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A Review on Neuroinflamatin and its role in neurodegenerative diseases: Future therapeutic Targets

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ABSTRACT
Neuroinflammation, an immune response within the central nervous system (CNS), plays a dual role in brain health—acting as both a protective mechanism and a contributor to neurodegeneration when chronically activated. Triggered by various factors including infections, trauma, toxic metabolites, and autoimmunity, neuroinflammation involves activation of glial cells and release of pro-inflammatory molecules such as cytokines and reactive oxygen species. While acute neuroinflammation may support tissue repair, prolonged inflammation can lead to neuronal damage and contribute to the progression of multiple neurodegenerative diseases.
This report explores the pathological and clinical interconnection between neuroinflammation and disorders such as Alzheimer's disease, Parkinson's disease, Amyotrophic Lateral Sclerosis (ALS), Multiple Sclerosis (MS), and Multiple System Atrophy (MSA). Each disease displays distinct clinical and neuropathological features, yet shares overlapping mechanisms involving immune dysregulation, protein aggregation, and glial activation. Current therapeutic strategies focus on targeting these pathways to halt or slow disease progression. Despite existing drug therapies offering symptomatic relief, there remains an urgent need for disease-modifying treatments. Emerging research emphasizes multi-target drug approaches, early diagnostic biomarkers, and personalized medicine as future directions in combating neurodegenerative disorders driven by neuroinflammation.

Keywords:- Neuroinflamation, neurodegenerative diseases, future therapeutic targets, alzheimer's diseases, parkinson diseases, amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), multiple system atrophy (MSA).

I. INTRODUCTION

Neuroinflamation:

Neuroinflammation refers to an inflammatory reaction in the brain or spinal cord. It is driven by the production of molecules such as cytokines, chemokines, reactive oxygen species (ROS), and secondary messengers, which are released by endothelial cells, immune cells from the peripheral system, and resident glial cells in the central nervous system (CNS), such as microglia and astrocytes.[1]

Neuroinflamation may be initiated in response to a variety of causes, including infection, traumatic brain injury, toxic metabolites, or autoimmunity and also impact In the central nervous system (CNS), including the brain and spinal cord.[2,3]

Although neuroinflammation has a protective role in defending the brain from harmful agents and assisting in tissue repair, it can become problematic when it is prolonged or excessive. Factors like genetic mutations, protein aggregation, infections, trauma, and certain drugs can all trigger sustained neuroinflammation, which in turn can hinder regeneration and contribute to neurodegenerative diseases.[4]

Neurodegeneration diseases:

Neurodegeneration corresponds to any pathological condition primarily affecting neurons. In clinical practice, neurodegenerative diseases represent a large group of neurological disorders, with various clinical and pathological characteristics affecting specific subsets of neurons in specific regions of the central nervous system (CNS).[5]

Role of Neuroinflamation in neurorodegenerative diseases:

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In clinical practice, neurodegenerative diseases represent a large group of neurological disorders, with various clinical and pathological characteristics affecting specific subsets of neurons in specific regions of the central nervous system (CNS).[6]

Diseases happen due to Neuroinflamation:
Some of the main types of degenerative brain diseases include :-
1.Alzheimer's disease
2. Parkinson's disease
3.Amyotrophic Lateral Sclerosis (ALS)
4. Multiple Sclerosis (MS)
5.Multiple System Atrophy (MSA)

Therapeutic targets:
A therapeutic target is a biological molecule, biological pathway, or physiolocal response that is associated with a particular disease process and may be inhibited or activated by a therapy in a way that will change the course of the disease in a positive way.[7]

CAUSES OF NEUROINFLAMATION:-
Neuroinflamation is basically brain related diseases till the now there no certain cause found for Neuroinflamation. Neuroinflamation is generally two types:-
A .acute neuroinflamation[8].
B. chronic neuroinflamation [9]

Common causes of chronic neuroinflammation include:
a.Toxic metabolites
b.Autoimmunity
c.Ageing
d.Microbes
e.Viruses
f.Traumatic brain injury
g.Spinal cord injury
h.Air pollution
i.Passive smoke
j.Blast injury[10]

Neuroinflammation can arise from various triggers, including infections, systemic inflammation, autoimmune disorders, and lifestyle factors so there is some factors:-
a) Infections and peripheral inflammation
b) Autoimmune disorders
c) Lifestyle factors
d) Stress and sleep deprivation:
e) CNS injuries[11]

CAUSES OF NEURODEGENERATIVE DISEASES:-
Some neurodegenerative diseases have a single cause that healthcare providers can identify. But in many cases, there isn't a single cause. Instead, research shows multiple factors probably contribute to neurodegenerative diseases. multiple study says there is no specific cause fond by reascher's And there are times when providers might not be able to find a cause — which can be frustrating for someone with one of these conditions or their loved ones.

