ISSN: 2457-0400

Impact Factor: 7.675

WORLD JOURNAL OF ADVANCE HEALTHCARE RESEARCH

www.wjahr.com

Volume: 10, Issue: 5

Page N. 01-08

Year: 2026

Review Article

Coden USA: WJAMA3

KLOTHO BIOMARKERS IN NEUROLOGICAL DISORDERS: EMERGING THERAPEUTIC INSIGHTS

Rafal Qasim Al-Azzawi, Tabark Hussein Al-Khafaji, Rahma Hamed Al-Darb, Thikra Ali Allwsh*

Department of Chemistry, College of Science, University of Mosul.

Article Received: 18 March 2026 **Article Revised:** 08 April 2026 **Article Published:** 01 May 2026

***Corresponding Author: Thikra Ali Allwsh**

Department of Chemistry, College of Science, University of Mosul.

DOI: https://doi.org/10.5281/zenodo.19910898

How to cite this Article: Rafal Qasim Al-Azzawi, Tabark Hussein Al-Khafaji, Rahma Hamed Al-Darb, Thikra Ali Allwsh* (2026). Klotho Biomarkers In Neurological Disorders: Emerging Therapeutic Insights. World Journal of Advance Healthcare Research, 10(5), 01–08.

ABSTRACT

Background: Neurological disorders are a major global health burden characterized by progressive neuronal dysfunction driven by complex molecular mechanisms, including neuroinflammation, oxidative stress, and protein aggregation. **Objective:** This review summarizes molecular mechanisms and highlights biomarkers to provide a comprehensive overview of the molecular mechanisms underlying neurological disorders and highlight the role of emerging biomarkers such as Klotho in disease progression and therapeutic targeting. **Methods:** A narrative review was conducted based on recent literature from peer-reviewed journals indexed in Scopus and Web of Science, focusing on neurodegenerative and neuroinflammatory diseases. **Results:** Evidence suggests that neuroinflammation plays a central role in disease pathogenesis, interacting with oxidative stress and protein misfolding pathways. Biomarkers such as Klotho demonstrate strong potential for early diagnosis and monitoring. Emerging therapies including immunotherapy, gene therapy, and precision medicine show promising results. **Conclusion:** Neuroinflammation interacts with oxidative stress and protein misfolding. Biomarkers show diagnostic potential. Understanding the interplay between inflammation, biomarkers, and neurodegeneration is essential for developing effective therapeutic strategies. Understanding these pathways is critical for developing therapies. Future research should focus on early detection and personalized medicine approaches.

KEYWORDS: Neuroinflammation, Klotho, Oxidative stress, Pathophysiological Mechanisms, Challenges and Limitations.

1. INTRODUCTION

Neurological disorders are among the leading causes of disability and mortality worldwide. It represents a major global health challenge due to its increasing prevalence and limited treatment options. Neurological diseases are the leading cause of global disability and the second leading cause of death, affecting over 3.4 billion people (43% of the world population) in 2021. The prevalence is rising due to population aging and growth, with stroke, migraine, and dementia causing the highest burden.[1] They include both neurodegenerative diseases and inflammatory or autoimmune conditions affecting the central and peripheral nervous systems. Despite extensive research, effective disease-modifying therapies remain limited, largely due to the complex and multifactorial nature of these conditions.[2-3]

Klotho protein, initially identified as an anti-aging factor, is expressed in the brain and plays a critical role in neuronal survival, synaptic function, and cognitive performance. Recent studies suggest that klotho deficiency may contribute to the pathogenesis of several neurological disorders.[4-5]

Several studies have demonstrated a strong association between klotho levels and neurological health. In Alzheimer's disease, reduced klotho expression has been linked to increased amyloid-beta accumulation and cognitive decline. In Parkinson's disease, klotho appears to mitigate oxidative stress and mitochondrial dysfunction. Additionally, klotho has shown anti-inflammatory effects in multiple sclerosis and protective roles in ischemic stroke models.[6-7]

This review aims to summarize and analyze current research on the role of klotho in neurological diseases.

