



Neurochemical Biomarkers in Alzheimer's Disease: A Practical Narrative Review of Analytical and Clinical Interpretation

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Abstract

Over the past years, there has been an evident change in the perspective of the Alzheimer disease field where descriptive clinical diagnosis has been replaced by a biological one where molecular marker that indicate amyloid deposition, tau protein phosphorylation abnormalities, and the degree of neuron and glial damage are measured. A β 42, A β 40, and the A β 42/A β 40 ratio, as well as total tau, p-tau181, p-tau217, p-tau231, neurofilament light chain (NfL) and GFAP, the most established neurobiological markers in this area, as they connect the disease on the one hand, and the possibility of early detection, biomarker classification, and longitudinal follow-up on the other. The purpose of the review is to put these markers in a practical context based on the nature of the biological sample and the laboratory platforms to measure them, the distinctions between conventional and automated immunoassays, ultra-sensitive Simoa methods, and LC-MS/MS mass spectrometry, and to discuss the strengths and weaknesses of each method. The review also covers issues of pre-analysis, analytical validation, compatibility with the platform and derivation of cutoff values, and then considers future trends that lead to more clinically useful blood tests, such as automated tests and those that have recently undergone sophisticated regulatory review. The review finds that the real worth of these biomarkers is not just in their availability but also in choosing the right biomarker to the right clinical question and in maintaining the integrity of the measurement chain between sample collection and interpreting the results.

Keyword : *Alzheimer's disease; Neurobiomarkers; amyloid-beta; phospho-tau; NfL; GFAP; Simoa; LC-MS/MS; CSF; plasma.*

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INTRODUCTION

The concept of Alzheimer disease is no longer considered as a clinical syndrome that is characterized by memory and cognitive functions only; on the contrary, it is also explained by its biological signature that can be identified in cerebrospinal fluid and blood and, in some cases, in combination with the markers of molecular imaging. This change has been codified in the most recent guidelines released by the Alzheimer Association which have embraced a biological definition of the disease in terms of the identification of abnormalities in key markers related to amyloid or tau. The significance of this change is explained by a rather simple but important fact: clinical manifestations can be years behind the development of the pathological process, and biomarkers can be detected at an earlier stage and with a higher level of objectivity. Thus, there has been a rapid change in scientific interest towards direct neurochemical markers, i.e., those that are indicative of the underlying pathophysiology of Alzheimer's disease, and not secondary, remote ones [2-4].

The most established form of this field consists of amyloid-beta markers, phosphorylated tau markers, neuronal degeneration and glial activation markers including NfL and GFAP [3,5-10].

Nevertheless, the meaning of a biomarker cannot be perceived without the context of its measurement. The clinical significance itself can be different based on the type of sample, the platform applied, the sensitivity of the assay and the preanalytical procedures before the sample is introduced into the instrument [4,11-14].

This is what this review aims to do: it is not just a description of the markers but puts them into a direct laboratory setting, how each marker is quantified, what each method adds, and what its limitations are [8-14].

The Pathophysiological Basis for Selecting Biomarkers

Key biomarkers in Alzheimer disease have been selected on the basis that at the molecular level the disease depends on two main axes which are the extracellular deposition of amyloid-beta peptides and the phosphorylation of tau protein in neurons resulting in the development of neurofibrillary tangles [1,2,6]. This pathological mechanism then converts into axonal damage, loss of synapses and glial responses which justifies the increase of NfL and GFAP markers at various stages of the disease progression [3,13-15]. Analytically, this classification can be useful in locating markers within the A/T/N framework; amyloid is located on the A axis, pathological tau on the T axis, and markers of neurodegeneration on the N axis, with GFAP being a complementary marker that is a significant indicator of astrocyte activation [1-4]. Since this framework is associated with the mechanisms of the disease and not the clinical presentation of the disease itself, these biomarkers have simultaneously gained diagnostic, exclusionary and predictive value [1,3]. The principal neurochemical biomarkers associated with Alzheimer’s disease and their pathological relationships are summarized in **Figure 1**.