So far, experts have identified dozens of possible causes or risk factors. These tend to fall into a few specific categories, including:
a) Age
b) Genetics
c) Environment
d) Medical history
e) Habits, routine and choice[12]

Mechanism of Neuroinflamation
Neuroinflammation denotes the innate and adaptive responses to harmful factors such as infections, ischemia, stress, and trauma.[13]

Within the context of neuroinflammation, it is hypothesized that four distinct features function as defining hallmarks: elevated cytokine release, microglial cell activation, migration of peripheral immune cells, and localized tissue damage.[14]

They are responsible for immune surveillance in the brain. Astrocytes control blood flow and extracellular neurotransmitter levels to ensure that the microenvironment in which they reside is optimal for neurological function.[15,16]

List of neurodegenerative diseases that happen due to Neuroinflamation
Many research have shown that there are few diseases and disorder which occur due to the inflammation in neurons. Ultimately leading to Neuroinflammation.
1.Alzheimer's disease
2. Parkinson's disease
3.Amyotrophic Lateral Sclerosis (ALS)
4. Multiple Sclerosis (MS)
5.Multiple System Atrophy (MSA)

Alzheimer's disease
Clinical characteristics:-
Alzheimer 's disease (AD) is an irreversible and incurable progressive

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neurodegenerative illness featuring cognitive and functional deficits as well as loss of functional independence and behavioural changes.[17]

Neurobiological characteristics:-

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common cause of dementia, accounting for 60% to 80% of cases. Early symptoms typically include difficulty remembering names and recent events, apathy, and depression. Later symptoms include worsening memory, impaired judgment, disorientation, confusion, behavioral changes, and difficulty speaking, swallowing, and walking.[18]

For clinical research, the classification of AD has recently been divided into 3 phases.

a) presymptomatic phase
b) symptomatic prodromal phase
c) final phase

Pathological characteristics:-

Impact of Aβ and APP:-

The amyloid hypothesis remains the dominant hypothesis in AD research due to the causal mutations found in both APP and presenilin genes. APP is processed via either the amyloidogenic or non-amyloidogenic pathway. For Aβ, APP is sequentially cleaved by the β- and γ-secretases, releasing the peptide into the cytosol . Functions of APP and Aβ are largely unknown, but they are thought to play a role in signal transduction for neuronal development, growth and survival.[19,20]

Aβ accumulation has been proposed to cause neuronal death via a number of mechanisms, including excitotoxicity, synaptic disruption, oxidative stress and mitochondrial dysfunction. Excitotoxicity can occur when NMDA receptors are continually activated, either by Aβ directly or by a downstream mechanism. In conjunction with synapse loss, both AD patients and animal models show reductions in the synaptic proteins synaptophysin and PSD-95.[21,22]

Parkinson's disease

Clinical characteristics:-

PD has been defined as a complex neurodegenerative disorder expressing various symptoms due to the dopaminergic neuronal cell death in the substantia nigra (SN).[23]

PD is identified as the second-most common neuropathological disorder after Alzheimer's disease associated with significant disability and decreased quality of life[24].

