascular disease; 326 million people suffer from migraine; 24 million are affected by Alzheimer disease and other dementias globally.

The most manifestations of neurological symptoms include:

- Paralysis-can be partial or complete
- Muscle weakness-causing uncoordinated movements or inability to perform simple actions
- Poor cognitive abilities
- Loss of sensation-partial or complete
- Seizures-of various types, including those that are life-threatening
- Mental in coordination-causing confusion or reading, writing and learning difficulties
- Unexplained pain-where the cause of pain is referred to as 'psychological'
- Compromised Consciousness-causing decreased alertness

Genetics

Genetic factors play a determining role for certain neurological disorders. However, the molecular basis for other psychiatric disorders has yet to be elucidated and there are complicating factors that bear on genetic research of complex behavioral disorders [2].

One of the most striking parallels emerging from recent studies of these different diseases is the extraordinary progress that has been made in identifying the specific genes that are significant risk factors for many of these illnesses and the ways in which proteins encoded by these genes are associated, directly or indirectly, with loss of functions or gain of adverse properties. Many of the genes that control neuronal migration have strong genetic or biochemical links to the cytoskeleton,

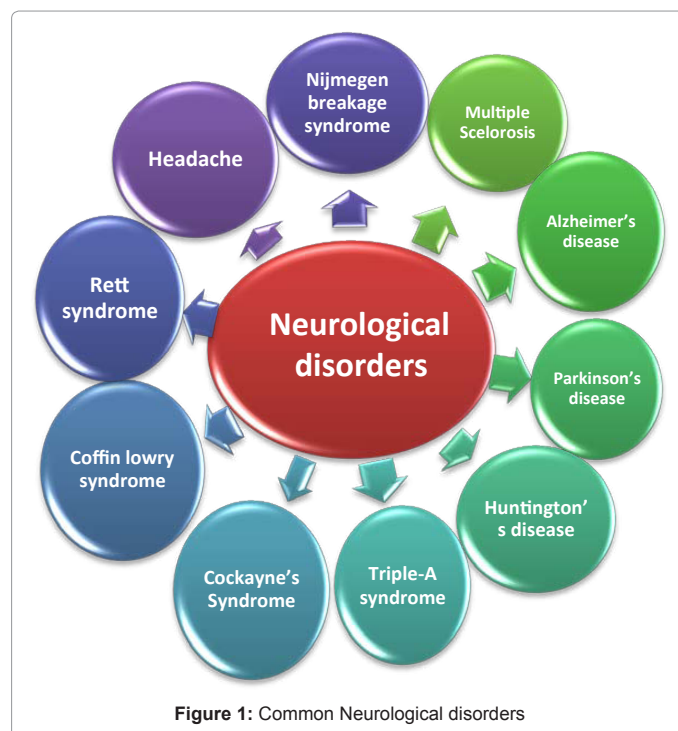


Figure 1: Common Neurological disorders

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Disorder	Main Symptoms	DNA Repair Defect	Mode of Inheritance
Xeroderma Pigmentosum	Sensitivity to sunlight; slow neurodegeneration; Skin Cancer	NER (7 variants) pol n	Autosomal recessive
Cockayne's Syndrome	Sensitivity to sunlight; growth retardation; neurological impairment; progeria	Defective NER and TCR	Autosomal recessive
Trichothiodystrophy	Sensitivity to sunlight; dystrophy; short brittle hair with low sulfur content; neurological defects	Defective NER, Particularly of ultraviolet induced damage; closely related to ERCC2 and ERCC3 defects	Autosomal recessive
Down syndrome	Mental retardation; progeria	Defective repair of oxidative DNA damage(trisomy of chromosome 21)	No precise mode of inheritance
Nijmegen breakage syndrome	Progeria; wheel chair dependency	Defective DNA damage response and DSB repair	Autosomal recessive
Alzheimer's disease	Memory loss; cognitive decline	Increased oxidative stress and damage; defective repair of oxidative damage and DSB repair	Autosomal dominant
Parkinson's disease	Tremor,bradykinosia,postural rigidity and postural instability	Oxidative Stress and DNA damage; mutations in alfa-synuclein and parkin variants	Autosomal dominant
Huntington's disease	Progressive chorea and dementia; severe neuronal loss in the striatum and cerebral cortex	CAG repeat expansion in huntingtin(HD) gene and oxidative damage to DNA	Autosomal dominant
Friedreich's ataxia	Limb ataxia; Sensory loss; skeletal deformities	GAA expanded repeats in frataxin(FXN) gene	Autosomal recessive
Myotonic dystrophy types 1 and 2	Muscle weakness; cataracts; testicular atrophy; cognitive decline	CTG expansion(type 1);CCTG expansion(type 2)	Autosomal dominant
Triple-A syndrome	Adrenal insufficiency; achalasia; alacrima; neurodegeneration; autonomic dysfunction	Mutation in AAAS gene, which encodes ALADIN protein	Autosomal recessive
Amyotrophic lateral sclerosis	Progressive degeneration of motor neurons; muscle weakness and atrophy, leading to fatality	Defective Cu-Zn superoxide dismutase (SODC; SOD1); Oxidative stress; defective DNA repair (BER?)	Autosomal recessive

