Diagnosis of Neurodegenerative Diseases (Arthritis) towards Adequate Treatment in Nanomedicine

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Abstract

Medical Laboratory Science is an autonomous profession that entails the examination of human, animal, and environmental samples for accurate diagnosis and illness treatment that is efficient and effective. has been overlooked in neurodegenerative illnesses in the past (NDDs). NDDs are progressive neurodegenerative illnesses that primarily affect the central nervous system, particularly the neurons of the brain. NDDs are most often represented by asynucleinopathies, Huntington's disease (HD), amyloidoses, Alzheimer's disease (AD), tauopathies, Parkinson's disease, amyotrophic lateral sclerosis (ALS), prion disease, and TDP-43 proteinopathies. Currently, cerebrospinal fluid (CSF) and blood are the most common diagnostic samples for neurodegenerative diseases (NDDs) based on the related biomarkers and nanoparticles. Although different forms of diagnosis and symptoms are utilised to diagnose NDDs, each NDD has a unique and particular Medical Laboratory diagnostic that is used to identify the many neurodegenerative diseases of public health significance. An efficient use of Medical Laboratory diagnostics in Nanomedicine for neurodegenerative illnesses would be a significant advancement in the field.

Keywords: Medical Laboratory diagnosis, Neurodegenerative diseases, NDDs, Nanomedicine

Introduction

Neurons are the brain cell type, and in most cases they cannot multiply or replace themselves. Neurodegenerative diseases (NDDs) are chronic conditions that deteriorate nerve cells in the brain and spinal cord over time (primarily neurons in the brain). The incidence rises as people become older. The most prevalent of them include a-synucleinopathies, HD, amyloidoses, AD, tauopathies, PD, ALS, prion disease, and TDP-43 proteinopathies. The illnesses, which are fatal and cause cognitive decline and dyskinesia, are defined by the slow and progressive death and

loss of particularly susceptible groups of neurons. **[1,2,4,5]**. The most common classification of the diseases based on their clinical manifestations are cognitive or behavioral disorders and extrapyramidal and pyramidal movement disorders. While some affected individuals have what could be termed "pure syndromes", majority have combined clinical features **[2]**. They are mainly caused by genetic mutations. Other causes may include apoptosis, protein misfolding, mitochondrial dysfunction, DNA damage, and necrosis. Neurodegeneration may be brought on by a number of different things, including genetic mutations, the accumulation of harmful proteins in the brain, and the creation of neurotoxic chemicals brought on by the loss of mitochondrial activities.**[5]**. There may be more than one neurodegenerative disease process in one person and the protein misfoldings and pathophysiological processes that characterize NDDs may be present long time prior to the appearance of clinical features **[2,3]**. The progressive death and loss of neurons cause problems with ataxias and dementias. Early diagnosis is particularly important for timely intervention and treatment **[4]**.

Neurodegenerative diseases provides evidence of neuronal loss of structures or neuronal death as seen in Alzehemer's disease (figure 1) and figure 2 due to tangles of neurones.

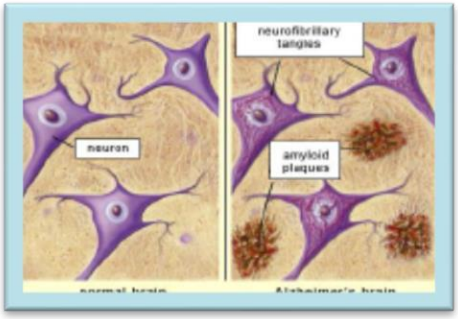

Figure 1. Neurodegenerative (Alzheimer's) disease when compared with normal neurones