Neurobiological characteristics:-

The main motor features of PD are the consequence of death of dopaminergic neurons in the substantia nigra pars compacta. However, other neurotransmitter systems (e.g. cholinergic, adrenergic, serotoninergic) also degenerate and cell loss is seen in other brain stem nuclei and the cortex. This nondopaminergic degeneration is a major cause of the nonmotor symptoms of PD (e.g. cognitive decline, autonomic dysfunction). Although they might sometimes precede the motor symptoms, they come to dominate the later stages of the disease.[25]

Pathological characteristics:-

A significant amount of work has been conducted so far to understand the pathophysiology of PD in depth. Preclinical and clinical studies are increasingly focused on understanding the underlying extraneuronal pathology. Among all extraneuronal cells discussed in the literature for PD, microglia have drawn the greatest attention in research over the past few decades.[26]

Amyotrophic Lateral Sclerosis (ALS):-

Clinical characteristics:-

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease of the central nervous system, it is a rare disease and is difficult to recognize, especially in its early stages.Identifying the phenotypic and clinical heterogeneity and gaining a clearer understanding of the multi systemic damage nature of ALS, including cognitive dysfunction and behavioural changes, can help physicians better identify it earlier in the course of the disease.[27]

Neurobiological characteristics:-

ALS mainly but not exclusively affects the lower motor neurons in the brainstem and ventral horn of the spinal cord (hence the name amyotrophic) and the upper motor neurons in the cortex that give rise to the corticospinal tract which descends through the lateral spinal cord (hence the name lateral sclerosis). This results in muscle atrophy and weakness, fasciculations, and spasticity.[28]

Pathological characteristics:-

The correlations between key clinical features of progressive muscle atrophy and muscle spasticity and key neuropathologic features of loss of anterior horn cells and sclerosis in the lateral

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columns of the spinal cord were first made by Charcot in the 1860's, and thus he named the clinical disease by its distinctive neuropathology.[29,30]

MultipleSclerosis(MS):-

Clinical characteristics:-

Multiple sclerosis (MS) is an inflammatory demyelinating central nervous system (CNS) disease. Its onset is typically in adults with peak age at onset between 20–40 years. There is a female predominance of up to 3:1. The course of MS is relapsing–remitting (RRMS) at onset in 85% with episodes of neurological dysfunction followed by complete or incomplete recovery.[31]

Neurobiological characteristics:-

The global burden of MS has a number of truly remarkable characteristics, including an increasing incidence over the past century, an influence of latitude on risk, and increased risk in both females and white populations, especially those of northern European ancestry.[32,33]

Pathological characteristics:-

MS refers to the plaques that form in the CNS combined with inflammation, demyelination, axonal injury and axonal loss. These plaques are found in the brain and spinal cord, essentially in the white matter around the ventricles, optic nerves and tracts, corpus callosum, cerebellar peduncles, long tracts and subpial region of the spinal cord and brainstem, but also in the gray matter.[34]

Multiple System Atrophy (MSA):-

Clinical characteristics:-

Multiple system atrophy (MSA) is a rare, fatal, rapidly progressive neurodegenerative disease of adulthood, characterized by severe autonomic failure, poorly L-Dopa-responsive parkinsonism, cerebellar ataxia, and pyramidal signs in any combination.[35]

Neurobiological characteristics:-

MSA belongs to the broad spectrum of α-synucleinopathies, a group of neurodegenerative disorders characterized by the abnormal accumulation of misfolded hyperphosphorylated α-synuclein.[36,37]

Pathological characteristics:-

Multiple System Atrophy (MSA) is a progressive and severe neurodegenerative disorder which is clinically characterized by variable degrees of parkinsonism, cerebellar ataxia and dysautonomia. Additional motor and non-motor symptoms can be detected as well.[38,39,40]

Future therapeutic targets for neurodegenerative diseases

Different therapeutic strategies have been developed to target to cellular pathways, and the drugs have been evaluated for the treatment of different neurodegenerative disorders.

However, the future challenges in drug discovery for neurodegenerative disorders are

(i) The detection of the earliest events in the neurodegenerative cascade

(ii) The identification of the pathways responsible for the specific vulnerability of cellular populations in each neurodegenerative disease.[41]

Future therapeutic targets for Alzheimer's diseases :-

For the future therapeutic targets of treatment of Alzheimer's diseases there is some multi targets compounds:-

Multi target compounds for the treatment of Alzheimer's diseases

Historically, drug development has been based on the view that one molecule is used for one target to treat one disease. However, there is growing recognition that drugs against a single target may be inadequate as the pathology of most diseases – including neurodegenerative disorders, cancer, and diabetes – is multifactorial.[42]

Consequently, a new strategy for drug design has been proposed whereby hybrid molecules are developed which consist of several distinct pharmacophores that act upon different targets involved in the disease, in order to create one multi-target-directed-ligand (MTDL) that has the capacity to interact with various targets and therefore treat complex multifactorial diseases.[43]