2. METHODOLOGY

A comprehensive literature search was conducted using Scopus, PubMed and Web of Science (Clarivate) databases. Keywords included 'Klotho protein', 'neurological diseases', 'Alzheimer's disease', and 'Parkinson's disease'. Studies published in English between 2010 and 2026 were included. Both review articles and original research studies were analyzed.

3. Global Epidemiology

In 2021, more than one-third of the world's population was affected by a neurological condition, with 3.4 billion people suffering from brain health problems. While age-standardized rates remained relatively stable, the absolute numbers increased significantly.[8] Deaths from neurological diseases rose by 39% over the past 30 years. Stroke is the leading cause of disability-adjusted life years (DALYs), followed by neonatal encephalopathy, migraine, and dementia 1. Studies have shown an increase in the incidence of Parkinson's disease and migraine (0.61% and 0.07% annually, respectively).[9]

Low- and middle-income countries bear nearly 80% of the global burden. Furthermore, as populations age, the prevalence of diseases, particularly neurodegenerative diseases, increases sharply with advancing age. The incidence of Parkinson's disease has increased from approximately 40 cases per 100,000 population (in the 40-49 age group) to over 1,900 cases per 100,000 population (in the over-80 age group).[10-11]

Gender disparities show that women often bear a greater burden, particularly with regard to migraine, multiple sclerosis, and Alzheimer's disease.[12] The increase in incidence is attributed to population growth, with over 64% of the increase in disability-adjusted life years (DALYs) and 35% to population aging.[13]

Among the regional highlights is the UAE, where the burden of age-related neurological diseases is increasing with rising life expectancy. In the North Africa and Middle East region, the prevalence of neurological disorders between 1990 and 2019 increased by 0.84%.[14-15]

Key risk factors for the prevalence of these diseases include high body mass index, high fasting blood glucose levels, and smoking. These are long-term trends.[16]

4. Etiology of Neurological Diseases

Neurological diseases result from structural, biochemical, or electrical malfunctions in the brain, spinal cord, or nerves, driven by genetic mutations, trauma, infections, autoimmune attacks, or degenerative processes. Common causes include neurodegeneration (Alzheimer's), injury (TBI), infection (meningitis), and lifestyle factors affecting vascular health (stroke).[17-18]

Key etiologies of neurological diseases include.[19-21]

Genetic Disorders: Inherited or de novo mutations cause conditions such as Huntington's disease, muscular dystrophy, and some epilepsies.

Neurodegenerative Diseases: Progressive neuron loss occurs in Parkinson's disease and Alzheimer's disease, often involving abnormal protein accumulation.

Trauma: Physical injury to the brain or spinal cord, such as falls or vehicle accidents, can cause lasting neurological damage.

Infections: Bacteria, viruses, fungi, or parasites can affect the nervous system, leading to meningitis, encephalitis, or infections like Lyme disease.

Autoimmune Disorders: The immune system mistakenly attacks neurons or myelin, causing conditions like Multiple Sclerosis (MS) or Guillain-Barré syndrome.

Environmental Factors & Lifestyle: Exposure to toxins, radiation, poor diet, lack of exercise, and chronic stress (e.g., alcohol use) contribute to conditions such as stroke.

Vascular Diseases: Disruptions in blood flow to the brain, such as strokes or aneurysms, are major causes of neurological morbidity.

Congenital Abnormalities: Developmental issues during fetal development, such as neural tube defects, can result in neurological disorders.

These conditions can be caused by a combination of factors, and sometimes the exact cause is unknown.

5. Major Neurological Disorders

5.1 Alzheimer's Disease (AD)[22]

- Most common cause of dementia
- Characterized by memory loss and cognitive decline
- Pathology: amyloid plaques and tau tangles

5.2 Parkinson's Disease (PD)[23]

- Movement disorder (tremor, rigidity)
- Loss of dopaminergic neurons in substantia nigra
- α-synuclein aggregation

5.3 Amyotrophic Lateral Sclerosis (ALS)[24]

- Progressive motor neuron degeneration
- Associated with TDP-43 pathology
- Leads to muscle weakness and paralysis

5.4 Multiple Sclerosis (MS)[25]

- Autoimmune demyelinating disease
- Involves inflammation and neurodegeneration
- Affects young adults predominantly

6. Pathophysiological Mechanisms

6.1 Protein Misfolding and Aggregation[26]

Protein aggregation is a hallmark of many neurodegenerative diseases.