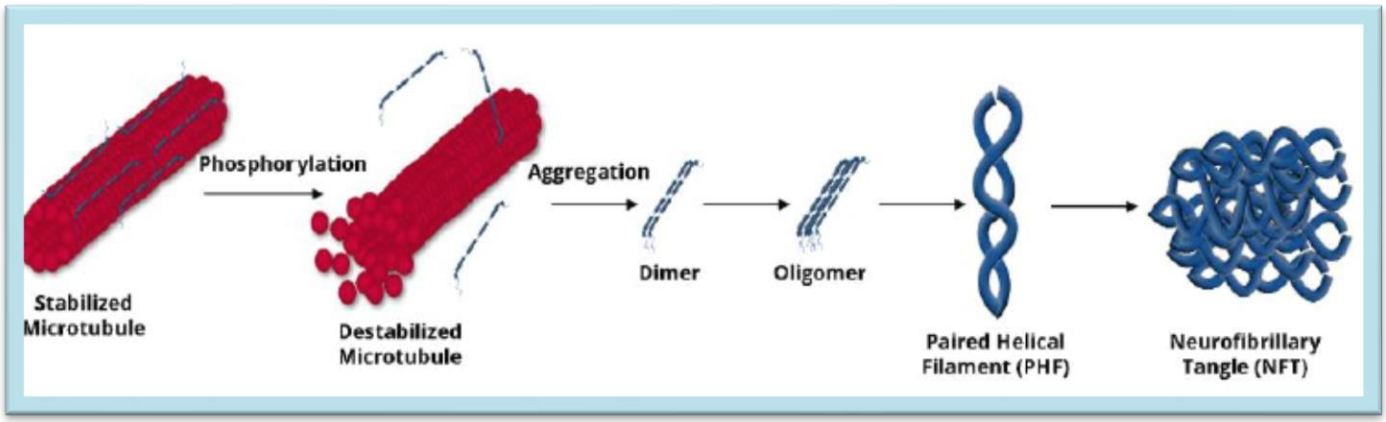

Figure 2. Stages of Neuronal Disease Development

Medical Laboratory Testing and Diagnostics contribute immensely to the clinical and medical cases available towards detection of diseases and monitoring of treatments. Studies have shown that medical laboratories contributes up to 70% of decisions taken on any clinical case. It also contributes up to 7o% of the income generated to any healthcare establishment **[6,7]**. Though, medical laboratory science may differ in nomenclature in various countries [8], their services remain same across the globe.

The contribution of medical laboratory science in disease management and treatment gives impetus to this chapter to provide a literature towards contribution of medical laboratory in the diagnosis and treatment of neurodegenerative diseases in general medical practice including nanomedicine.

This chapter provides a short review, summary, and discussion of ND disorders and their laboratory diagnostics for successful treatment in nanotechnology-based nanomedicine. Nanobiotechnology is a contemporary scientific discipline that has the potential to enhance medical practise and may play a significant role in the study and treatment of neurodegenerative disorders (NDDs). It may be used in neurodegenerative disease diagnosis, medicine delivery, and treatment.**[1,9]**.

