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Contemporary techniques to the laboratory diagnosis of cognitive dysfunction (Dementia) in elderly patients.

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Abstract

Dementia is a serious condition affecting more than 55 million people worldwide. In elderly patients, it leads to an overall decline in memory and thinking skills. It affects not only the patient but also those around the patient, including family and caregivers. The symptoms can become so severe that the person's ability to perform everyday activities becomes compromised. This study aims to search and collect information about the sensitivity and specificity of available laboratory diagnostic methods for patients with Dementia and identify if these methods will be effective in giving a specific and definitive diagnosis. The specificity and sensitivity of four main laboratory testing methods have been included in this review: blood panels, cerebrospinal fluid, plasma biomarkers, hormone testing, and genetic testing. The methods are each explained separately with details of their importance and which specific parameters they screen for have haven included. Numerous blood panels and laboratory diagnostic techniques have been suggested for the timely and accurate diagnosis of Dementia and its various types; however, when the sensitivity and specificity of these techniques are considered, cerebrospinal fluid (CSF) and plasma biomarkers are found to be the most effective. Alzheimer's disease (AD) and other types of Dementia are now diagnosed using the biomarkers amyloid- (A), tau, and phosphorylated tau (p-tau181). With 93 percent accuracy in diagnosis, the innovative Precivity AD test created by the Washington University School of Medicine in St. Louis might be regarded as both highly sensitive and specific.

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1. INTRODUCTION

WHO defines Dementia as "a syndrome, which is characterized as chronic or progressive in nature, and it will lead to deterioration in of the ability of the thought process, which is also known as the cognitive function, beyond what might be expected from the usual consequences of biological aging"[1]. The aftermath of this syndrome could lead to impairment of memory, thinking, orientation in time and place and comprehension, problems with learning capacity and concentration, and judgement[1]. This syndrome could result from primary rain injuries or secondary diseases such as stroke or Alzheimer's disease, the latter being the most common form of Dementia and may contribute to 60-70% of cases [1]. The syndrome mentioned above is mostly prevalent in older age; but is not an inevitable consequence of aging. It is a syndrome that not only affects an individual physically and psychologically but also takes a toll on the families and caretakers of the patients.

1.1. Relevance of problems in cognitive dysfunction in elderly patients with Dementia.

The World Health Organization statistics show that Dementia is a serious syndrome affecting more than 55 million people worldwide, which leads to impairment of memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement in patients suffering from this syndrome[2]. It is not only a condition affecting the patient but also those around the patient, including family, caregivers, and even society. In elderly patients, it leads to an overall decline in memory and thinking skills

Which is so severe that the person's ability to perform everyday activities becomes compromised[2].

Hence, the first assistance both patients and families require when elderly

People who start demonstrating the signs of this impairment will be required from GPs who can further examine and direct patients to adequate help.

1.2. Prevalence of Dementia in the world

According to WHO, in the world today, "Dementia is one of the primary causes of disability and dependency among older people and the seventh largest cause of death among all diseases. Currently, more than 55 million people live with Dementia worldwide, and there are nearly 10 million new cases every year, with over 60% living in low- and middle-income countries. This number is predicted to increase to 78 million in 2030 and 139 million in 2050 because the share of older people in the population is rising in almost every country."[1].

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1.3. Purpose and objectives of the study

The purpose of this study is to highlight the available methods of laboratory diagnostics in patients with Dementia and to estimate the sensitivity and specificity of the available methods of laboratory testing in patients with Dementia.

The objective of this study is to search and collect information about the sensitivity and specificity of available laboratory diagnostic methods for Patients with Dementia, identify whether these methods will be effective in giving a specific and definitive diagnosis.

1.4. Objects of study

Technologies of modern methods of laboratory diagnosis in elderly patients with Dementia from in practice of GPs from the point of view of evidence-based medicine.

1.5. Materials and research methods

For this research, a thorough literature review was performed through articles in WebMD, WHO, NIA, PubMed, Medline, and Stanford Health care.

Recommendations in this review are derived from the most recent guidelines on evidence-based practice in Dementia in elderly patients.

Methods: Critical, Statistical, and comparative analysis.

1.6. The practical significance of work

Systemic effectiveness of the use of laboratory diagnostic methods in diagnosing elderly patients with Dementia in the practice of GPs from the point of view of evidence-based medicine and the application of the most sensitive methods of laboratory diagnosis for early detection of Dementia to start timely therapy to prevent progressive forms of the disease.

2. General principles and requirement of organization of laboratory diagnostic methods in the examination of patients with cognitive impairments in Dementia.