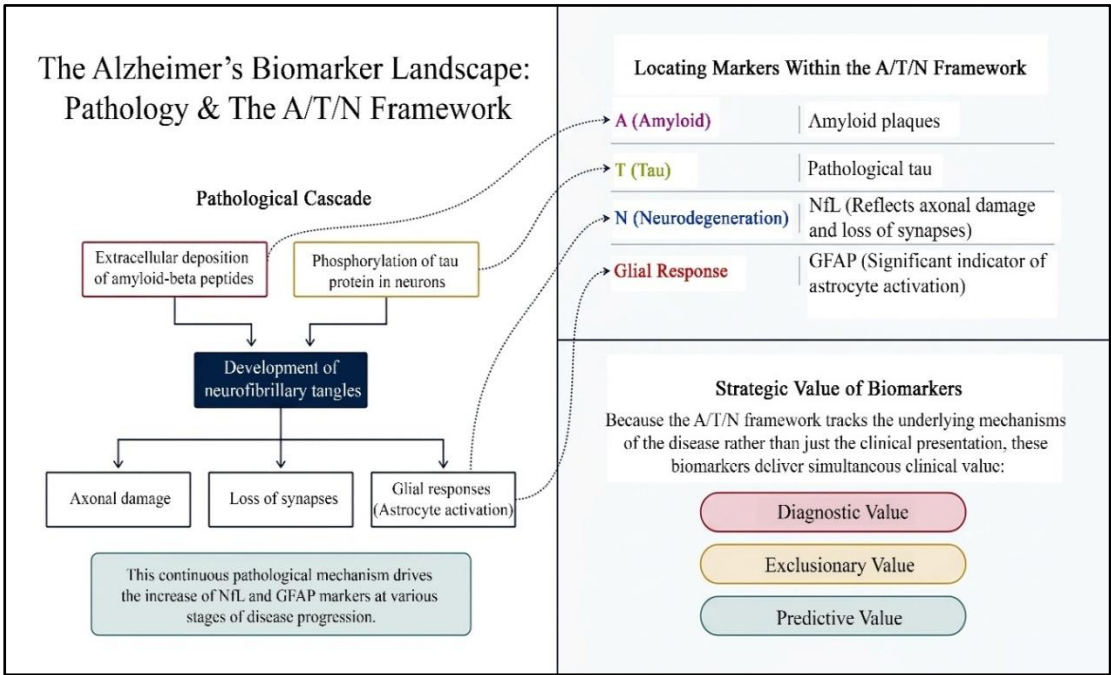


Figure 1. Pathological cascade and classification of Alzheimer’s disease biomarkers within the A/T/N framework

Key Neurochemical Biomarkers Directly Associated with Alzheimer’s Disease

1. Amyloid-beta markers

The oldest and most established liquid markers in the diagnosis of Alzheimer disease is Aβ₄₂ because its decrease in cerebrospinal fluid is an indication of its accumulation in the brain tissue in amyloid plaques [1,4-7]. Nonetheless, the use of Aβ₄₂ in isolation might not be as reliable as the use of Aβ₄₂/Aβ₄₀ ratio, because the ratio helps to eliminate some of the personal and analytical variability of

total amyloid production [4-8]. This is even more important in plasma samples; the concentrations are lower, the interference of proteins is greater and the pathological signal is not as strong as in cerebrospinal fluid, so the ratio of $A\beta_{42}/A\beta_{40}$ is the most significant readout of the sample as opposed to measuring each peptide individually [8-10]. Cross-platform comparisons have demonstrated that certain plasma assays can enhance the prediction of amyloid PET positivity, but the performance of the assays differs greatly according to the methodology of the technique, which should not be overlooked when interpreting results or applying cutoff values between different platforms [9,10]. LC-MS/MS studies have also shown that mass spectrometric measurement of plasma amyloid has good practical value in screening patients with a low probability of amyloid disease, particularly in the context of pre-screening prior to PET or CSF testing [8].

2. Tau markers: total tau and phospho-tau

Although the amyloid axis is useful in demonstrating the presence of the disease, the tau axis gives a more precise readout of the Alzheimer disease, especially when it is used to measure particular phosphorylated forms [3-6].

CSF total tau has been traditionally considered a measure of neuronal damage, but is less specific than phospho-tau; it can be increased in other conditions other than Alzheimer disease [4-7].

p-tau181 was the most frequently used liquid marker of pathological tau over the years, until comparative studies revealed that p-tau217 can more effectively differentiate between Alzheimer and other neurodegenerative diseases, both in cerebrospinal fluid and in blood [7,9].