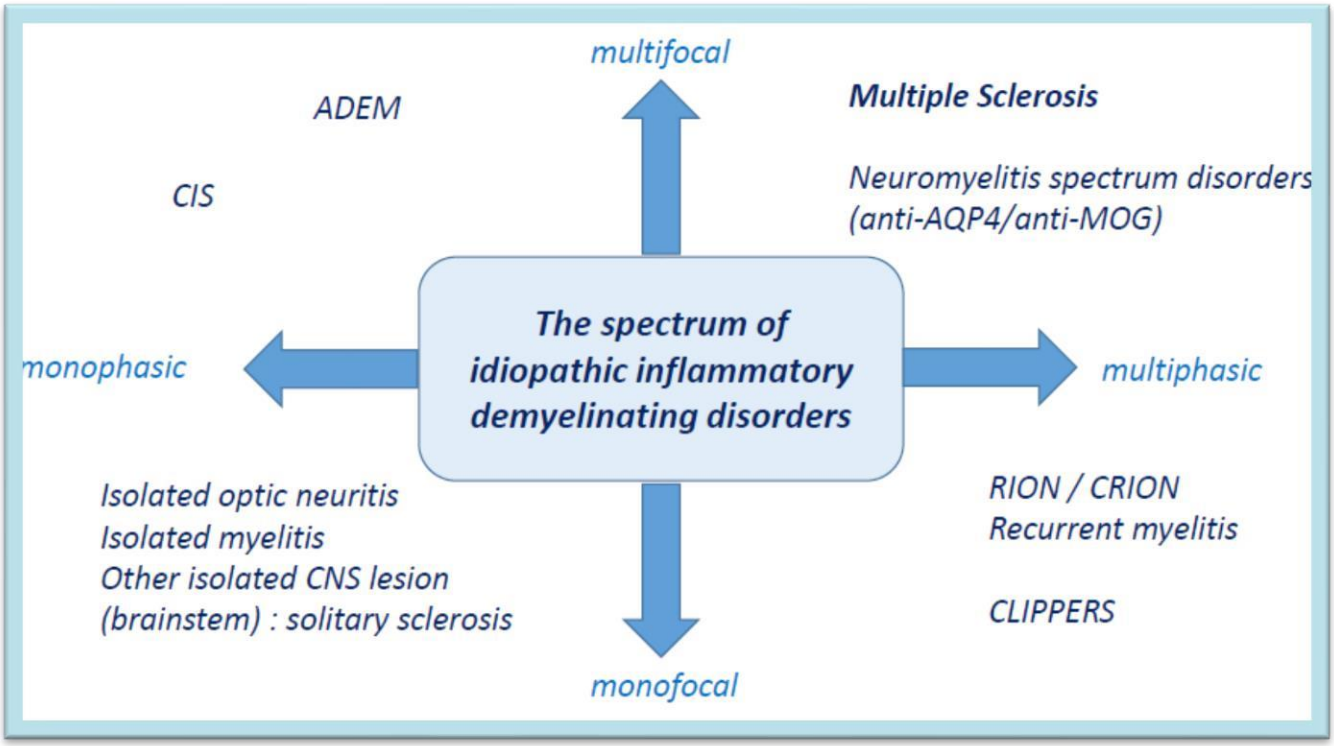

Figure 3. Nueroinflammatory or Neurodegenerative Disorders

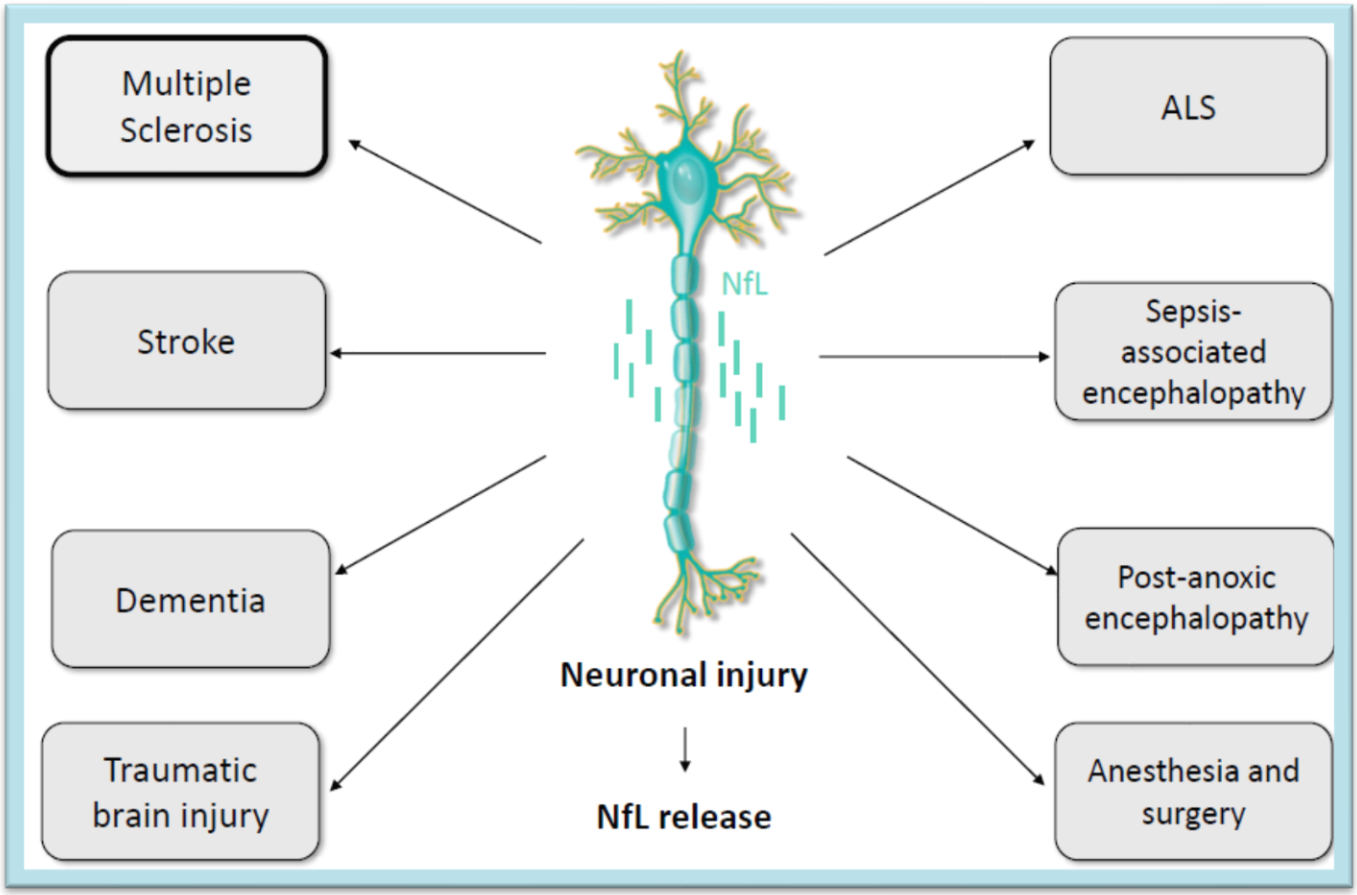

Figure 4. various Neuronal damages leading to Neurofilament release with various biomarkers

Medical Diagnosis of NDDs-neurodegenerative diseases

There has been detailed information gathered from successful thorough examination of neurodegenerative disease (NDDs) especially in histology, there are still limitations on the early diagnoses and treatment of the NDDs from routine medical laboratory perspective. This is attributable to the fact that majority of drugs and agents that effectively treat the disorders cannot pass through the blood–brain barrier (BBB) **[1,9]**.