- Amyloid-β and tau in Alzheimer's disease
- α-synuclein in Parkinson's disease
- TDP-43 in ALS and frontotemporal lobar degeneration (FTLD)

These misfolded proteins disrupt neuronal function, impair synaptic signaling, and trigger neurotoxicity.

6.2 Neuroinflammation[27-28]

Chronic activation of microglia and astrocytes leads to sustained release of pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6. This inflammatory environment contributes to neuronal damage and disease progression.

6.3 Oxidative Stress[28]

Reactive oxygen species (ROS) accumulation leads to.

- Lipid peroxidation
- DNA damage
- Mitochondrial dysfunction

Oxidative stress plays a critical role in diseases like Parkinson's and Alzheimer's.

6.4 Genetic and Epigenetic Factors[29]

Mutations in genes such as.

- APP, PSEN1/2 (Alzheimer's)
- SNCA, LRRK2 (Parkinson's)
- C9orf72, TARDBP (ALS)

Epigenetic modifications also influence disease susceptibility and progression.

7. Clinical Features for Neurological Diseases

Neurological diseases present with diverse, location-specific symptoms, frequently including chronic headaches, limb numbness/tingling, muscle weakness, gait disturbances, tremors, vertigo, visual changes, and cognitive deficits. Early detection is key, as conditions often manifest as subtle cognitive, behavioral, or motor changes.[19,30]

Common Clinical Features by Type[22-23,26]

Neurodegenerative (e.g., Alzheimer's, Parkinson's): Progressive memory loss, cognitive decline, resting tremors, muscle rigidity, and bradykinesia (slowed movement).

Autoimmune (e.g., Multiple Sclerosis): Visual disturbances, numbness, tingling, fatigue, and muscle weakness.

Cerebrovascular (e.g., Stroke): Sudden onset of facial weakness, speech difficulties, and unilateral limb weakness.

Paroxysmal Disorders (e.g., Epilepsy): Seizures, loss of consciousness, and sensory disturbances.

Peripheral Nerve Disorders: Localized pain, neuropathic burning, tingling, and numbness, often in a "stocking-glove" distribution.

Headache Disorders: Migraines (throbbing, light/sound sensitivity, nausea) or tension headaches (pressure, tightness).

Common Diagnostic Approaches[31-32]

Neurological disorders are often diagnosed through imaging (MRI/CT), Electromyography (EMG) for muscle/nerve function, electroencephalogram (EEG) for electrical brain activity, and lumbar puncture for CSF analysis.

8. Therapeutic Strategies

8.1 Pharmacological Treatments[33]

- Cholinesterase inhibitors (AD)
- Levodopa (PD)
- Immunomodulators (MS)

8.2 Targeting Neuroinflammation[34-35]

- Anti-inflammatory drugs
- Monoclonal antibodies

8.3 Antioxidant Therapy[36]

- Vitamin E, Coenzyme Q10
- Targeting mitochondrial dysfunction

8.4 Gene and Stem Cell Therapy[37]

- CRISPR-based gene editing
- Stem cell transplantation

8.5 Future Directions[38]

- Precision medicine
- Biomarker-guided therapy
- Early diagnosis using AI and omics technologies

9. Biomarkers Klotho Protein in Neurological Disorders

Klotho is an anti-aging protein with neuroprotective properties.