A study by Janelidze and others was a breakthrough as it showed that p-tau217 in CSF is more accurate than p-tau181 in detecting Alzheimer disease and its relationship with tau and amyloid deposits [7].

p-tau231 has also become a valuable early indicator in plasma and especially in the early phases of the disease, its increase can be observed before some of the clinical changes are apparent [8].

Nevertheless, these indicators cannot be regarded as being in constant competition with each other. Both have their own biological window; p-tau231 is usually sensitive to very early stages, and p-tau217 provides in most studies the best compromise between sensitivity and specificity throughout the disease spectrum [3,8,11,12]. Thus, the practical question becomes not: Should we measure tau? Instead, which isoform are we going to measure, on what platform, and in what clinical scenario? [11,12].

3. Markers of Neurodegeneration and Glial Activation: NfL and GFAP

NfL is an established axonal damage marker; it is not selective to Alzheimer disease per se, but acquires interpretative value when used in combination with amyloid and tau markers [14,15].

Increased NfL in CSF or blood can be a good indicator of ongoing neurodegeneration and can be useful in estimating the disease severity or rate of disease progression but its low specificity should be noted when used alone [13,15].

GFAP, however, is an astrocyte activation marker that has received growing interest over the past few years due to its early increase in the bloodstream and its linkage with amyloid disease and the potential risk of cognitive impairment in several clinical trials [14,15].

Recent clinical trials have proposed that serum GFAP could be better than NfL in differentiating between Alzheimer disease and mild impaired cognitive in some situations, and the diagnostic value is even greater when the two markers are used together [14].

Practically, neither NfL nor GFAP can be used to replace $A\beta_{42}$, the $A\beta_{42}/A\beta_{40}$ ratio and p-tau markers; they are an extra interpretive layer that demonstrates the degree of neuronal damage and the glial response and adds value to the combined clinical evaluation [13-15].

The main analytical platforms used for the measurement of Alzheimer's disease biomarkers are compared in **Figure 2**.

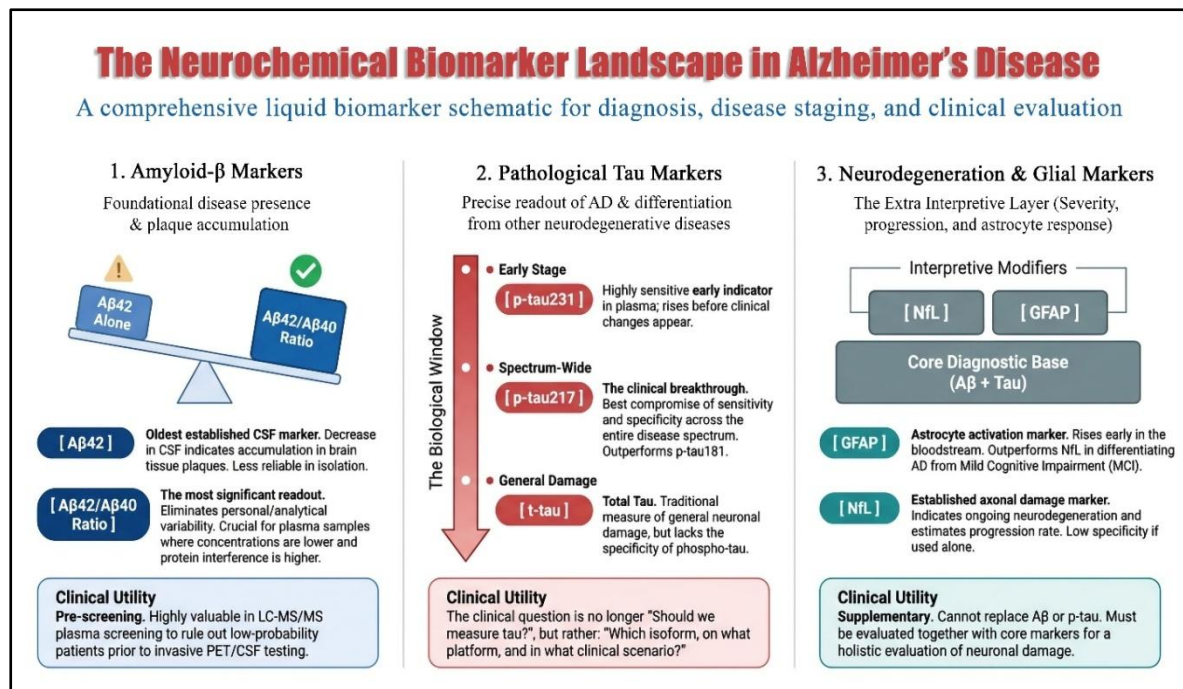


Figure 2. Neurochemical biomarker landscape in Alzheimer's disease, highlighting the complementary roles of amyloid- β , pathological tau, neurodegeneration, and glial activation markers.