Autopsy and examination of neuropathologic findings after a patient's death have remained the gold standard for diagnosing neurodegenerative illness at this time. There is a paucity of information on the available diagnostic biomarkers for the illnesses, except in rare instances when a genetic mutation is established to be the cause of the disease. **[2,10]**. There is a significant societal cost associated with diagnosing and treating NDDs; as a result, advances in the medical laboratory are desperately needed. To a large extent, a differential diagnosis of NDDs is based on observation of clinical symptoms. However, neurodegenerative illnesses

cannot be diagnosed just by clinical physical examination. Hence, economical, specific, and sensitive biomarkers are recommended **[4]** and this chapter shall provide an insight.

Diagnosis of NDDs may involve stepwise processes (Figure 5) like taking the patient's medical history, neuropsy testing, neuroimaging techniques, and estimation of blood and/or CSF biomarkers (CSF Aβ42, CSF Tau,) **[11]**.

Figure 5. Steps for Clinical use of Neurofilaments in Neurological disease management

Biomarkers of Neurodegenerative Diseases

Biomarkers are "biological molecules found in blood and other body fluids or tissues that indicate sign of normal or abnormal process in normal or diseased conditions". A biomarker can be referred to as nanomolecule or nanoparticle and has helped in detecting how the normal or diseased body responds to various normal or disease conditions [12].

Nanoparticles with sizes of about 1–100 nm can provide innovative approach towards solving issues associated with ND diseases. The small sizes of nanoparticles make them able to cross the BBB and can interact with biological and biochemical systems at cellular levels. Thus, their biochemical and physical properties can be exploited for diagnosis, therapy, tissue regeneration, and drug administration **[1]**.

Biomarkers are used in nanomedicine and general medical practice for diseases management and not an exception in neurodegenerative diseases. Such biomarkers are mostly used in Medical Laboratory Science, imaging technologies and advanced medical and diagnostic techniques. The biomarkers has a relation with proteinopathies /proteopathies especially when it involves neurodegenerative diseases [13,14] no wonder the biomarkers of neurodegenerative diseases are mostly proteins (figure 6). The tables 1 & 2 presents biomarkers based on sample or types of neurodegenerative diseases involved.

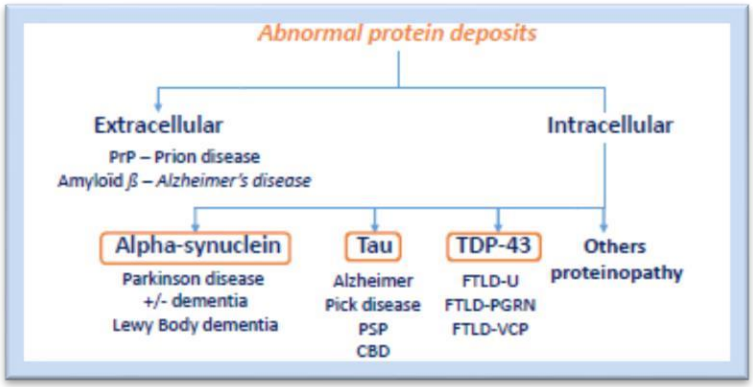

Figure 6. Some Abnormal proteins involved in NDDs

For successful treatment, the therapeutic process has to be initiated at the point between the asymptomatic and mildly symptomatic stages of the disease. However, clinical diagnosis does not give accurate results at these stages. The early detection of the onset of neurodegenerative disease is very vital. This is because, it gives an opportunity for early treatment which could be helpful to prevent the progression of the neurodegenerative disease in question **[10,12]**. There have been concerted efforts by different research groups to develop criteria that define the diseases at prodromal or preclinical stages, using biomarkers that characterize features of pathophysiological changes **[3]**.

Fluid biomarkers may be very useful to detect patients who are in the course of the disease already among those at risk for developing neurodegenerative disorders.

The biomarkers in blood that could be estimated/analysed to diagnose NDDs include Aβ Peptides, T-Tau, P-Tau181, P-tau Alternative Isoforms, and Nfl [3]. Biomarkers in cerebrospinal fluid and/or blood (figure 7) and imaging techniques are useful in diagnosis of NDDs, especially in early and differential diagnosis to choose the right treatment [4]. Biomarkers can be determined or measured using some advanced imaging techniques like magnetic resonance imaging (MRI), positron emission tomography (PET), and nuclear magnetic resonance spectroscopy (NMRS) [6].