- Reduces oxidative stress
- Enhances synaptic plasticity
- Associated with improved cognitive function

Low Klotho levels have been linked to neurodegeneration.[39] klotho is a transmembrane protein primarily produced in the kidney and brain (specifically by choroid plexus, Purkinje cells, and hippocampal neurons) that acts as a potent anti-aging, antioxidant, and anti-inflammatory agent. Its soluble form circulates in the blood and cerebrospinal fluid (CSF), making it a valuable, albeit evolving, biomarker for diagnosing and determining the prognosis of various neurological disorders. Reduced levels are associated with cognitive decline, while higher levels are linked to neuroprotection.[40-41]

9.1 Key Neurological Associations

- **Alzheimer's Disease (AD) and Dementia:** Reduced levels of CSF Klotho are associated with increased cognitive decline and higher amyloid-β and tau protein burden. Klotho protects hippocampal

neurons from Amyloid-induced toxicity and glutamate damage.[42]

- **Parkinson's Disease (PD):** Studies have found that early-stage PD patients may have altered Klotho levels, with CSF levels showing an inverse association with -α-synuclein levels. Individuals with the haplotype (which reduces function) experience more aggressive PD phenotypes, including severe motor impairment and faster cognitive decline.[43]
- **Stroke and Vascular Cognitive Impairment:** Serum Klotho acts as an anti-aging and anti-inflammatory marker and its deficiency is correlated with vascular damage.[44]
- **Traumatic Brain Injury (TBI):** Elevated serum Klotho levels have been observed in TBI patients, potentially acting as an acute injury marker, with a high predictive value (ROC value 0.832) for assessing long-term prognosis.[43-44]
- **Neurodevelopmental Disorders:** Recent research suggests that lower Klotho levels may be a novel biomarker for ADHD.[42]

9.2 Potential as a Biomarker[45-46]

- **Diagnostic & Prognostic Value:** Klotho can act as a marker for assessing the severity of cognitive impairment and the progression of neurodegeneration.
- **Systemic Readout:** Blood-based Klotho acts as a systemic readout of oxidative stress and inflammation, providing insight into the neurodegenerative processes.
- **Therapeutic Target:** Increasing Klotho levels has been shown in models to enhance brain resilience and cognitive ability.

9.3 Current Research Challenges

Based on current research, here are the primary challenges regarding Klotho as a biomarker in neuropsychiatric disorders.[47-50]

- **Limited Data:** Studies on the diagnostic/prognostic efficacy of Klotho in neuropsychiatric disorders are still limited, with fewer large-scale studies. While the role of Klotho as an anti-aging and neuroprotective protein is established, studies validating its diagnostic and prognostic efficacy in human neuropsychiatric disorders (such as Alzheimer's, Parkinson's, and Depression) are relatively limited. Most existing evidence relies on small-scale studies or animal models, requiring larger, longitudinal human cohorts to establish definitive clinical utility.
- **Measurement Variability and Standardization:** Standardizing measurement protocols remains a critical challenge. There are discrepancies in how Klotho is measured in different fluids, specifically serum versus cerebrospinal fluid (CSF). While serum is easier to collect, CSF may better reflect CNS changes, and there is a need for standardized, high-sensitivity assays to ensure consistency across studies.
- **Complex Human Pathophysiology:** Unlike animal models where Klotho depletion produces consistent, predictable results, human studies face confounding factors, including age, comorbidities, and genetic variants (e.g., genotype), which affect Klotho levels and make clear diagnostic thresholds difficult to establish.
- **Contradictory Findings in Neuropsychiatric Subtypes:** While many neurodegenerative disorders show decreased Klotho levels, some studies suggest that Klotho levels may vary or even be higher in specific conditions (e.g., certain stages of schizophrenia) compared to others like Alzheimer's or depression, adding complexity to its role as a universal biomarker.

10. Research trends 2026

Future efforts are focusing on defining standard thresholds for "normal" versus "pathological" serum Klotho and investigating its role in neuroplasticity and cognitive function to transition from academic research to clinical application.[51]

11. Emerging Technologies

Emerging technologies are revolutionizing the diagnosis, treatment, and rehabilitation of neurological diseases (e.g., Alzheimer's, Parkinson's, stroke, ALS), transforming management from reactive care to proactive, personalized interventions. Key advancements include AI-powered diagnostics, wearable monitoring, brain-computer interfaces (BCIs), and neurostimulation.[52]

11.1 Artificial Intelligence (AI) and Machine Learning (ML)[53]

AI algorithms analyze complex, massive datasets to detect subtle patterns in neuroimaging and patient history, enabling earlier and more accurate diagnosis.