Biological Samples Used in Measurement

Cerebrospinal fluid (CSF) is the best biological reference to measure important biomarkers of the Alzheimer disease, as its composition is closer to that of the central nervous system, and its signal-to-noise ratio is greater than plasma in most of the key biomarkers [1,4-7].

This is why CSF markers, especially the A β_{42} /A β_{40} ratio and p-tau/ A β_{42} , remain a reference in numerous contemporary guidelines and expert laboratories [4,5].

Nevertheless, lumbar puncture cannot be applied to all patients and not all healthcare environments, and its practical acceptability differs across healthcare systems, physicians, and patients [4,5].

Plasma, on the other hand, is characterized by ease of collection, reproducibility, and the ability to integrate into large-scale care pathways, but it requires more sensitive platforms and greater rigor in preanalytical steps [3,8-13].

Therefore, the analogy between CSF and plasma is not a question of right and wrong, but of a highly biologically relevant reference on one hand, and a highly scalable clinical alternative on the other [3-5,11].

Laboratory Tools and Techniques Used for Measurement

1. Traditional Immunoassays: Enzyme-Linked Immunosorbent Assay (ELISA)

ELISA has been central to the history of Alzheimer biomarkers, and it has been used to establish routine detection of A β_{42} , t-tau and p-tau in cerebrospinal fluid before the widespread use of automated systems [4-7].

Though this method is still applicable and is still in use in research and certain laboratories, its shortcomings have become evident: The method is more labor intensive, more susceptible to batch-to-batch and interlaboratory variations, and has a comparatively long turnaround time [5,7].

When the goal is clinical expansion and standardization of results across centers, these limitations have a direct impact on cut-off values and the comparability of studies [4,13].

2. Automated Immunoassays: CLEIA, ChLIA, and ECL

Chemiluminescence or electrochemiluminescence automated platforms have brought a major change in this area, since they have minimized the manual handling, enhanced the stability of the analytical process and the turnaround time has been shortened [11-13].

A notable example of such platforms is the Lumipulse system; this is an CLEIA-based system that has been extensively used to measure important CSF markers, and subsequently some plasma assays [11,13,19]. Recent research has indicated that new automated assays such as the chemiluminescent assays of EUROIMMUN can provide stable analytical performance and fair accuracy in the measurement of $A\beta_{1-40}$, $A\beta_{1-42}$, t-tau and (p-tau181) in cerebrospinal fluid [12].

The significant practical benefit of these platforms is that they make Alzheimer testing more akin to the logic of everyday clinical laboratory practice, i.e. the logic of standardized testing, short turnaround times and the capacity to conduct tests on an ad hoc basis, as opposed to the logic of restricted research chains [11-13].

3. Ultra-sensitive Simoa technology

With the change in interest to CSF to blood, a technological requirement was created, since the concentrations of neuroproteins in plasma are significantly lower and can be below the detection limits of traditional tests [3,13].

In this case, the Simoa system acquired a special significance, since it allows measuring molecules at very low concentrations and has contributed to the fact that such markers as p-tau217, p-tau231, NfL, and GFAP were brought to the center of research and subsequently subclinical application [8,11-14].

But high sensitivity is not a virtue in itself; it must be carefully calibrated, analytical contamination monitored, and the distinctions between reagents and platforms precisely understood, lest technical differences are reflected in false interpretive differences [11,13].

4. LC-MS/MS

High quality of analysis and the ability to differentiate between molecular structures are the main features of LC-MS/MS, which is especially appealing to the measurement of plasma amyloid and some sophisticated tau assays [8-10].

Recently, LC-MS/MS-based $A\beta_{42}/A\beta_{40}$ assays have proved to have significant use in the primary screening of patients and in the determination of the probability of amyloid positivity [8].

Moreover, there have been comparisons that indicate that the diagnostic sensitivity of some of the more sophisticated spectroscopic tests can be comparable, and in some cases even better, than automated immunoassays, but the infrastructure needs and technical skills are comparatively greater [10,11].