Table 1.Some Biomarkers in Medical Laboratory Samples

SN	Samples	Biomarkers
1	**Blood**	Aß, Tau, NFl, GPAP, SNAP-25, Neurogranin
2	**CSF**	Tau, Aß-42

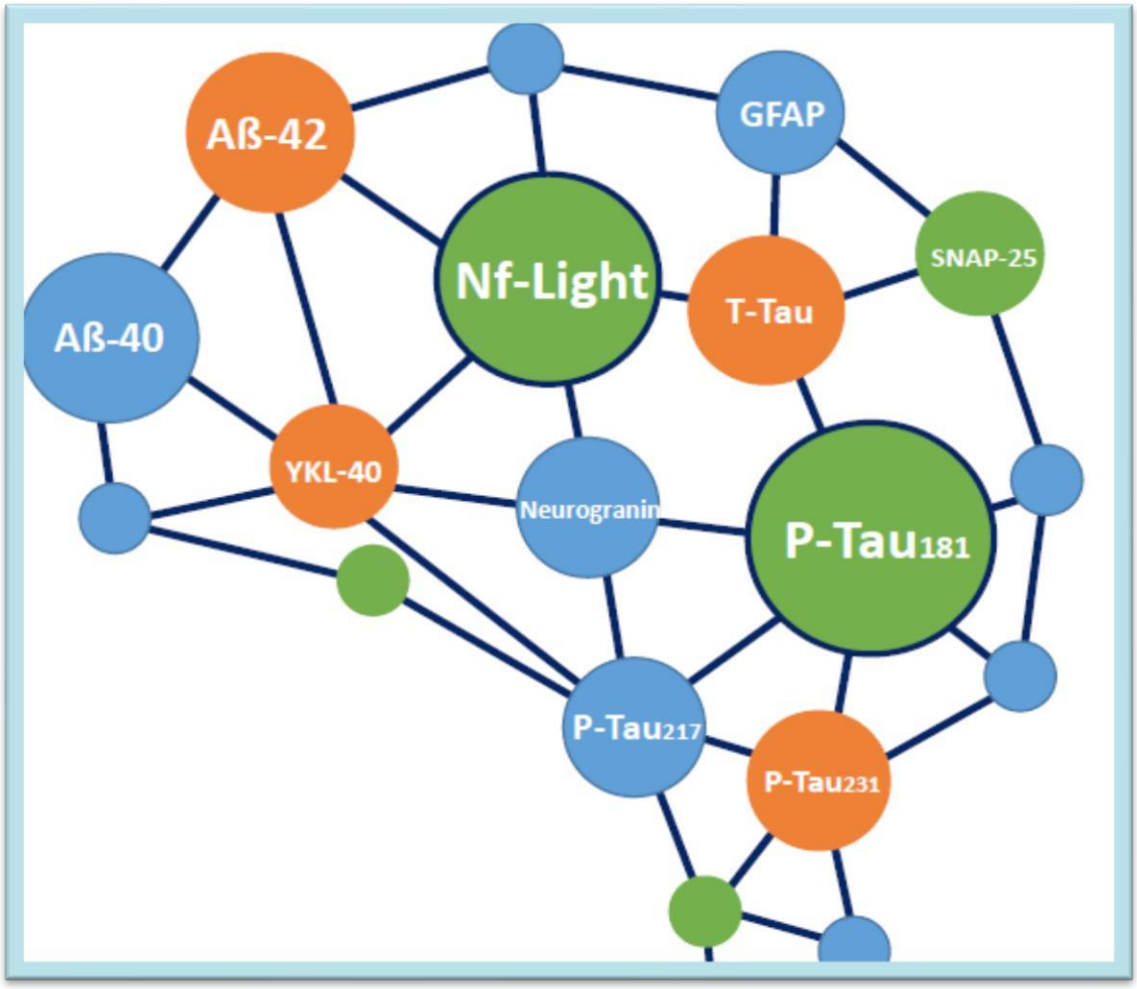

Figure 7 Biomarkers found in blood for diagnosis of NDDs

Medical Laboratory Diagnosis of NDDs

Clinical course, diagnosis, disease progression monitoring, and patient recruitment for targeted therapy [14] all require the validation and use of large panels of biomarkers that reflect specific pathophysiological mechanisms such as synaptic dysfunction, accumulation of misfolded proteins, neuroinflammation, neuronal injury, genetic expression and regulation. Current Alzheimer's disease-specific pathophysiological biomarkers for neurodegenerative illnesses are costly to acquire and/or entail intrusive sampling of bodily fluids, making them unsuitable for application in broad populations. The ideal screening tests would have a high NPV, low false-positive rates, and be simple to apply. If you need a sample that fits these requirements, blood is your best bet. Nonetheless, other types of samples, such olfactory mucosa, retina, and saliva, are currently being tested for their usefulness. Protein misfolding cyclic amplification (PMCA) tests and cerebrospinal fluid (CSF) biomarkers may also be used to characterise NDDs.**[3]**.