Early Detection & Imaging: AI tools (e.g., convolutional neural networks) can identify early signs of Alzheimer's years before symptoms appear. Advanced MRI and CT analysis can detect subtle brain abnormalities, such as ischemic strokes in real time.

Parkinson's Disease.[54]: ML algorithms analyze voice, gait, and handwriting to determine disease severity.

Treatment Planning: AI helps optimize parameters for Deep Brain Stimulation (DBS) in Parkinson's, enhancing effectiveness.

Predictive Analytics: AI calculates potential disease progression, helping providers create tailored treatment strategies.

11.2 Brain-Computer Interfaces (BCIs) and Neural Interfaces[55-56]

BCIs bypass damaged nerve pathways to allow direct communication between the brain and external devices.

Motor Restoration: BCIs enable paralyzed patients to control robotic limbs, exoskeletons, or computer cursors through thought, aiding in motor recovery.
Speech and Communication: BCI systems are being developed to convert neural signals into text or speech for patients with speech impairments or locked-in syndrome.
Closed-Loop Systems: Next-generation BCIs are bidirectional, reading brain signals and providing sensory feedback simultaneously, enhancing neuroplasticity.
Emerging Players: Companies like Neuralink and Synchron are advancing implantable BCI technology for human trials.

11.3 Neurostimulation and Neuromodulation[56-57]

Non-invasive and minimally invasive techniques modulate neural activity to treat functional impairments.
Transcranial Magnetic Stimulation (TMS): Uses magnetic fields to stimulate the cortex, approved for depression and migraine treatment, and widely researched for stroke rehabilitation.
Focused Ultrasound (FUS): A non-invasive technique that can target deep brain structures to ablate tissue (for tremor-dominant Parkinson's) or temporarily open the blood-brain barrier for localized drug delivery.
Deep Brain Stimulation (DBS): An invasive, well-established treatment involving implanted electrodes that is increasingly becoming "adaptive" (closed-loop), sensing brain activity in real time and adjusting stimulation.

11.4 Wearable Sensors and Remote Monitoring[58-59]

Wearables provide continuous, real-time data to monitor symptoms and track rehabilitation outside clinical settings.
Movement Disorders: Smartwatches and biosensors track tremor frequency, gait, and Bradykinesia in Parkinson's disease.
Epilepsy Monitoring: Wearable devices can detect seizures and alert caregivers.
Rehabilitation Tracking: Wearable sensors allow for home-based exercise monitoring by therapists, ensuring continuity of care.

11.5 Robotics and Virtual Reality (VR)[60-62]

These technologies promote neuroplasticity through high-intensity, repetitive, task-specific training.
Exoskeletons: Robotic suits (e.g., Lokomat, HAL) assist patients with severe lower limb impairments in walking, facilitating rehabilitation in stroke and spinal cord injury (SCI).
VR/AR Rehabilitation: Immersive, engaging virtual environments are used to improve motor skills, balance, and cognitive function, making therapy more motivating than traditional methods.

11.6 Challenges and Future Directions[63-64]

Despite the potential, several challenges hinder widespread adoption.
Access and Cost: Many of these technologies are expensive and not widely available.
Technical Limitations: Need for improved battery life, device portability, and better long-term signal stability for implants.
Ethics and Privacy: Data security and the ethical implications of modulating brain activity with AI.
Regulation: The need for standardized clinical protocols for these novel therapies.
Future research aims to integrate these technologies into "closed-loop" systems that can read, write, and modify brain signals in real time to fully optimize neurological recovery.

12. Challenges and Limitations

Neurological diseases—including Alzheimer's, Parkinson's, stroke, and epilepsy—are the leading cause of disability-adjusted life years (DALYs) and the second leading cause of death worldwide. These conditions present profound challenges due to the complexity of the human brain, limitations in medical technology, and significant gaps in healthcare access, particularly in low- and middle-income countries (LMICs).[65]
Here are the key challenges and limitations for neurological diseases.