Thus, LC-MS/MS is not considered as an alternative tool, but as a reference platform that can be used to support verification, optimization, and standardization, especially when quality results are required or multicenter comparisons are to be made [8-10].

4.1. Multimarker Assays

The recent development in the area is to abandon single-marker assays wherever feasible, since Alzheimer disease is a complicated biological process, and since the joint measurement of amyloid, tau, and indicators of neuronal harm give a more consistent image [1,3].

This is why several types of dual or composite ratios are applied nowadays, including p-tau217/ $A\beta_{42}$ and $A\beta_{42}/A\beta_{40}$, and multi-marker blood panels are under testing to enhance accuracy and decrease the gray zone [11,20].

Nevertheless, success here is not based on the number of combined markers, but on the quality of measurement of each component and the validity of the model to relate them clinically [9,11]. An integrated framework for the clinical interpretation of Alzheimer's disease biomarkers is presented in **Figure 3**.

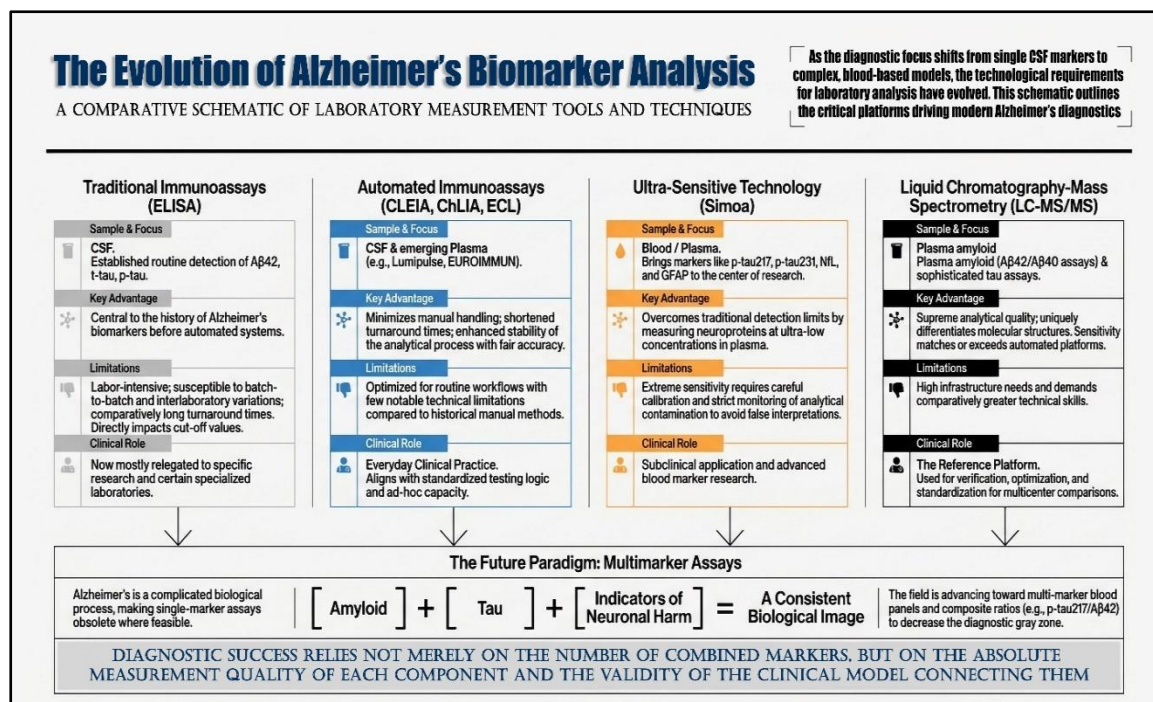


Figure 3. Comparative overview of analytical platforms used for Alzheimer's disease biomarker measurement and their transition toward multi biochemical markers assays.

4.2. Comparative Evaluation of Analytical Platforms

ELISA is still appropriate in research and educational use, and in small-volume labs, but is inappropriate in high-volume service workflows where speed and high reproducibility are needed [4,5]. Automated systems like CLEIA and ChLIA, however, provide an acceptable tradeoff between precision, user-friendliness, and the capability to fit into the normal laboratory workflow; thus, they seem to be the most similar to structured clinical use at present [11-13].