Future therapeutic targets for Parkinson's diseases :-

PD has a heterogeneous pathogenesis, and although years have passed since its definition, there is still no disease-modifying treatment.Numerous protein and molecular pathways are involved in its pathophysiology[44,45]

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Future therapeutic targets for Amyotrophic Lateral Sclerosis (ALS) diseases:-

Yet, the anti-inflammatory and neuroprotective tyrosine kinase inhibitor, masitinib, showed new possibilities for cure of amyotrophic Lateral Sclerosis (ALS) diseases.Indeed, in a randomized controlled trial, when added to riluzole, it showed slight positive effects to be further evaluated.[46]

Future therapeutic targets for Multiple Sclerosis (MS) diseases:-

The autoimmune disease multiple sclerosis (MS) is the leading cause of non-traumatic neurological disability arising in young adults.[47,48]

MS is characterized by two pathological hallmarks:

a) inflammation with demyelination
b) astroglial proliferation (gliosis) and neurodegeneration.

Tissue damage in MS is restricted to the central nervous system (CNS), sparing the peripheral nervous system.
Clinically, MS can follow two paths:
(i) relapsing
(ii) progressive.

Most commonly, onset is a relapsing form of MS (RMS), manifested as discrete episodes of neurological dysfunction followed by partial, complete, or no remission. Over time, relapses usually decrease in frequency but a gradual worsening often supervenes, resulting in uninterrupted progression.[49].

Future therapeutic targets for Multiple System Atropy (MSA) diseases:-

Based on the key role of alpha-synuclein aggregation in MSA, transgenic animal models and genetic strategies have been developed. Transgenic animal models allow the expression of alpha-synuclein in oligodendrocytes under control of specific promoters.[50,51,52]

Drug used in prevention and diagnosis of neurodegenerative diseases

The various drug are used in prevention of brain reated drug that are known as neurodegenerative diseases.

Drug that are used in diagnosis of alzheimer's diseases :-

1.Donepezil
2.choline alphoscerate
3.dextromethorphan
4.plamitoylethanolamide
5.Citalopram
6.Resveratrol
7.Solanezumab.[53]

Drug that are used in diagnosis of parkinson's diseases:-

1. levodopa
2. Dopamine agonists
3. Monoamine Oxidase B (MAO-B) inhibitors
4. Catechol-O-methyl transferase inhibitors
5. Anticholinergics
6. Amantadine.[54]

Drug that are used in diagnosis of Amyotrophic Lateral Sclerosis (ALS) diseases-

1. Qalsody
2. Relyvrio
3. radicava
4. Rilutek
5. Tiglutik
6. Exservan
7. Nuedexta.[55]

Drug that are used in diagnosis of Multiple Sclerosis (MS) diseases:-

1. cyclophosphamide (Cytoxan)
2. Mitoxantrone.[56]

Drug that are used in diagnosis of Multiple System Atrophy (MSA) diseases:-

1. Clonazepam
2. propanolol
3. baclofen
4. amantadine
5. gabapentin
6. buspirone.[57]

II. CONCLUSION

Neuroinflammation plays a dual role in the central nervous system—it is essential for defending against harmful stimuli and supporting repair, but when dysregulated, it contributes significantly to the onset and progression of various neurodegenerative diseases. Chronic neuroinflammation, driven by factors such as infections, toxic metabolites, autoimmune responses, and environmental stressors, can disrupt neural homeostasis, leading to the degeneration of

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specific neuronal populations in diseases like Alzheimer's, Parkinson's, ALS, Multiple Sclerosis, and Multiple System Atrophy.

The close association between neuroinflammatory processes and neurodegeneration highlights the importance of understanding underlying mechanisms such as microglial activation, cytokine release, oxidative stress, and immune cell infiltration. Current treatments offer symptomatic relief, but they do not halt disease progression. Thus, identifying early biomarkers and novel therapeutic targets is crucial for developing effective disease-modifying therapies.

Advancements in multi-target drug development, immunomodulation, and neuroprotective strategies represent promising future directions. A deeper understanding of the interplay between inflammation and neurodegeneration may ultimately pave the way for more precise, preventive, and curative approaches to these complex and debilitating disorders.

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