A laboratory test or method specific for the diagnosis of Dementia in elderly patients Is not available; however, for timely diagnosis and detection of the disease, the routine blood checkup is given to eliminate any other causes of symptoms that can be confused with Dementia and to rule out reversible causes that can lead to Dementia in these patients. In most cases, these blood tests will be full blood counts including ESR, Liver function test, kidney function tests, thyroid function tests, hemoglobin A1c, vitamin B12, and folate

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levels[4].

2.1. Summary of recommendation of laboratory diagnostic methods in patients with Dementia

A patient may be advised to undergo a range of laboratory tests to either confirm or rule out the presence of Dementia, such as testing for vitamin deficiency or hormone balance, which can reveal underlying causes of cognitive impairment. A summary of these tests can be CBC, blood glucose tests, urinalysis, drug, and alcohol test (toxicology screening), CSF analysis, and analysis of thyroid and thyroid-stimulating hormone levels [5]. Other tests can include the elimination of certain infections that can lead to Dementia or Dementia infections, such as sexually transmitted diseases, for improve the accuracy of a diagnosis [5].

These tests are recommended for patients to eliminate any other causes of symptoms that can be confused with Dementia and to rule out reversible causes that can lead to Dementia in these patients.

2.2. The principal reasons for the requirement of laboratory diagnosis in elderly patients with Dementia.

A laboratory test assigned to diagnose Dementia must be a test to rule out a cause of the symptom of the disease or to rule out a reversible cause of Dementia that can be causing the symptoms. Symptoms of Dementia such as forgetfulness, unexplained falls, aggression, agitation, and late-onset depression are not only due to Alzheimer’s disease. Still, they can be due to other reasons such as other degenerative diseases such as Parkinson's, Huntington’s Chorea disease, and Pick disease, which should be eliminated.

Furthermore, nutritional deficiencies such as Vitamin B12 deficiency or folate deficiency and a history of diseases of other body systems, including liver and kidney diseases, and systemic diseases such as Diabetes, are questionable too. Another paramount logic can be put to various types of poisoning, including lead and heavy metal poisoning and drug and alcohol poisoning, which can lead to symptoms of cognitive impairment like that are exhibited in Dementia too.

A foremost yet rare etiology of Dementia can be various infections such as HIV and syphilis. Oral herpes, pneumonia, and spirochete infection are a few of the illnesses suspected to be related to Alzheimer's [7].

The last addition to the above list can be interactions of medications, their side effects, and

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poly-pharmacy, which can lead to symptoms, and Other Psychiatric disorders should be eliminated and differentiated from Dementia

3. Basic methods of laboratory diagnosis of cognitive dysfunction in elderly patients with Dementia.

In this section, I will be looking into details of the laboratory diagnostic methods prescribed to elderly patients who may be suspected cases of Dementia.

3.1. Blood tests for Dementia

Patients with Dementia are given a complete blood count because there are several causes of Dementia besides Alzheimer's disease [6]. Sometimes forgetfulness may be common and not cause for alarm unless it interferes with regular tasks. Hence, it is necessary to rule out the causes of no concern.

CBC gives essential quantitative information about RBCs, WBCs, and platelets. A CBC will include ESR, too, which can give information about any inflammatory activity in the body. ESR, or erythrocyte sedimentation rate, is a nonspecific test that can help diagnose conditions associated with acute and chronic inflammation, such as infections, cancers, and other autoimmune diseases [6]. It does not help a healthcare provider to decide where the inflammation is or its cause; hence, this test is nonspecific.

However, this test can be used to monitor disease activity and dynamics. Other measures that can be estimated by a CBC are WBC, RBC, Hemoglobin, Hematocrit, MCV, MCH, MCHC, RDW, Platelets, Neutrophils, Lymphocytes, Monocytes, Eos, Basophils, Neutrophils (Absolute),

Lymphocytes (Absolute), Monocytes (Absolute), Eos (Absolute), Basophils (Absolute), Immature Granulocytes, Immature Granulocytes (Abs). Any abnormalities of these parameters can point out various diseases, such as low RBC and Hb being signs of anemia, neutrophilia, or an increase in neutrophils or shift in the neutrophil formula to left or right, indicating various inflammatory conditions.

LFT or liver function test: abnormal levels of liver enzymes are linked with some types of Dementia. Researchers found that abnormal levels of liver enzymes were associated with Alzheimer's disease in a study by the Alzheimer Disease Metabolomics Consortium, a part of the NIA-led Accelerated Medicines Partnership-Disease Alzheimer's Target Discovery and Preclinical Validation Project, which included data from 407 healthy controls and 862 people

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with memory issues or mild cognitive impairment.[8].