Table 1: Various Neurological Disorder with a link to defective DNA repair

suggesting that the field of neuronal migration might be closing in on the underlying cytoskeletal events. The genetics of common neurological diseases has been investigated in variations in the DNA sequences of people suffering from common neurodevelopmental disorders, namely migraine, epilepsy, schizophrenia and autism etc (Table 1) [3].

The disorders along with the known genetic DNA repair defect and the nature of the inheritance. In addition, there are a handful of syndromes with an etiological link to DNA damage and repair that exhibit symptoms of accelerated aging but have no striking neurological symptoms. Such syndromes include Werner's syndrome, Bloom syndrome and Rothmund–Thomson syndrome. Some neurological disorder with DNA repair link is listed in Table 1.

Etiology

The etiology of most neurodegenerative disorders is multifactorial and consists of an interaction between environmental factors and genetic predisposition. Free radicals derived primarily from molecular oxygen have been implicated and considered as associated risk factors for a variety of human disorders including neurodegenerative diseases and aging. Many common neurological disorders, such as Parkinson's disease, stroke and multiple sclerosis, are caused by a loss of neurons and glial cells. In recent years, neurons and glia have been generated successfully from stem cells in culture, fuelling efforts to develop stem-cell-based transplantation therapies for human patients [4]. A number of neurological disorders seem to have an etiological connection to defects in one or more DNA repair pathways. Acute multiple sclerosis-like leukoencephalopathy revealing HIV infection may also occur in rare cases [5-7]. Berger et al. first described 7 HIV patients with neurological diseases resembling multiple sclerosis [8-10].

Paraneoplastic neurological disorders (PNDs) are rare syndromes that are caused by, or associated with, an underlying neoplasm. The detection of antibodies against onconeural antigens points to the diagnosis of a paraneoplastic syndrome and focuses the search for an underlying tumor to a few organs [11-13].

Since the first mutations of the neuronal sodium channel SCN1A were identified 5 years ago, more than 150 mutations have been described in patients with epilepsy. Many are sporadic mutations and cause loss of function, which demonstrates haploinsufficiency of SCN1A. Mutations resulting in persistent sodium current are also common. The rapid pace of discoveries suggests that sodium channel mutations are significant factors in the etiology of neurological disease and may contribute to psychiatric disorders as well [14]. The rapid pace of discoveries suggests that sodium channel mutations are significant factors in the etiology of neurological disease and may contribute to psychiatric disorders as well [15].

Epigenetic Mechanism

Epigenetic mechanisms such as DNA methylation and modifications to histone proteins regulate high-order DNA structure and gene expression. Aberrant epigenetic mechanisms are involved in the development of many diseases, including cancer. The neurological disorder most intensely studied with regard to epigenetic changes is Rett syndrome; patients with Rett syndrome have neurodevelopmental defects associated with mutations in MeCP2, which encodes the methyl CpG binding protein 2, that binds to methylated DNA. Other mental retardation disorders are also linked to the disruption of genes involved in epigenetic mechanisms; such disorders include mental retardation X-linked syndrome, Rubinstein-Taybi syndrome and Coffin-Lowry syndrome. Moreover, aberrant DNA methylation and histone modification profiles of discrete DNA sequences and those at a genome-wide level, have just begun to be described for neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease and Huntington's disease and in other neurological disorders such as multiple sclerosis, epilepsy and amyotrophic lateral sclerosis [16].

It is becoming increasingly clear that epigenetic modifications are critical factors in the regulation of gene expression. With regard to the nervous system, epigenetic alterations play a role in a diverse set of processes and have been implicated in a variety of disorders.