Simoa is very appealing in cases where the objective is to measure low-abundance proteins in blood, especially in translational studies, early-phase studies, and longitudinal follow-ups [13,14].

Conversely, LC-MS/MS has a high quality of analysis and good traceability, yet its price, technical demands, and the technical expertise necessary to operate it can restrict its use beyond advanced facilities [8-10].

To conclude, the practical question is not: Which is the best instrument in general? Instead: What platform is best suited to the desired biomarker, the nature of the sample at hand, and the desired clinical or research application? [8-14].

in table 1. is intended as a practical overview rather than a definitive statement; the actual performance of any platform varies depending on the assay, the reagent, the pre-analytical protocol, and the nature of the clinical cohort studied [3-5, 8-14].

Table 1. A brief comparison of the leading platforms used to measure Alzheimer’s biomarkers

Platform	Common Biomarkers	Strengths	Key Limitations	Most Suitable Setting
ELISA	A β ₄₂ , t-tau, and p-tau in CSF	Long-established methodology, lower cost, and suitability for research applications	Manual workflow and greater inter-laboratory variability	Research laboratories
CLEIA/ChLIA/ECL	Core CSF biomarkers and selected plasma assays	Greater automation, improved analytical stability, and shorter turnaround time	Variability across manufacturers and assay-specific cutoff values	Specialized clinical laboratories
Simoa	p-tau ₂₁₇ , p-tau ₂₃₁ , NfL, and GFAP in plasma	Ultra-high sensitivity for low-abundance analytes	Higher cost and greater dependence on precise calibration	Translational studies and advanced clinical settings
LC-MS/MS	A β ₄₂ /A β ₄₀ and selected advanced assays	High analytical specificity and potential for reference-method validation	Requires specialized infrastructure and operational expertise	Reference centers

METHODOLOGICAL AND ANALYTICAL CHALLENGES

The greatest mistake in this area is to take the test result as a value that is not dependent on the process of its production, but preanalytical procedures can modify the result before the sample is even presented to the instrument [20-22].

The type of tube used, the time of separation, storage, the number of freeze-thaw cycles, and even the patient selection criteria can all affect measured concentrations and their capability to differentiate between samples [4,21].

Next is the problem of cross-platform compatibility; the same numerical value cannot be transferred mechanically between ELISA and Lumipulse or between Simoa and LC-MS/MS since each system quantifies the molecule in a different chemical environment [13, 23].

The other problem is the indeterminate zone or gray zone - a region between positive and negative where one reading is not enough to make a good clinical decision - which has prompted multiple studies to suggest two-cut strategies rather than one cut-off [11, 23].

Other variables in blood, including age, renal function, and some comorbidities come into play in blood, which may affect some of the markers, especially p-tau₂₁₇, NfL, and GFAP, and require a more conservative and accurate interpretation [11,23].

FUTURE TRENDS

The discipline is evidently heading towards automated, highly scalable blood tests that can be incorporated into the clinical care pathway without undue compromise of biological accuracy [1,3,24].

In this respect, the p-tau₂₁₇-based automated tests and their ratios with A β ₄₂/A β ₄₀ have acquired a special significance as they are bringing Alzheimer closer to the model of routine laboratory testing than the reference centers alone [19,20,24].

In 2025, the U.S. Food and Drug Administration (FDA) announced approval of the first blood test to aid in the diagnosis of Alzheimer’s disease, the Lumipulse G pTau₂₁₇/β-Amyloid 1-42 Plasma Ratio test, to be used within a specialized care setting and in conjunction with other clinical information, not as a substitute for it [19,20]. This move has a meaning not just to the device itself, but it is an indication that the field is no longer in the research validation stage, but in the organized translation stage, where questions of standardization, external validation, and indication control are at least as important as the accuracy of the test itself [20-23]. It is probable that the near future will be a blend of three factors: automated blood-based platform, multivariate interpretive algorithm, and selective application of reference tests like CSF or PET in inconclusive cases [15,24].

CONCLUSION

Neurochemical biomarkers directly related to Alzheimer disease are not just auxiliary tools anymore, but have become part of the knowledge base on which the disease is perceived, defined and categorized. Amyloid and tau are still the cornerstones of biological definition, and NfL and GFAP provide a valuable interpretive layer concerning the degree of neuronal damage and glial activation. The replacement of the traditional ELISA with automated assays, SIMOA, and LC-MS/MS, in the laboratory, was not only a change in the speed of the test but also a change in the philosophy of measurement: the test as a limited research test has been replaced by a diagnostic framework that can be used to stage the clinical.