According to the test's findings, a diagnosis of AD was related to decreased levels of ALT and elevated aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio [8]. Elevated liver enzyme levels have consistently been linked to cognitive decline, demonstrating the role of metabolic abnormalities in the pathogenesis of AD [8].

Electrolytes: Mild cognitive impairment and various degrees of Dementia have been associated with abnormal levels of electrolytes in the body. Electrolytes help regulate chemical reactions within the body, maintaining the balance between fluids intra-cellularly and extra-cellularly. This panel includes Sodium levels (Na+), Potassium levels (K+), Magnesium levels (Mg2+), Calcium (Ca2+), Chloride (Cl-), Phosphate (-), and Bicarbonate (-) mainly.

Of these components, Sodium and Potassium levels are the two main electrolytes shown to have a significant risk of MCI. Potassium plays a role in basic function in brain neurons and has been proven to reduce oxidative damage from free radicals; low levels of this electrolyte may be commonly manifested as memory loss and confusion; in elderly patients who may be on diuretic medications, potassium losses will be increased and lead to MCI. Although intersection serum sodium levels and cognitive impairment are rarely investigated, there have been correlations between low levels of sodium or hyponatremia associated with MCI. Hyponatremia is the most common electrolyte disorder with CNS affection resulting in coma, confusion and seizures, and MCI with an increased risk of progression to dementia [21].

Both these parameters are important while running a blood panel for diagnosis of Dementia as these are major factors that can contribute to MCI, which may progress to various forms of Dementia, including both AD and non-AD forms. Kidney function tests and Urinalysis: Incidence of Dementia and AD was independently associated with low GFR levels and may be considered as a marker of an individual's susceptible to cognitive decline. For kidney function tests fasting blood samples were drawn for studies, and Serum creatinine and cystatin C were determined. But the main marker for the above tests was GFR levels.

Blood Glucose tests: Since Diabetes is a risk factor for developing Dementia, this test is also a paramount test for a blood test panel of Dementia. Even if an individual is not a diabetic patient, obesity and Diabetes are risk factors for Dementia due to likely effects on metabolism [10]. Studies have indicated that high blood glucose levels may have negative effects on the aging brain,

although excessive levels of glycated hemoglobin or postprandial glucose have also been

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linked to rates of cognitive decline or changes in hippocampus volume [10]. Dementia risk was raised due to factors like acute and chronic hyperglycemia, insulin resistance, increased microvascular disease of the CNS, and more.

Toxicology studies (drug and alcohol testing): ARD or alcohol-related Dementia has been a test subject in many studies, which have led to conclusions that the prolonged and extreme use of alcohol could be a cause of cognitive impairment due to both structural and functional damage to the brain.

These studies showed that cognitive defects are commonly observed in domains of visuospatial functions, memory, and executive tasks [12]. While mild to moderate consumption of alcohol may not be associated with the risk of developing Dementia, the key factor is noted to be long-term consumption and excessive use of alcohol.

Similar to alcohol, which alters mental status, other drugs such as cannabis, benzodiazepines, and similar drug usage has proven to be correlated to the development of Dementia in later stages of life. Anticholinergic and psychotropic drugs can impair cognitive function and make Dementia more common among the elderly. A thorough toxicology report is necessary to eliminate the possible causes for timely treatment of Dementia.

3.2. Hormonal test for Dementia

Hormones, specifically sex hormones, have been proven important in the etiology of Dementia due to their strong influence on cognition and cognitive decline.

While hormone tests are not specific for the diagnosis of Dementia, it is necessary to conduct these tests for patients who may have a higher risk of developing Dementia, one of the higher-risk groups is female gender, as there are 65% more females who currently have this condition than males though age maybe the higher risk factor [14]. Studies have shown that hormones play a major role in the convergence of vascular risk, inflammation, and neurodegenerative disease, and various hormone therapy methods have shown inconclusive outcomes on cognition and dementia risk (Lee, Park, Joung, & Kim, 2020).

In this section, sex hormone studies are important as experimental, epidemiological studies suggest that androgens, estrogens, and even progesterone can reduce the risk for Dementia. Other tests include thyroid hormone panels.