Gaining a more complete understanding of the essential components and underlying mechanisms involved in epigenetic regulation could lead to novel treatments for a number of neurological and psychiatric conditions [17].

Many neurological and most psychiatric disorders are not due to mutations in a single gene; rather, they involve molecular disturbances entailing multiple genes and signals that control their expression. Recent research has demonstrated that complex epigenetic mechanisms, which regulate gene activity without altering the DNA code, have long-lasting effects within mature neurons [18,19].

The autism spectrum disorders (ASD) comprise a complex group of behaviorally related disorders that are primarily genetic in origin. Involvement of epigenetic regulatory mechanisms in the pathogenesis of ASD has been suggested by the occurrence of ASD in patients with disorders arising from epigenetic mutations (fragile X syndrome) or that involve key epigenetic regulatory factors (Rett syndrome). Moreover, the most common recurrent cytogenetic abnormalities in ASD involve maternally derived duplications of the imprinted domain on chromosome 15q [11–13]. Thus, parent of origin effects on sharing and linkage to imprinted regions on chromosomes 15q and 7q suggest that these regions warrant specific examination from an epigenetic perspective, particularly because epigenetic modifications do not change the primary genomic sequence, allowing risk alleles to evade detection using standard screening strategies [20].

In one experimental system epigenetic marks at the level of chromatin structure (histone acetylation) have been linked to the recovery of memories. Environmental enrichment has long been known to have positive effects on memory capacity and recent studies have suggested that these effects are at least partly due to the recruitment of epigenetic mechanisms by environmental enrichment. Finally, an uncoupling of signal transduction pathways from the regulation of epigenetic mechanisms in the nucleus has been implicated in the closure of developmental critical periods. Taken together, these eclectic findings suggest a new perspective on experience-dependent dynamic regulation of epigenetic mechanisms in the adult nervous system and their relevance to biological psychiatry [21].

Peroxisomal disorders are lethal inherited diseases caused by either defects in peroxisome assembly or dysfunction of single or multiple enzymatic function(s). The peroxisomal matrix proteins are targeted to peroxisomes via the interaction of peroxisomal targeting signal sequences 1 and 2 (PTS1 or PTS2) with their respective cytosolic receptors.

Several signs and rhythm tapping are more prevalent in mood-disorder patients than in schizophrenia patients. Only lack of extinction, dysdiadochokinesia, poor tandem walk, finger-thumb-opposition and articulation are significantly more prevalent in schizophrenia compared to mood-disorder patients. Impaired motor coordination seems most specific to schizophrenia [22,23].

Epilepsy is a chronic neurological disorder affecting both sexes and all ages, with worldwide distribution. The term is also applied to a large group of conditions characterized by common symptoms called “epileptic seizures”, which may occur in the context of a brain insult that can be systemic, toxic or metabolic [24].

Multiple sclerosis (MS) is an inflammatory demyelinating condition of the central nervous system (CNS) that is generally considered to be autoimmune in nature. In people with MS, the immune trigger is unknown, but the targets are myelinated CNS tracts. In regions

of inflammation, breakdown of the blood–brain barrier occurs and destruction of myelin ensues, with axonal damage, gliosis and the formation of sclerotic plaques.

Pathogenesis of diseases

The pathogenesis of these illnesses are as varied as the clinical signs. The mechanisms at work include: ischaemia/hypoxia; free radical damage; necrosis and/or apoptosis; excitotoxicity; inflammatory and immunemediated processes; impaired interactions between molecules; sequestration of essential molecules; formation of intra- and extracellular aggregates and fibrils; acquisition of toxic properties by mutant proteins and pathological reorganization of neural circuits. For each disorder, there has been significant progress in clarifying these mechanisms. It is believed that most are caused by an immune response against onconeural antigens [25]. Defective Fas function causes the autoimmune lymphoproliferative syndrome, but it is also involved in common autoimmune disorders [26–28].

Clinical trials of several neurodegenerative diseases have increasingly targeted the evaluation of the effectiveness of various antioxidants. Aging is one of the most significant risk factors for degenerative neurological disorders. For each disease, the clinical manifestations reflect the involvement of cells in different brain regions and circuits as well as the character and evolution of the biochemical and cellular abnormalities. The diagnosis of chronic isolated CNS infection can be complex, because the serological tests. The better therapy for neurohistoplasmosis is unknown [29]. Natural killer (NK) cell function was investigated in Malaysian HIV patients beginning antiretroviral therapy (ART) with advanced immunodeficiency [30–33]. The pathogenesis of gastrointestinal diseases are unclear. The strategy of any medical regimen for management of any disease is usually dependent on the mechanism by which this disease has developed [34,35].