Protein misfolding amplification assays are among the most accurate diagnostic tests for prion diseases. They play a significant role in the in vivo analysis of protein accumulation abnormalities and misfolding. They are essential in NDDs due to their ability to identify and quantify misfolded proteins, as well as to perform amplification tests. The RT-QuIC and the PMCA are the two most important tests created so far. They are useful for detecting low levels of misfolded proteins because, in theory, these proteins will cause the nearby unfolded proteins to also misfold.**[3]**.

Both techniques involve fragmentation step, detection and quantitation of the misfolded proteins [14].

Utilizing mechanical shaking, RT-QuIC detects and quantifies misfolded proteins in real time by using a fluorescent dye that generates a signal upon interacting with fibrils. Misfolded proteins increase the signal's strength.**[3]**.

In PMCA, the fragmentation is done by a sonication process. Quantification of the misfolded proteins is not done in real-time during the reaction. Rather, it occurs after the amplification phase. Conventional immunoassays such as Western blotting are coupled to PMCA reaction process to enhance the quantification of misfolded proteins **[3]**.

The medical laboratory diagnosis of neurodegenerative diseases has grown from manual / ELISA (figure 8) to automation (figure 9) and to advanced techniques such as fully automated systems as the case of SIMOA Technology (figure 10)

Figure 8. Manual / ELISA methods of NDDs Biomarkers Testing

Figure 9. Automations in NDDs Biomarker Assays

Figure 10. Digital neurodegenerative Disease Biomarker Assay using SIMOA Technology

The methodologies and Procedures employed are based on the neurodegenerative diseases of interest or the diagnostic method adopted which maybe manual, semi-automated or fully automated. The methodology also has to follow the manufacturers' instructions and procedures Basically, Recombinant protein is incubated with the biological sample containing the misfolded protein to be quantified for a given time duration at a specific temperature. This

promotes further misfolding of recombinant protein and the elongation of the fibrils (nucleation).

In most cases, the sample undergoes a sonication (PMCA) or shaking (RT-QuIC) to promote fragmentation of the fibrils and amplification of the protein species, thereby promoting further misfolding and amplification.

The incubation-sonication/shaking cycles are repeated several times, enabling the amplification of small amounts of misfolded proteins **[3]**.

Discussion on Medical Laboratory Diagnosis of Specific NDDs Alzheimer's Disease (AD)

Alzheimer's disease is the most common NDD, responsible for 60-70 percent of dementia cases. It is characterised by the presence of protein tangles (tau) within neurons and the presence of the protein fragment -amyloid (plaques) outside neurons in the brain. Simply put, death results from the destruction of neurons necessary for basic somatic processes like walking and swallowing. Patients must be identified and treated for the illness in the preclinical stage if they are to experience any relief from the symptoms.

To diagnose Alzheimer's disease effectively, it is necessary to observe signs/symptoms of AD with at least one biomarker. The core biomarkers include Aβ42, t-tau and p-tau18.

The National Institute of Aging-Alzheimer's Association (NIA-AA) proposed the "A/T/N" framework that categorizes AD biomarkers into three according to 3 brain pathological changes associated with AD [5].

"A" is Aβ42 in the cerebrospinal fluid (CSF) and other biomarkers that can represent βamyloid.

"**T"** represents p-tau in CSF. p-tau181 reflects the level of neurodegeneration and the decrease in cognitive ability. The specificity of p-tau increases with the progression of AD.

"N" represents neurodegeneration **[4]**.