Sex hormones:

In women, estrogen and progesterone are the main sex hormones, the synthesis of which is controlled by the hypothalamic-pituitary-gonadal axis (HPG). In the case of estrogen, ongoing

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production of this hormone has been shown to increase cerebral blood flow and glucose utilization and show a favorable outcome on brain tissue and cognition in later life. In women of elderly age, decreasing the production of estrogen leads to menopause together with problems in cognition, physiology, and various effects on brain tissue, as there will be a subsequent decrease in the neuroprotective effect [14]. Interaction of both Estrogen and progesterone have neuroprotective properties, and decreased levels of these hormones in the body could be a reason or risk factor for the development of Dementia in females.

To consider the risk factors associated with female sex hormones in women, one should also consider the levels of testosterone in elderly women, which in women is produced by the ovaries in smaller amounts and by the adrenal glands by cholesterol. As testosterone can be converted to estrogen and provide the effect of estrogen in women, it can show significantly better performance in verbal learning and memory in postmenopausal women who will have decreased concentration of this hormone beyond age 65 [15].

Decreased cognition and a strong association with Dementia have also been shown in elderly men with low levels of testosterone [18].

Thyroid hormones have also been associated with cognitive impairment; the brain is highly sensitive to thyroid hormone levels. TSH, or thyroid stimulating hormone, help to evaluate thyroid function and diagnose thyroid disorders such as Subclinical Hypothyroidism which has been associated with cognition in elderly. A drop in levels of these hormones drop, in other words; hypothyroidism can cause CI which can be reversible when levels of thyroid hormone are restored, and this is one of the reasons why thyroid hormone test is specifically important for diagnosing dementia [23].

3.3. Cerebrospinal fluid and plasma biomarkers

Cerebrospinal fluid is a transparent fluid surrounding the brain and spinal cord that provides the brain with protection and insulation while supplying nutrients and chemicals that keep the brain cells healthy and nourished. CSF biomarkers are valuable, sensitive, and a specific tool for early detection of neurodegenerative disorders. Currently biomarkers amyloid-β (Aβ), tau and phosphorylated tau (p-tau181) are now used for the diagnosis of Alzheimer's disease (AD) and various types of Dementia [25]. Characteristic of progression of AD related dementia forms is reduction in levels of amyloid-β (Aβ) protein (that is, low CSF Aβ42 level) and an increase of neuronal degeneration biomarkers (that is, increase of CSF total tau and phosphorylated tau (p- tau181) levels) in CSF of subjects with AD [25].

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The operation used in CSF analysis, also known as a spinal tap or lumbar puncture, lasts 30 to 60 minutes. Under local anesthesia, a small needle is placed under local anesthesia into the area between the spine's bones, and CSF is slowly sucked out using a syringe [26]. These CSF assays will reveal levels of tau, phospho- tau, and beta-amyloid 42, which is the main component of amyloid plaques in the brain (the major components of tau tangles in the brain). Compared to levels in people without Alzheimer's or other forms of Dementia, beta-amyloid 42 levels in CSF are low in people with Alzheimer's, whereas tau and phospho-tau are high [26].

Although CSF analysis is highly specific, it is a complex and invasive procedure, while plasma biomarkers for diagnosis of cognitive impairment can be used, which are easily accessible and non-invasive. Recent advances in blood-based biomarkers of Alzheimer's disease classic pathology—amyloid (A) and phospho-tau (pTau)—and neurodegeneration hold promise for making an "ATN" diagnosis of Alzheimer's disease4 without the use of cerebrospinal fluid testing or positron emission tomography (PET) neuroimaging. Since changes in the traditional Alzheimer's disease biomarkers or the ATN classification scheme do not reflect changes in the pathophysiology of Alzheimer's disease and dementias are not limited to the Aβ cascade and tauopathy. Instead, processes like inflammation, vascular injury, oxidative injury, and disruption of metabolic pathways may also contribute to the progression of the disease. To predict the change of MCI to Dementia, it is therefore anticipated that combinations of blood-based protein biomarkers reflecting many pathways will boost the sensitivity and specificity of a single biomarker test. Several initiatives have been made to create multivariate biomarker panels that can forecast MCI's clinical course development. Some of these studies claim to have a high degree of accuracy in predicting the transition from MCI to dementia [27].

3.4. Genetic testing for Dementia

A genetic test is a medical examination examining DNA from the patient's blood or saliva to ascertain their genetic make-up.

The likelihood of getting a condition that causes Dementia may vary depending on several genetic combinations.

Genetic testing may be a technique for avoiding Dementia or early detection and rapid treatment in those with a family history of Dementia.

People with Dementia are at an increased risk of developing Dementia later in life. However,

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genetic testing in Dementia is mostly promising when only a single-gene mutation is responsible for Dementia. An accurate molecular diagnosis is provided by a positive genetic test, which can also enable affected family members assess their own risk, serve as a foundation for reproductive decisions, and provide opportunities for clinical trials.