Astrocytes are involved in the pathology of most neuronal disorders, including brain ischemia, Alzheimer’s disease and epilepsy. In the pathology of brain tumors, gap junctions may be related to the degree of malignancy and metastasis.

Therapeutic Analysis

The identification of mutant genes responsible for inherited neurological disorders gives an opportunity to consider new approaches to their treatment. Although replacement of defective genes in postmitotic neurons is unlikely to be possible in the near future, the identification of gene products and definitive delineation of the cellular dysfunction and death that result from mutated gene products, may suggest new therapeutic options [36]. Silicone oils are used for ocular endotamponade to treat complicated retinal detachments. Neurological complications of silicone oil endotamponade are uncommon. Silicone oil can migrate into the nervous system and may provoke optic neuritis [37,38]. The anti-GQ1b IgG antibody positivity in Miller Fisher syndrome (MFS) alone has extended to involve a spectrum of related disorders, as well as relevant implications on therapy [39,40].

Recent work on glial cell physiology has revealed that glial cells and astrocytes in particular, are much more actively involved in brain information processing than previously thought. This finding has stimulated the view that the active brain should no longer be regarded solely as a network of neuronal contacts, but instead as a circuit of integrated, interactive neurons and glial cells. Consequently, glial cells could also have as yet unexpected roles in the diseased brain. An improved understanding of astrocyte biology and heterogeneity and

the involvement of these cells in pathogenesis offers the potential for developing novel strategies to treat neurological disorders [41].

Many common neurological disorders, such as Parkinson's disease, stroke and multiple sclerosis, are caused by a loss of neurons and glial cells. In recent years, neurons and glia have been generated successfully from stem cells in culture, fuelling efforts to develop stem-cell-based transplantation therapies for human patients [42]. Protein p21 in Control of Secretory Activity of Porcine Ovarian Cells [43]. One research has highlighted a drug target named Monoamine oxidase B (MAO B) is a mitochondrial outer membrane flavoenzyme that is a well-known target for antidepressant and neuroprotective drugs. The enzyme binds to the membrane through a C-terminal transmembrane helix and apolar loops located at various positions in the sequence. The recognition site for the substrate amino group is an aromatic cage formed by Tyr 398 and Tyr 435. The structure provides a framework for probing the catalytic mechanism, understanding the differences between the B- and A-monoamine oxidase isoforms and designing specific inhibitors [44]. Glutamate decarboxylase (GAD) antibody has been found in patients with recent-onset insulin dependent diabetes mellitus (IDDM) [45,46].

Another Drug target named Rho kinases (ROCKs), the first Rho effectors to be described, are serine/threonine kinases that are important in fundamental processes of cell migration, cell proliferation and cell survival. Abnormal activation of the Rho/ROCK pathway has been observed in various disorders of the central nervous system. Inhibition of ROCKs results in accelerated regeneration and enhanced functional recovery after spinal-cord injury in mammals and inhibition of the Rho/ROCK pathway has also proved to be efficacious in animal models of stroke, inflammatory and demyelinating diseases, Alzheimer's disease and neuropathic pain. ROCK inhibitors therefore have potential for preventing neurodegeneration and stimulating neuroregeneration in various neurological disorders [47]. Encapsulating cytotoxic drugs in liposomal vehicles allows for the targeting of tumors while protecting the drugs from premature degradation [48,49].

Gap junctions are intercellular channels which directly connect the cytoplasm between neighboring cells. In the central nervous system (CNS) various kinds of cells are coupled by gap junctions, which play an important role in maintaining normal function. Neuronal gap junctions are involved in electrical coupling and may also contribute to the recovery of function after cell injury. However, the role of connexins, gap junctions and hemichannels in the pathology of the diseases in the CNS is still ambiguous. A better understanding of the role of gap junctions may contribute to the development of new therapeutic approaches to treating diseases of the CNS [50].