12.1 Scientific and Diagnostic Limitations[66]

Irreversible Damage & Non-Regenerative Neurons: Many neurological diseases are neurodegenerative, meaning they involve the loss of neurons that cannot regenerate, making cures difficult.
Delayed Diagnosis: Conditions are often diagnosed only when nerve damage is severe, missing the optimal time for intervention.
Lack of Biomarkers: A critical shortage of validated, predictive biomarkers makes it difficult to detect early-stage diseases or track progression, complicating the development of new drugs.
Blood-Brain Barrier (BBB): This protective barrier makes delivering therapeutic drugs to the brain highly challenging, reducing the efficacy of many treatments.
Inaccessibility of the Brain: The physical inaccessibility of the brain limits the use of traditional diagnostic methods like biopsies.

12.2 Treatment and Research Challenges[67]

High Clinical Trial Failure Rates: Neuroscience clinical trials have high failure rates, often due to poor understanding of disease mechanisms, high variability in patient populations, and inadequate preclinical models.
Slow Drug Development: The R&D process for new neurological drugs is long, complex, and costly, leading to fewer new treatments compared to other fields.
Unpredictable Outcomes: Many diseases, such as Multiple Sclerosis (MS) or Parkinson's, have unpredictable courses, making it difficult to set clear rehabilitation goals.

12.3 Healthcare Access and System Limitations[68]

Shortage of Specialists: There is a severe shortage of neurologists, particularly in LMICs, where the ratio can be less than 0.1 per 100,000 population.

Treatment Gap: Over 80% of neurological deaths occur in LMICs. In some regions, up to 90% of people with epilepsy are inadequately treated.

Cost of Care: The high cost of diagnostics (MRI, CT scans) and long-term treatment is a major barrier for patients, especially in regions with limited health insurance.

12.4 Socioeconomic and Caregiver Burden[69]

Stigmatization and Discrimination: Many patients face social stigma, discrimination in the workplace, and human rights violations.

Caregiver Burden: Chronic neurological diseases require long-term care, often leading to severe financial, physical, and psychological distress for caregivers, who are frequently family members.

Impact on Daily Life: Symptoms like memory loss, cognitive impairment, and physical disability significantly lower the quality of life, leading to social isolation.

12.5 Emerging Challenges[65]

Aging Population: As life expectancy increases, the prevalence of age-related neurological disorders, such as Alzheimer's and other dementias, is increasing rapidly, putting immense pressure on health systems.

Long-Term COVID-19 Impact: Recent data shows significant neurological symptoms, such as cognitive issues and Guillain-Barre Syndrome, associated with COVID-19, adding to the global burden.

Addressing these challenges requires a "big science" approach with international cooperation, increased funding for research, improved infrastructure for diagnostics and rehabilitation, and stronger public health strategies for prevention 1.

13. DISCUSSION

Overall, the reviewed studies support the neuroprotective role of klotho protein. However, variations in study design, sample size, and measurement techniques have resulted in inconsistent findings. While experimental data are promising, clinical evidence remains limited.

Most available studies are preclinical or observational, with a lack of large-scale clinical trials. Future research should focus on standardized measurement of klotho levels and its potential as a biomarker or therapeutic agent.

14. CONCLUSION

Neurological disorders are complex diseases driven by multiple interacting mechanisms, including protein aggregation, inflammation, and oxidative stress. Klotho protein plays a significant role in neurological health and disease. Its neuroprotective properties suggest potential therapeutic applications, promising tools for early diagnosis and disease monitoring; however, further clinical studies are required to validate its effectiveness in neurological disease management.

Future therapeutic approaches focusing on personalized medicine and molecular targeting may significantly improve patient outcomes.

15. ACKNOWLEDGMENTS

The authors extend their thanks to the administration of Department of Chemistry, College of Science, University of Mosul for facilitating the completion of the research.

16. OTHER INFORMATION

Source of financing: None.

Conflicts of interest: None.

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