If you want an accurate diagnosis of Alzheimer's disease, nothing beats neuropathology analysis performed on a deceased patient (AD). Evaluating using magnetic resonance (MR) or computed tomography (CT) imaging is helpful, and positron emission tomography (PET) combined with single-photon emission computed tomography (CT) aids in the differential diagnosis of AD from other dementias. Cerebrospinal fluid (CSF) samples are often employed in clinical labs for biomarker detection. The levels of cortisol, pancreatic polypeptide, 2 microglobulin, insulin-like growth factor binding protein 2, and vascular cell adhesion molecule 1 are elevated in the plasma. CD40, carcinoembryonic antigen, matrix metalloprotein 2, macrophage inflammatory protein 1, superoxide dismutase, and homocysteine are increased,

whereas apolipoprotein E, epidermal growth factor receptor, haemoglobin, calcium, zinc, interleukin 17, and albumin are all reduced. Using this plasma biomarker panel, we found that we could successfully distinguish between AD patients and cognitively healthy controls.**[15]**.
Some of the most common causes of Alzheimer's disease are mutations in genes that produce proteins like presenilin 1 (PSEN1), presenilin 2 (PSEN2), and amyloid precursor protein (APP) (APP). Cerebrospinal fluid (CSF) may be used to diagnose Alzheimer's disease (AD) due to the accumulation of amyloid- (A) as senile plaques and the aggregation of hyperphosphorylated tau-mediated neurofibrillary tangles (NFTs) in the brain.[14, 15].

Prion Disease

Transmissible spongiform encephalopathies is another name for prion disease (TSEs). Conformational alterations in cellular prion proteins (PrPc) lead to the accumulation of pathogenic prion proteins (PrPsc), which are responsible for the disease. Creutzfeldt-Jakob disease (CJD), kuru, fatal familial insomnia, Gerstmann-Sträussler-Scheinker disease, and variably protease-sensitive prionopathy are all examples of human illnesses. The most prevalent prion disease is Creutzfeldt-Jakob Disease (CJD), with 0.85% of all CJD cases being caused by sporadic instances.
Proteins 14-3-3, tau, NSE (Neuron-specific enolase), and S100B are all indicators for prion disease.
It has been discovered that 14-3-3, an acidic soluble protein with extensive evolutionary conservation, is present in a broad range of eukaryotic cells. Neuronal injury, prion disease, and other neurological illnesses may be indicated by its detection at elevated levels in cerebrospinal fluid. Patients with Creutzfeldt-Jakob disease also have an abnormally high concentration of the protein tau in their cerebrospinal fluid (CSF) [14].
For example, NSE is an enolase that helps in the glycolytic process. The brain is where it is most active. Neurodegenerative diseases are triggered by abnormal NSE, which is seen in the cerebrospinal fluid (CSF) of Creutzfeldt-Jakob disease (CJD) patients.
A higher concentration of S100B, a protein found in astrocytes, is associated with an uptick in astrocyte activity.
It's possible that a more precise and accurate diagnosis might be made by combining test findings from several biomarkers. Protein 14-3-3 and protein tau in CJD patients might have a specificity and sensitivity of 96% and 84%, respectively; at a low p-tau (phosphorylated tau)/t-tau (total protein tau) ratio, the combined 14-3-3 test has a specificity and sensitivity of 96%

and 79%, respectively. These tests are now the gold standard for diagnosing CJD. They have not yet been implemented outside of the lab.**[4].**

Electroencephalography (EEG), computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) are all used to diagnose prion disease because of the damage they may detect to nerves and eyes. Cerebrospinal fluid (CSF) has been primarily obtained by spinal taps for medical study for quite some time. The increased levels of 14-3-3 protein, S-100, and neuronal-specific enolase (NSE) in the cerebrospinal fluid (CSF) are encouraging. The disease-causing PrP isoform may be measured by utilising a technique called conformation-dependent immunoassay (CDI), which examines both the protease-resistant and protease-sensitive forms of PrPSc . **[ ]**.

Table 2. Biomarkers Present in some NDDs

SN	NDDs	Biomarkers
1	Alzheimer's disease	Aß, Tau, APP, GASR1ά, PSEN1
2	Amyotrophic lateral sclerosis	Neurofilament
3	Frontotemporal dementia	Tau
4	Huntington's disease	Huntington
5	Parkinson's disease	ά-synaclein
6	Prick's disease	Tau
7	Prion disease	PrP, TSE

Parkinson's Disease (PD)

The worldwide incidence rate for PD is around 3.0 x 10-3, making it the second most frequent NDD. Muscular stiffness, rest tremor, and bradykinesia are typical clinical manifestations. Over 80-year-olds have a higher incidence rate. Dopaminergic neuron loss in the substantia nigra pars compacta (SNpc) at an early stage and aberrant accumulations of synuclein protein, known as Lewy bodies and Lewy neurites, are the predominant clinical characteristics.

At present, PD does not have specific CSF or other laboratory tests to detect it. However, some biomarkers in blood and CSF are potential markers for early detection and differential diagnosis of PD. These include DJ-1, αsynuclein, glial fibrillary acidic protein (GFAP) and coenzyme Q10. However, their specificity and sensitivity are not reliable [14].