However, the final outcome will still depend on the proper choice of the marker, the nature of the sample, the platform, the clinical indication, and the level of consideration of pre-analytical and analytical variables. From this perspective, a good laboratory does not merely provide a number, but rather a number that is valid for interpretation. This is what makes the difference between a useful and a misleading measurement.

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Author Contributions

Mustafa Alburhan conceived the review, developed the main intellectual concept, designed the review structure, defined the thematic framework, and supervised the overall preparation of the manuscript. He also contributed substantially to the interpretation of the scientific literature, development of the conceptual narrative, and drafting of the manuscript. Abdulla Munthir Sulaiman contributed to literature screening, organization of the selected references, critical appraisal of the included evidence, and refinement of the analytical and interpretative sections. Bakr Aldoori contributed to the critical review of the scientific content, refinement of the clinical interpretation, and revision of the manuscript for intellectual accuracy and clarity. All authors contributed to the literature review, manuscript preparation, critical revision, and final intellectual refinement of the article entitled “Neurochemical Biomarkers in Alzheimer’s Disease: A Practical Narrative Review of Analytical Platforms and Clinical Interpretation.” All authors read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Data Availability

Not applicable. The current narrative review was founded solely on the literature and scientific sources published in the past and available publicly. No original datasets were created or analyzed when preparing this manuscript.

Consent to Participate

Not applicable. This narrative review did not engage human subjects, personal information, clinical interventions, or personal contact with patients; thus, no written informed consent was needed.

Consent to Publish

Not applicable. No personal-level data, clinical images, videos, case-specific information, or other identifiable personal information are provided in this narrative review. Thus, no consent to publish was needed.

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المؤشرات الحيوية الكيميائية العصبية في مرض الزهايمر: مراجعة سردية عملية للتفسير التحليلي والسريري الملخص

شهدت السنوات الماضية تحولاً واضحاً في مجال مرض الزهايمر، حيث استُبدل التشخيص السريري الوصفي بتشخيص بيولوجي يعتمد على قياس المؤشرات الجزيئية التي تدل على ترسب الأميلويد، واضطرابات فسفرة بروتين تاو، ودرجة تلف الخلايا العصبية والخلايا الدبقية. وتُعدّ A β 42 و A β 40 ونسبة A β 42/A β 40، بالإضافة إلى تاو الكلي، و p-tau181 و p-tau217 و p-tau231، وسلسلة نيوروفيلامنت الخفيفة (NfL)، و GFAP، من أكثر المؤشرات الحيوية العصبية رسوخاً في هذا المجال، إذ تربط هذه المؤشرات بين المرض من جهة، وإمكانية الكشف المبكر عنه، وتصنيف المؤشرات الحيوية، والمتابعة الطولية من جهة أخرى. تهدف هذه المراجعة إلى وضع هذه المؤشرات الحيوية في سياق عملي، استناداً إلى طبيعة العينة البيولوجية والمنصات المختبرية المستخدمة لقياسها، والفروقات بين المقاييس المناعية التقليدية والآلية، وطرق Simoa فائقة الحساسية، وقياس الطيف الكتلي LC-MS/MS، ومناقشة نقاط القوة والضعف لكل طريقة. كما تتناول المراجعة مسائل ما قبل التحليل، والتحقق التحليلي، والتوافق مع المنصة، واستنباط القيم الحديثة، ثم تستعرض التوجهات المستقبلية التي تُفضي إلى فحوصات دم أكثر فائدة سريريًا، مثل الفحوصات الآلية وتلك التي خضعت مؤخراً لمراجعة تنظيمية دقيقة. وتخلص المراجعة إلى أن القيمة الحقيقية لهذه المؤشرات الحيوية لا تكمن فقط في توافرها، بل أيضاً في اختيار المؤشر الحيوي المناسب للسؤال السريري المناسب، وفي الحفاظ على سلامة سلسلة القياس بين جمع العينة وتفسير النتائج.

الكلمات المفتاحية: مرض الزهايمر؛ المؤشرات الحيوية العصبية؛ بروتين بيتا النشواني؛ بروتين تاو المفسفر؛ NfL؛ GFAP؛ Simoa؛ LC-MS/MS؛ السائل النخاعي الشوكي؛ البلازما.