A gene panel and C9orf72 expansion testing are typically the best genetic tests for normal Dementia because they balance the likelihood of discovery with expenses and reduce variants with ambiguous relevance. Single-gene tests are justified in certain circumstances, such as conventional Huntington disease, prion disease, or to confirm a known familial mutation. However, atypical syndromes may call for whole-exome sequencing (WES), whole- genome sequencing (WGS), and C9orf72 expansion testing [29].

Patients must provide blood, DNA that has been extracted, or saliva that will be tested for the APOE E4/E4 haplotype to participate in genetic testing for dementia [30]. Even though genetic testing for Dementia has some drawbacks, some of the most common genetic syndromes, including Alzheimer disease, frontotemporal dementia, vascular dementia, Parkinson disease dementia/dementia with Lewy bodies, and some less common types of genetic dementias, may be quickly diagnosed and timely treatment may be started with the help of genetic testing.[31].

3.5. A novel biomarker test- Precivity AD

A blood test that is up to 93% accurate at identifying people at risk of Alzheimer's Dementia has been developed using mass spectrometry in Washington University School of Medicine in St. Louis. The blood test, known as Precivity AD, can drastically cut the time and cost of identifying patients for clinical trials and new treatment options. Furthermore, it boosts timely and accurate diagnosis for patients with the condition.

By comparing the ratio of the blood levels of the amyloid beta proteins A42 and A40, the blood test created by Bateman and colleagues determines if amyloid plaques have started to build up in the brain. When blood amyloid levels were combined with another major Alzheimer's risk factor – the presence of the genetic variant *APOE4*– the accuracy of the blood test was 88% when compared to brain imaging and 93% compared to spinal tap [33]. Compared to previous techniques for detecting brain amyloid, the Precivity AD test is significantly less intrusive, more practical, and less expensive [34]. The sooner a patient is diagnosed with Alzheimer's, the sooner a care plan can be established for them and alternative options, such clinical research, can be investigated. Clinical studies for AD can take many

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forms, such as those investigating new preventative measures or early-stage treatments.[34].

Conclusion:

For the timely and accurate diagnosis of Dementia and its various types, several blood panels and laboratory diagnostic techniques have been proposed; however, when the sensitivity and specificity of these techniques are considered, cerebrospinal fluid (CSF) and plasma biomarkers are found to be the most effective. Biomarkers amyloid-β (Aβ), tau, and phosphorylated tau (p-tau181) are now used for the diagnosis of Alzheimer's disease (AD) and various types of Dementia. The novel Precivity AD test developed by Washington University School of Medicine in St. Louis, with 93% accuracy in the diagnosis, could also be considered highly sensitive and specific.

Other blood tests, including Complete blood count, Kidney function tests, Liver Function tests, Electrolytes, Blood Glucose levels, and toxicology screening, is only necessary for the determination of causes and high-risk patients to consider the probability and possibility of development of the disease and to eliminate any causative factors in patients who may be demonstrating the symptoms of Dementia. But in terms of the sensitivity and specificity of these methods to the diagnosis of Dementia, they are not recommended.

The same conditions apply to genetic testing; even though some studies have shown promising results with genetic testing, it is not routinely used in the clinical setting to diagnose or predict the risk of developing Dementia or AD; genetic testing has many pros and cons which need to be carefully considered first.

In the case of hormone tests, both sex hormone and thyroid tests can also be considered nonspecific, as these tests also reveal certain etiological aspects, indicating the risk factors that an aging person may have regarding depleting hormone levels;

Also be ruled out in terms of sensitivity and specificity for identifying Dementia.

However, for a timely and accurate diagnosis of Alzheimer's related Dementia, in clinical practice, blood panels, hormone tests, CSF, or Plasma Biomarkers must be evaluated along with instrumental techniques and adequate collection of anamneses with other cognitive function tests that are necessary.

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Index 1 Abbreviations:

ESR- erythrocyte
sedimentation rate CBC:
complete blood count

CSF: cerebrospinal fluid

HIV: human immunodeficiency
virus WHO: World Health
Organization AD: Alzheimer's
disease

GFR: Glomerular Filtration
rate CNS: Central Nervous
System

HPG: hypothalamic-pituitary-gonadal
axis MCI: Mild Cognitive
Impairment

TSH: thyroid stimulating
hormone β A β: β- amyloid

ATN: β- amyloid/tau/neuronal
damage pTau: phospho-tau

PET: positron emission tomography WES: whole-exome sequencing WGS: whole-genome sequencing