When it comes to diagnosing PD, imaging biomarkers fare the best. Dopamine transporter single-photon emission computed tomography scans (DAT SPECT), magnetic resonance imaging, transcranial sonography, and fluorodopa positron emission tomography are all examples (F-DOPA PET). Dopamine depletion in the nigro-striatum may be shown on DAT SPECT. Regular use of magnetic resonance imaging (MRI) in the diagnosis of PD is now the gold standard for ruling out any confounding factors.**[4]**.

Molecular diagnostics also provide a powerful method to detect and diagnose various neurological diseases.

Using a variety of neuroimaging modalities may improve the accuracy of diagnosing complex NDDs. Imaging techniques such as positron emission tomography (PET), positron emission tomography (SPECT), magnetic resonance imaging (MRI), and computed tomography (CT) scans all belong (CT). Brain physiology and biochemistry may be studied using several magnetic resonance techniques, such as perfusion SPECT and MRI, magnetization transfer MRI, 1H and 31P magnetic resonance spectroscopy (MRS), and magnetic resonance spectroscopic imaging (MRSI). These techniques might be used to learn how certain brain processes contribute to the onset of disease. **[12, 16]**.

Human, cell, and animal model studies have shown that the nanotheranostics method offers revolutionary promise for treating a variety of neurodegenerative illnesses.**[5]**.

Through the use of designed materials and technologies that interact with biological systems on a molecular level to trigger, respond to, and intermix with target locations to promote biological responses while decreasing side effects, nanotechnology may be employed in the medical industry to better control NDDs. The BBB poses a significant challenge to the delivery of pharmaceuticals for the diagnosis, targeting, and treatment of NDDs [5]. Drugs administered through these ways often fail to treat NDDs because they are unable to cross the BBB.

The translational usefulness and safety of nanotheranostic techniques is a major worry, despite the fact that research is assuring their evolution from animal to human models. This need an in-depth knowledge of how various bodily systems interact with nanomaterials. For both the diagnosis and therapy of these NDDs, numerous nanobioactive substances derived from plants have been found to be useful**[5]**.

Computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and single-photon emission tomography (SPECT) have all proven useful in diagnosing Parkinson's disease, but pinpointing the precise alterations has proven more difficult. Microscopical postmortem research in the medical laboratory or pathology have uncovered a characteristic of cell death linked to Parkinson's disease: the presence of widespread Lewy bodies. Having Lewy-type -synucleinopathy in the submandibular glands is indicative of Parkinson's disease at autopsy. **[14, 16]**.

Nano-Medicine and Medical Laboratory Diagnostics of NDDs

Nanotheranostics is the practise of injecting nanoparticles (NPs) for diagnostic purposes via different drug particles. Once the medicine has reached its destination, the outer coating will begin to break down, allowing the active ingredients to seep out. This helps narrow down the potential causes of the disease to certain substances or neurons. It's tailored specifically to each patient's illness and needs, and it ultimately helps the field as a whole to advance (personalized medicine).

Confirmation of the diagnosis helps with early detection and medical counselling, which directs individual patients toward therapy. Because of this, we can learn more about the causes of NDDs and how to treat them. **[5, 8, 12,17]**.

Improvements in nanomedicine may help treat diseases for which there are now few treatment options thanks to recent findings in polymer science and cell-based delivery methods. The development of effective and safe therapeutic and diagnostic methods is hampered by the difficulty of low molecular weight chemicals and biomacromolecules (such as imaging contrast agents, medicines, nucleic acids, and proteins) accessing the brain [12]. Since exosomes may traverse the BBB unhindered, they are also being exploited as nanobiomaterials for therapies and medication delivery in neurodegenerative disorders.**[2]**.

Conclusion

There is a general growth in the medical laboratory testing for NDDs using various samples and techniques for detecting the biomarkers. Automation in neurochemistry allows for better

standardization and faster Turn-Around-Time for more accessible biomarkers in the diagnosis of NDDs. Blood-based biomarkers provides easier and cheaper tool for the diagnosis, treatment and follow-up of different neurological disorders. However, there are still some limitations which makes the CSF OCB detection to remain the gold-standard in NDDs in addition to autopsy because of the detection of intrathecal IgG synthesis in neuroinflammatory disorders. Application of nanotechnology in medicine is a promising field in the diagnosis using various samples and nano-compliant products and management of neurodegenerative diseases with the aid of nano-medicine of which medical laboratory component shall not be ignored.

The practices involving nanaoparticles works efficiently under automated medical laboratory facilities which are currently lacking in very low income / developing countries. Such facilities needs to be established in poor countries for optimum usage especially in the nanodiagnosis of NDDs and for better practices for quality public health medical laboratory services.

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