It is hypothesised that the DRD2 is a reinforcement or reward gene. This gene has been implicated in Tourette's syndrome (TS), post-traumatic stress disorder (PTSD) and certain symptoms associated with affective disorders and schizophrenia. Further, DRD2 variants have been implicated in Parkinson's disease (PD) and in iatrogenically-induced movement disorders, as well as in certain migraineurs. The involvement of the DRD2 gene in certain neuropsychiatric disorders opens up the potential of a targeted pharmacogenomics approach to the prevention and treatment of these disorders [51]. Chronic inflammatory demyelinating polyneuropathy (CIDP) is considered to be an autoimmune disorder of the peripheral nervous system. It has been experimented that the measurement of visual evoked potentials was a useful technique for the diagnosis of visual pathway involvement, but was of no value for monitoring the effect of treatment in CIDP patients [52,53]. Compounds acting specifically to antagonise excitatory

neurotransmission offer a novel therapeutic approach to these disorders [54]. Recent studies suggest that the epigenetic modifications that regulate transcription are critical for memory storage. Thus, genetic studies have demonstrated that memory formation requires molecular processes that regulate neuronal transcription after learning and suggest that the epigenetic modifications may store information that guides behaviour [55,56]. The use of transskull High Intensity Focused Ultrasound (HIFU) for immediate clot lysis without the need of further drugs and disregarding individual skull bone characteristics is feasible in vitro [57,58].

Given their clinical importance for the treatment of acute and chronic neurodegenerative diseases in humans including nerve injuries (e.g. Alzheimer's disease, Parkinson's disease, diabetic neuropathy) a number of different approaches were pursued to obtain selectively acting FK506-binding protein (FKBP) ligands: computational methods and target-oriented screening of natural compound and synthetic product libraries. The resulting monofunctional ligands, which inhibit the peptidyl prolyl cis/transisomerase activity of FKBP, highlight the role of these enzymes in neuronal signaling and acts as novel therapeutics for neurological disorders [59].

Future Research

Excessive excitation by neurotransmitters can cause the death of neurons. This excitotoxic action may be responsible for neuronal loss in stroke, cerebral palsy, epilepsy, ageing and Alzheimer's disease, Huntington's disease and other chronic degenerative disorders. Compounds acting specifically to antagonise excitatory neurotransmission offer a novel therapeutic approach to these disorders [60]. Treatment of psychosocial aspects in the level of quality of life among brain tumor patients deserves special attention in further research [61-63]. Research on several other neurodegenerations, including Parkinson's, Alzheimer's and prion diseases, provides support for the development of intrabodies directed against specific targets, or possibly against more common downstream targets, as novel therapeutics and as drug discovery tools [64]. Neuropsychiatric syndromes are retrospective and primarily descriptive in nature, further investigations using more recently developed advanced structural and functional neuroimaging techniques, including automated volumetric and functional connectivity analyses, are needed to provide added specificity to the delineation of structure-function relationships in these patient populations [65,66]. Chronic neutrophilic leukemia (CNL) is an extremely rare myeloproliferative disorder that presents diagnostic challenges for both pathologists and treating clinicians. Because this disease entity is very rare and because it is typically a diagnosis of exclusion, it is important for pathologists and hematologists to be familiar with CNL when approaching the patient with a myeloproliferative clinical picture [67-69]. Spasmodic dysphonia is a primary focal dystonia manifested by loss of control of the vocal muscles during speech secondary to laryngeal muscle spasms. The pathophysiology is not well understood. Deep brain stimulation surgery (DBS) for other focal dystonias has been well reported [70-72]. The outcome of current intense research into the genetics of neurological disorders will hopefully be the introduction of new diagnostic tools and the discovery of potential targets for new and more effective medications and preventive measures [73]. More recently, efforts have been extended to stimulating the formation and preventing the death of neurons and glial cells produced by endogenous stem cells within the adult central nervous system. The next step is to translate these exciting advances from the laboratory into clinically useful therapies.

Growing evidence on genetic components of neurological

diseases have been collected during recent years. Genetic studies have opened the way for understanding the underlying pathology of many neurological disorders.

Conclusion

The outcome of current intense research into the genetics of neurological disorders will hopefully be the introduction of new diagnostic, therapeutic tools and the discovery of potential targets for new and more effective medications and preventive measures. As this reviews illustrates, substantial progress has been made over the past few years in understanding a variety of devastating neurological illnesses. Model systems are now being used for molecular and cell biological studies of pathogenic mechanisms and for identification of new therapeutic targets. The efficacies of new drugs can be examined in these models.

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